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ZHENSHENG DING

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**VANOL AND VAPOL CHEMISTRY: NEW METHODOLOGIES,
LARGE SCALE SYNTHESIS, DERIVATIVES, AND
SYNTHETIC APPLICATIONS**

VOLUME I

By

Zhensheng Ding

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ABSTRACT

VANOL AND VAPOL CHEMISTRY: NEW METHODOLOGIES, LARGE SCALE SYNTHESIS, DERIVATIVES, AND SYNTHETIC APPLICATIONS

By

Zhensheng Ding

Two members of a class of vaulted biaryl ligands, 3,3'-diphenyl-2,2'-bi-1-naphthol (VANOL) and 2,2'-diphenyl-3,3'-bi-4-phenanthrol (VAPOL) are synthesized through the oxidative coupling reactions using air under neat conditions, which suffers from some drawbacks. Thus, new conditions in mineral oil are established, optimized and used to prepare these two ligands on large scale. The different methods to access VANOL monomer are studied and it is found that preparation from commercially available 4-chloro-1-naphthol is the most efficient pathway, which is used to generate VANOL monomer on large scale. VAPOL monomer, on the other hand, is synthesized on large scale by the CAEC cascade reaction of 2-naphthylacetic acid by using isobutyric anhydride as trapping agent.

Different methodologies to access the derivatives of VANOL are explored, which has greatly increased the structural diversity of this ligand. These efforts lead to the possibility to screen for the optimal catalyst for a given asymmetric organic reaction, which is highlighted by the way that it enables the elucidation of the mechanism of Atilla-Wulff aziridination reaction.

Efficient methods for the resolution of both VANOL and VAPOL ligands are developed and optimized. Consequently, these optically pure ligands and their derivatives have been successfully used in creating effective asymmetric environments for many mechanistically unrelated reactions, such as Diels-Alder reaction and Imino-Aldol reaction.

*To everyone who loves me as a whole
Who helped make it all possible
Who helped make it all worthwhile
Who sees and solves the big problems
With perseverance, innovation, and style*

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TABLE OF CONTENTS

LIST OF TABLES	xvii
LIST OF SCHEMES	xx
LIST OF FIGURESS	xxiv
ABBREVIATIONS	xxv
CHAPTER ONE	
INTRODUCTION	
1.1 Ligands for asymmetric reactions: an overview	1
1.2 BINOL: A versatile chiral ligand	5
1.2.1 Asymmetric AZ reaction using BINOL and derivatives as ligand	6
1.2.2 Limitations in the 3,3'-disubstituted BINOL design	7
1.3 VANOL and VAPOL: A new high performance ligand platform	9
1.4 The VAPOL / VANOL ligands in asymmetric catalysis– a brief introduction	10
1.5 Preparation of the VANOL/VAPOL ligands: precedent methods	14
1.6 Main goals of this thesis work	16
1.7 Conclusion.....	17
CHAPTER TWO	
SYNTHESIS OF 3-PHENYL-1-NAPHTHOL AS VANOL MONOMER	
2.1 Introduction.....	20
2.2 Synthesis of 16a by dehydrogenation of 3-phenyl-1-tetralone.....	22
2.2.1 Considerations for large-scale synthesis	23
2.2.2 Optimization of the Michael addition to ester 23 on small scales	24
2.2.3 Summary of optimizations of the Michael addition on small scales	34
2.2.4 Scale up of the Michael addition reaction.....	35
2.2.5 Intramolecular Freidel-Crafts reaction to generate tetralone 20	36
2.2.6 Generation of the VANOL monomer 16a via dehydrogenation of 20	38
2.2.7 Modified methods to synthesize 16a by reconstruction of double bond	42
2.2.8 Summary of route involving dehydrogenation of tetralone 20	43
2.3 Synthesis of 16a through the Reformatsky-cycloacylation pathway	45
2.3.1 Retrosynthetic strategy for the Reformatsky-cycloacylation pathway	45
2.3.2 Optimizations of the Reformatsky reaction	46
2.3.3 Development and optimization of the cycloacylation reaction of 27	48
2.3.4 Summary	52

2.4 Concluding remarks on the linear (<i>de novo</i>) approaches to 16a	53
2.5 Synthesis of 16a through carbocation rearrangement (Part I)	53
2.5.1 Introduction to carbocation rearrangements	54
2.5.2 Synthesis of 16a by dienone-phenol rearrangement-retrosynthetic analysis	56
2.5.3 Introduction to dienone-phenol rearrangement	57
2.5.4 Synthesis of <i>p</i> -quinols: an overview	58
2.5.5 Synthesis of 37 via nucleophilic 1, 2-addition to 33	60
2.5.6 Summary of dienone-phenol rearrangement	63
2.6 Synthesis of 16a through carbocation rearrangement (Part II)	64
2.6.1 Preparation and rearrangement of 4-phenyl-1-naphthol: the ideas	64
2.6.2 Synthesis of 16a by condensation of 42 with benzene	66
2.6.3 Optimization of the chlorination of 1-naphthol	69
2.6.4 Preparation of 4-chloro-1-naphthol 42 on large scale	77
2.6.5 Summary for chlorination of 1-naphthol	77
2.6.6 Preparation of the VANOL monomer 16a on large scale	78
2.6.7 Mechanistic considerations and extension of the condensation reaction ...	80
2.6.8 Limitations and future work	88
2.6.9 Summary	91
2.7 Thermal rearrangement of 3,4-diphenylcyclobutenone to prepare naphthol 16a	92
2.7.1 Introduction of ketenes	93
2.7.2 Introduction to the [2+2] cycloaddition reaction of ketenes	95
2.7.3 Optimization of the CAEC cascade reaction to produce 16a	96
2.7.4 New conditions and future work	101
2.7.5 Summary	102
2.8 Route comparisons	103
2.9 Concluding remarks	104

CHAPTER THREE

SYNTHESIS OF 2-PHENYL-4-PHENANTHROL AS VAPOL MONOMER

3.1 Introduction	106
3.2 Synthesis of 16b via the benzannulation of a carbene complex	110
3.2.1 Carbene complexes and their benzannulation reaction with alkynes	111
3.2.2 Preparation of chromium-based carbene complexes: an overview	112
3.2.3 Preparation of chromium-based alkoxyl carbene complexes: optimization	114
3.2.4 Benzannulation reaction of carbene complexes 14b with phenylacetylene 63a	119
3.2.5 Reductive deprotection of 4-acetoxyl group of 15b	121
3.2.6 Summary	124
3.3 Synthesis of VAPOL monomer 16b via a thermal CAEC cascade reaction	124

3.3.1 Background.....	125
3.3.2 Solvent effects on the thermal CAEC cascade reaction	125
3.3.3 Optimization of the thermal CAEC cascade reaction in mineral oil	127
3.4 The CAEC cascade approach with <i>in situ</i> trapping of the phenol moiety.....	129
3.4.1 Protecting phenols: an overview	129
3.4.2 Thermal CAEC cascade reaction utilizing acid chlorides as trapping agents	130
3.4.3 Thermal CAEC cascade reaction using anhydrides to trap 16b <i>in situ</i>	133
3.4.4 Summary of the role of trapping agents in the CAEC cascade reaction ..	136
3.5 Optimization of the CAEC reaction using 93 as trapping agent	137
3.5.1 Efforts to minimize the formation of the byproduct 92b	138
3.5.2 Investigation of the effects of the chlorinating agent.....	139
3.5.3 Summary of optimizations of the CAEC cascade reaction.....	141
3.6 Preparation of phenol 16b on large scale <i>via</i> the CAEC cascade strategy.....	141
3.6.1 Exploration of workup methods on large scale	141
3.6.2 Isolation of 16b by filtration and crystallization on large scale	144
3.6.3 Summary of large-scale synthesis.....	144
3.7 Summary: the CAEC cascade reaction for the preparation of 16b	145
3.8 Future work.....	146
3.9 Conclusions	148

CHAPTER FOUR

SYNTHESIS OF VANOL AND VAPOL BY OXIDATIVE COUPLING

4.1 Introduction.....	150
4.1.1 Oxidative phenolic coupling reaction	150
4.1.2 Oxidative coupling reaction for naphthol-containing substrates	151
4.1.3 VANOL (VAPOL) synthesis <i>via</i> oxidative coupling reaction: early work...	152
4.1.4 Main purposes	154
4.2 Dimerization of the VANOL monomer 16a using the first generation method (under neat conditions).....	155
4.2.1 Preliminary studies on small scale	155
4.2.2 Condition optimizations on large scale	157
4.2.3 Summary	159
4.3 Dimerization of 16a to prepare VANOL using mineral oil as solvent: small scale	160
4.3.1 Introduction	161
4.3.2 Temperature effects on the dimerization reaction of 16a	163
4.3.3 Concentration effects on the phenol coupling reaction	165
4.3.4 Summary of small scale reaction	165

4.4 Preparation of VANOL: large scale	166
4.5 Preparation of VAPOL with mineral oil as solvent	167
4.5.1 Preparation of VAPOL on small scale: conditions optimization.....	167
4.5.2 Large-scale preparation of VAPOL.....	168
4.6 Scope and limitations of the coupling reaction using mineral oil as solvent	169
4.6.1 Electronic effects	170
4.6.2 Steric effects	171
4.7 Future perspective	173
4.8 Conclusive remarks	174

CHAPTER FIVE

UNRAVELING THE RESOLUTION OF THE VANOL AND VAPOL LIGANDS

5.1. Introduction.....	176
5.2 Preparation of VANOL– and VAPOL–phosphoric acid	177
5.3 Resolution of VANOL–phosphoric acid 104 : 1 st generation method	180
5.3.1 Introduction	180
5.3.2 Investigations of crystallization solvents for the resolution of 104	181
5.3.3 Strategies for the purification of the diastereomerically impure salts	183
5.4 Resolution of 104 by using 1,2-dichloroethane (DCE).....	185
5.5 Resolution of VANOL–phosphoric acid: 2 nd generation method	186
5.5.1 Introduction	187
5.5.2 Initial optimizations of the resolution using DCE on small scale	188
5.5.3 Effects of the purity of brucine on the resolution of 104	190
5.6 Summary of the optimization of the resolution of phosphoric acid 104	191
5.7 Large scale resolution of VANOL–phosphoric acid 104	192
5.8 Resolution of VAPOL–phosphoric acid	194
5.8.1 Introduction	194
5.8.2 Large-scale resolution of VAPOL phosphoric acid 105	195
5.8.3 Summary	197
5.9 Liberation of the optically enriched VANOL and VAPOL from the salts	197
5.9.1 Reductive cleavage of optically pure salts of VANOL and VAPOL	199
5.9.2 Methods for the purification of non-racemic enantiomeric mixtures	200
5.10 Concluding remarks	202

CHAPTER SIX

STRUCTUALLY MODIFIED VANOL AND VAPOL: DESIGN AND SYNTHESIS

6.1 Introduction.....	205
6.1.1 Reasons for synthesis of derivatives VANOL and VAPOL	206
6.1.2 Methods to derivatize the VANOL and VAPOL ligands	207
6.2 Approaches to the preparation of immobilized VANOL and VAPOL ligands.....	208

6.2.1 Introduction	208
6.2.2 Preparation of immobilized VANOL <i>via</i> oxidative cross-coupling reaction.....	210
6.2.3 Preparation of 16c with benzannulation reaction.....	215
6.2.4 A modular approach to the synthesis of immobilized VANOL ligands.....	218
6.2.5 Summary	220
6.3 <i>De novo</i> synthesis of the VANOL derivatives.....	221
6.3.1 Introduction	221
6.3.2 Synthesis of the VANOL derivatives using the CAEC cascade reaction..	223
6.3.3 Proposed synthesis of VANOL derivatives by cross coupling reaction	226
6.3.4 Attempted preparation of H8-VANOL <i>via</i> condensation reaction	227
6.3.5 Summary of de novo method to derivatize VANOL monomers.....	228
6.4 Modular synthesis of the VANOL derivatives	229
6.4.1 Introduction	229
6.4.2 Attempted synthesis of 8,8'-disubstituted VANOL by direct lithiation reaction.....	231
6.4.3 C_1 - and C_2 -symmetric ligands: possible applications of 8-substituted VANOL	236
6.4.4 The 8,8'-disubstituted VANOL ligands: future perspective.....	238
6.4.5 Proposed modular synthesis of H8-VANOL (H4-VAPOL) <i>via</i> reduction...	240
6.4.6 Summary of the modular preparation of VANOL derivatives	242
6.5 Concluding remarks	243
CHAPTER SEVEN: EXPERIMENTAL SECTION	245
REFERENCES.....	341

LIST OF TABLES

Table 2.1 Optimization of the amount of solvent in the Michael addition	27
Table 2.2 Optimization of the reagent stoichiometry of the Michael addition	29
Table 2.3 Optimization of the amount of TMEDA and THF in the Michael addition	31
Table 2.4 Optimization of the Grignard reagent stoichiometry in the Michael addition ...	33
Table 2.5 The Michael reaction using 20 grams of methyl cinnamate (23)	33
Table 2.6 Comparison of different conditions for the Michael reaction	35
Table 2.7 Large-scale preparation of 21 via the Michael reaction	35
Table 2.8 Cycloacylations of 21 on different scales	37
Table 2.9 Solvent effects on the dehydrogenation of 20	39
Table 2.10 The dehydrogenation of 20 in mesitylene	41
Table 2.11 Optimization of the Reformatsky reaction of 29 and 30	47
Table 2.12 The acid facilitated cycloacylation reaction of 27	49
Table 2.13 The Lewis acid facilitated cycloacylation reaction of the acid chloride from 27	51
Table 2.14 Synthesis of 32 by nucleophilic addition to 1,4-naphthoquinone	61
Table 2.15 Optimization of the reaction of 42 with benzene	67
Table 2.16 Solvent effects on the syntheses of 42 by chlorination of 43	72
Table 2.17 The effect of the rate of addition of SO ₂ Cl ₂ on the chlorination of 43 in CH ₂ Cl ₂	73
Table 2.18 The effects of the rate of addition of SO ₂ Cl ₂ on the chlorination of 43 in DCE	76
Table 2.19 Preparation of 4-chloro-1-naphthol 42 on large scale in DCE	77
Table 2.20 Synthesis of 16a by condensation of 42 with benzene	78
Table 2.21 Conversion of 40 to the VANOL monomer 16a	81
Table 2.22 The condensation reaction of the mixture of 42 and 44 with benzene	85

Table 2.23 Condensation reaction of benzene with different starting materials.....	87
Table 2.24 Condensation of the crude product of chlorination reaction of 43	88
Table 2.25 The thermal CAEC reaction to prepare 16a	97
Table 2.26 The CAEC reaction of 18a and 63a in the presence of triethylamine	99
Table 2.27 Attempts at the CAEC cascade reaction using Hunig's base	101
Table 3.1 Preparation of carbene complex 14b	115
Table 3.2 Preparation of carbene complex 14b in heptane-THF at 0 °C.....	118
Table 3.3 Benzannulation reaction of 14b with 63a in THF.....	120
Table 3.4 Generation of 16b by reacting 15b with <i>n</i> -PrSH and AlCl ₃	123
Table 3.5 Preparation of 16b from 17b and 63a with or without solvent	126
Table 3.6 Preparation of 16b from 17b and 63a with or with different solvents.....	128
Table 3.7 Preparation of 16b using acid chlorides as trapping agents	131
Table 3.8 Preparation of 16b using anhydrides as trapping agents	134
Table 3.9 Optimization of the reaction with isobutyric anhydride as trapping agents....	137
Table 3.10 Variation of the conditions to minimize the formation of 92b	139
Table 3.11 Preparation of 16b using oxalyl chloride to generate 18b	140
Table 3.12 Large-scale preparation of phenol 16b from acid 17b	142
Table 3.13 Large-scale preparation of 16b using a combination of filtration and filtration to isolate the product.....	144
Table 4.1 Oxidative coupling of monomer 16a to prepare VANOL 9a on 100 g-scale..	158
Table 4.2 Concentration effects of oxidative coupling of 16a in mineral oil	165
Table 4.3 Preparation of VANOL 9a via oxidative coupling reaction in mineral oil	166
Table 4.4 Temperature effects on the oxidative coupling of 16b in mineral oil	168
Table 4.5 Large-scale preparation of VAPOL in the presence of mineral oil	169
Table 4.6 Preparation of VANOL derivatives via the phenol coupling reaction.....	170
Table 5.1 Preparation of 104 (from VANOL) and 105 (from VAPOL) via the reported procedure.....	178

Table 5.2 New procedures to prepare 104 (from VANOL) and 105 (from VAPOL)	179
Table 5.3 Solubility tests of the diastereomeric salts formed by 104 and brucine.....	182
Table 5.4 Resolution of 104 in DCE by slowly adding brucine solution: small scale.....	188
Table 5.5 Resolution of acid 104 using technical grade brucine on large scale	193
Table 5.6 Large-scale resolution of 105 in EtOH and acetone/ 2-PrOH	196
Table 5.7 Reductive liberation of optically enriched VANOL from the salts of 104	199
Table 5.8 Reductive liberation of optically enriched VAPOL from the salts of 105	200
Table 6.1 Attempted preparation of VANOL monomer derivatives from 42	211
Table 6.2 Attempted preparation of 16c from 59 with expanded conditions	214
Table 6.3 Synthesis of 115 by Sonogashira reaction	216
Table 6.4 Preparation of electronically modified VANOL monomers.....	225
Table 6.5 Directed mono <i>peri</i> -lithiation reaction of 131	235

LIST OF SCHEMES

Scheme 1.1 Asymmetric alkylation of cyclohexanone	3
Scheme 1.2 Asymmetric AZ reaction promoted by chiral Lewis acids	7
Scheme 1.3 Pd-catalyzed asymmetric allylation reactions with ligands 8a-f	8
Scheme 1.4 Aziridination reactions using VANOL/VAPOL as ligands.....	10
Scheme 1.5 Examples of asymmetric reactions using VANOL/VAPOL ligands	11
Scheme 1.6 Reactions catalyzed by chiral VAPOL/VANOL-phosphoric acid.....	13
Scheme 1.7 Preparation of VANOL or VAPOL ligands	15
Scheme 2.1 General strategies for synthesis of the VANOL and VAPOL ligands	19
Scheme 2.2 Other linear syntheses of the VANOL monomer 16a	21
Scheme 2.3 Industrial method for preparation of 1-naphthol	22
Scheme 2.4 Ferreira's procedure ³⁰ for Michael addition	25
Scheme 2.5 Tetralone versus hydrindone products in cycloacylations of 21	36
Scheme 2.6 Direct cycloacylation of ester 22 to generate tetralone 20	38
Scheme 2.7 Synthesis of enoates by dehydrosilylation of silyl enol ether.....	42
Scheme 2.8 Revised synthetic plan using Saegusa's dehydrosilylation reaction ⁶⁴	43
Scheme 2.9 Dehydrosilylation of 25 (See Section 7.2.1.4 of Chapter Seven).....	43
Scheme 2.10 Overview of the synthesis of 16a from 23	44
Scheme 2.11 The structure of the proposed precursor (27) to 16a	45
Scheme 2.12 The retrosynthetic analysis to 16a via Reformatsky reaction route.....	46
Scheme 2.13 The results of the cycloacylation reaction by Pakrashi	51
Scheme 2.14 Carbocation and rearrangement of carbocations	55
Scheme 2.15 Examples of selective carbocationic rearrangements	55
Scheme 2.16 Retrosynthetic analysis of 16a by dienone-phenol rearrangement.....	56
Scheme 2.17 General methodologies to prepare <i>p</i> -quinols	58

Scheme 2.18 Synthesis of 32 <i>via</i> oxidation of 1,4-diphenylnaphthalene (34).....	58
Scheme 2.19 Reductive single electron-transfer (SET) of <i>p</i> -quinone.....	59
Scheme 2.20 Synthesis of quinols <i>via</i> quinone alkylation using R ₂ Cd reagents.....	60
Scheme 2.21 Proposed synthesis of 36 <i>via</i> alkylation of quinone 33	60
Scheme 2.22 Nucleophilic alkylation to 1,4-naphthoquinone 33 by R ₂ Cd	62
Scheme 2.23 Nucleophilic alkylation of PhLi to 1,4-naphthoquinone derivative 38	63
Scheme 2.24 Proposed dienone-phenol type rearrangement of “perturbed” 40	64
Scheme 2.25 Tautomerization of 1-naphthol with or without AlBr ₃	65
Scheme 2.26 Synthesis of 40 from 42 in the presence of AlCl ₃	66
Scheme 2.27 Synthetic plans of the VANOL monomer 16a from 42	66
Scheme 2.28 Preparation of 42 by chlorination of 1-naphthol 43	69
Scheme 2.29 Preparation of 42 , 44 and 45 by chlorination reactions	71
Scheme 2.30 Proposed mechanism of the condensation of 42 with benzene.....	82
Scheme 2.31 A possible mechanism for the formation of 16a from complex 50	82
Scheme 2.32 A possible mechanism for the formation of 46 from intermediate 50	83
Scheme 2.33 A proposed mechanism for the condensation of 44 with benzene	84
Scheme 2.34 Synthesis of 59 and its application in the synthesis of 16a	89
Scheme 2.35 Synthesis of 60 using toluene as alkylation agent.....	90
Scheme 2.36 Synthesis of 16a using HUSY zeolite.....	91
Scheme 2.37 Attempted preparation of the VANOL monomer derivatives.....	92
Scheme 2.38 Mechanism for the rearrangement of cyclobutenone 61a to naphthol 16a	93
Scheme 2.39 Possible products from the reaction of 18a and Et ₃ N	100
Scheme 2.40 Synthesis of 16a and its derivatives in isobutyric anhydride.....	102
Scheme 2.41 Route comparison of the syntheses of VANOL monomer 16a	104
Scheme 3.1 Proposed pathways to synthesize 16b	107
Scheme 3.2 Preparation of monomer 16b <i>via</i> the Snieckus phenol synthesis	107

Scheme 3.3 Synthesis of VAPOL monomer 16b <i>via</i> the benzannulation reaction	109
Scheme 3.4 Methods for the alkylation of the lithium acylmetalate 74	113
Scheme 3.5 The reported protocols to prepare 14b	114
Scheme 3.6 <i>In situ</i> formation of 14e and its conversion to 14b <i>via</i> methylation	116
Scheme 3.7 Possible competing reactions of <i>n</i> -BuLi with Cr(CO) ₆ and 13b	117
Scheme 3.8 Lithium-halogen exchange reaction of 79 in heptane at 0 °C	117
Scheme 3.9 Mechanism of the benzannulation reaction of 14b with 63a	120
Scheme 3.10 Mechanism of reductive deprotection of 15b to produce 16b	121
Scheme 3.11 Possible side reaction of 16b under given conditions	122
Scheme 3.12 Overview of the synthesis of VAPOL monomer 16b from 13b	124
Scheme 3.13 Mechanism of the CAEC cascade reaction of ketene 85 with 63a	127
Scheme 3.14 <i>In situ</i> protection protocol for phenol 16b	130
Scheme 3.15 Formation of 92b <i>via</i> double insertion of phenylacetylene 63a to 85	133
Scheme 3.16 Product distribution using isobutyric anhydride as trapping agent	136
Scheme 3.17 Synthesis of 95 for preparation of Sildenafil citrate (Viagra).....	146
Scheme 3.18 Preparation of other phenanthrene derivatives using [2+2] protocol	147
Scheme 3.19 Synthesis of 98 as intermediate to prepare furaquinocins.....	147
Scheme 4.1 Preparation of VANOL and VAPOL from their monomeric precursors	149
Scheme 4.2 Biosynthetic pathways for morphine alkaloid <i>via</i> oxidative coupling	151
Scheme 4.3 Mechanism of oxidative coupling reaction of phenol	151
Scheme 4.4 Synthesis of 102 <i>via</i> oxidative coupling reaction of monomeric 101	152
Scheme 4.5 Preparation of VANOL and VAPOL <i>via</i> oxidative coupling reaction	153
Scheme 4.6 Synthesis of VANOL using controlled airflow under neat conditions	156
Scheme 4.7 Synthesis of VANOL from 16a in the presence of mineral oil	162
Scheme 4.8 Steric effects of the oxidative coupling reaction	172
Scheme 4.9 Efficient oxidative dimerization of 103 to 104	174
Scheme 4.10 Chiral vanadium(V) catalysts for the oxidative coupling of 105	174

Scheme 5.1 The published procedure for the resolution of 9a and 10a	177
Scheme 5.2 Published procedure to liberate 9a / 10a from the resolved salts	198
Scheme 6.1 Aziridination reactions using VANOL/VAPOL as ligands.....	205
Scheme 6.2 Pathways to prepare solid-supported VANOL ligands.....	209
Scheme 6.3 Attempted preparation of VANOL derivatives from naphthol 59	212
Scheme 6.4 Synthesis of 60 using toluene as alkylation agent.....	213
Scheme 6.5 Proposed pathway to prepare polymer-bound VANOL 110 from 60	214
Scheme 6.6 Preparation of 16c by Wulff-Dötz benzannulation reaction	216
Scheme 6.7 Oxidative cross-coupling reaction of 16a with 16c to prepare 111	217
Scheme 6.8 Preparation of NOBIN <i>via</i> oxidative cross-coupling reaction	218
Scheme 6.9 Claisen rearrangement of allyl phenyl ether.....	219
Scheme 6.10 Attempted synthesis of mono-allylated VANOL (114) using K ₂ CO ₃	220
Scheme 6.11 Retrosynthetic analysis of VANOL derivatives 120	224
Scheme 6.12 Proposed synthesis of modified VANOL by cross coupling reactions.....	226
Scheme 6.13 Attempted synthesis of 16w by condensing 123 with benzene	228
Scheme 6.14 Possible ways to prepare (<i>S</i>)- 9 by condensing 125 with benzene.....	229
Scheme 6.15 Preparation of 4,4'-dinitroVANOL (<i>S</i>)- 128 by Dr Gang Hu	230
Scheme 6.16 Directed <i>ortho</i> -lithiation reaction of heteroatom substituted arenes.....	232
Scheme 6.17 Attempted directed lithiation-substitution of unprotected VANOL	233
Scheme 6.18 O -methylation of VANOL by CH ₃ I under different conditions.....	234
Scheme 6.19 Novel VANOL-derived monodentate ligands with P stereogenic center .	237
Scheme 6.20 Applications of monodentate ligands with P stereogenic centers	238
Scheme 6.21 Regiospecific arylation of 43 mediated by palladium catalysis	239
Scheme 6.22 Proposed synthesis of (<i>S</i>)- 129 <i>via</i> Miura's protocol	239
Scheme 6.23 Proposed methods to access hydrogenated VANOL and VAPOL.....	241

LIST OF FIGURES

Figure 1.1 Examples of privileged ligands	4
Figure 1.2 BINOL complexes.....	5
Figure 1.3 VANOL, VAPOL and BINOL ligands.....	10
Figure 2.1 Temperature effects on chlorination of 43 in different solvents	75
Figure 2.2 Overview of ketenes: types and methods to synthesize.....	94
Figure 3.1 Fischer carbene complexes: discovery and structural features	111
Figure 3.2 Effects of anhydrides for CAEC cascade reaction to prepare 16b	135
Figure 4.1 The yield of 9a on different scales of the coupling reaction.....	157
Figure 4.2 The temperature effect on the coupling reaction of 16a in mineral oil	164
Figure 5.1 Resolution of 104 on 112.8 g scale using EtOH.....	181
Figure 5.2 Resolution of 104 in CH ₂ Cl ₂ / hexanes.....	183
Figure 5.3 Resolution of 104 in 1,2-dichloroethane (DCE).....	186
Figure 5.4 Effects of the purity of brucine on resolution of 104	191
Figure 6.1 Crystal structure of the complex generated from the 118 and imine 5b	222
Figure 6.2 Study of π - π stacking by using modified VANOL ligand (S)- 9	223
Figure 6.3 H8-VANOL 9w and the retrosynthetic analysis	227
Figure 6.4 BINOL, H8-BINOL, H8-VANOL and H4-VAPOL ligands	240
Figure 6.5 Pathways to produce skeleton-modified VANOL ligands	244

ABBREVIATIONS

VANOL : vaulted 3,3'-diphenyl-[2,2'-binaphthalene]-1,1'-diol

VAPOL : vaulted 2,2'-diphenyl-[3,3'-biphenanthrene]-4,4'-diol

BINOL : 1,1'-bi-2-naphthol

AZ : asymmetric aziridination

Boc : *tert*-butoxycarbonyl

TMS : trimethylsilyl

dppe : 1,2-bis(diphenylphosphino)ethane

CAEC cascade reaction : [2+2] cycloaddition/ electrocyclization cascade reaction

DCE : 1,2-dichloroethane

Bh : benzhydryl

MEDAM : bis(3,5-di-methyl-4-methoxyphenyl)methyl

BUDAM : bis(3,5-di-*tert*-butyl-4-methoxyphenyl)methyl

TMEDA : tetramethylethylenediamine

PPA : polyphosphoric acid

TLC : thin layer chromatography

DMSO : dimethyl sulfoxide

NBS : *N*-bromosuccinimide

THF : tetrahydrofuran

Mp : melting point

Bp : boiling point

DCM : dichloromethane

Red-Al : sodium bis(2-methoxyethoxy)aluminumhydride

DMF : *N,N*-Dimethylformamide

CHAPTER ONE

INTRODUCTION

The biological activity of a majority of natural products and pharmaceutical drugs is strongly associated with their absolute molecular configuration; thereby the demand to make chiral compounds efficiently in optically pure forms is growing intensively particularly for the pharmaceutical industry. However, while nature takes advantage of elaborate and efficient devices to synthesize optically enriched molecules, organic chemists are still in the "stone age" with respect to the pursuit of optical efficacy. However, for natural processes this high efficacy is normally gained at the cost of a limited substrate scope. In fact, enzymes are typically substrate-specific, whereas synthetic catalysts usually possess a broader substrate scope. Even so, there has not been delivered a general synthetic catalyst, one that is good for every reaction and every substrate. Diversity in asymmetric catalysts is important and necessary: a flexible collection of catalysts enhances the chances to find systems with optimum performance (reactivity and selectivity) for different substrates. Consequently, new and effective catalysts for asymmetric reactions are continuously generating tremendous academic and industrial interest.

1.1 Ligands for asymmetric reactions: an overview

Most asymmetric catalysts that have been developed are metal complexes with chiral ligands. While metals possess a range of properties in terms of their reactivities, the chiral ligands modify the reactivity and selectivity of the metal center in such a way that only one of the enantiomeric products is formed

preferentially. Additionally, the Lewis acidity of the metal center, one of the fundamental properties for many transformations, can also be influenced to a great extent by the ligands. Based on this concept, such ligands function as templates that regulate reactions occurring in the coordination sphere of the metal center; therefore a delicate balance between the steric and electronic factors of a catalysis system determines the efficiency of a given process.

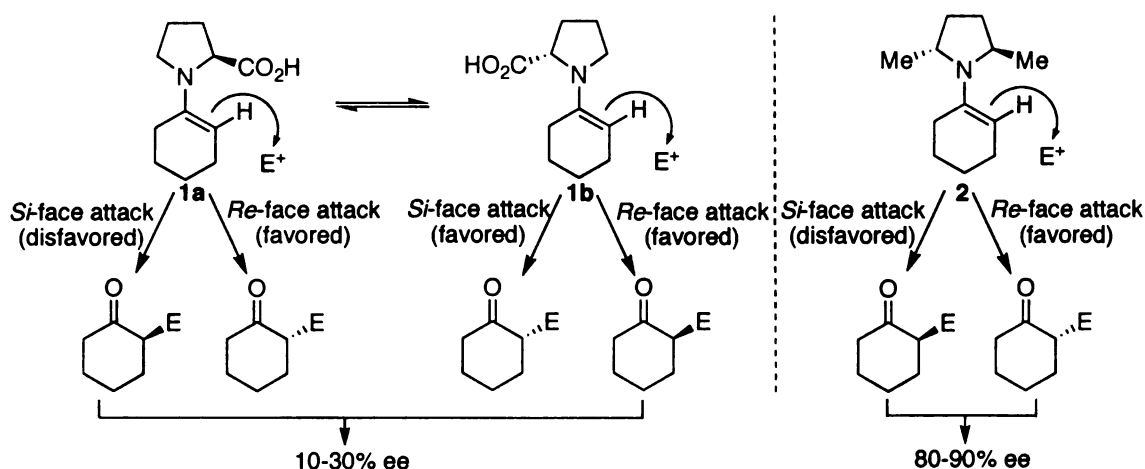
Despite impressive progress in the field of catalytic asymmetric synthesis,¹ design of high performance ligand platforms for a particular transformation remains essential to meet the endless needs. To develop an effective ligand, consideration of its steric, electronic and conformational properties is necessary. It is generally believed² that conformationally rigid metal-ligand complexes give higher chiral induction compared to those with conformational ambiguity (also see section 1.2). Chemically, catalysts require certain stability to survive various reaction conditions while simple structural modifications of modular ligands can be achieved easily to improve selectivities in the sense of not only optimized steric interactions, but also finely tuned electronic effects. For practical reasons, it is also desirable to prepare ligands from readily available starting materials.

Theoretically, a chiral ligand doesn't require having symmetric elements.² However, the presence of such elements in a chiral ligand can reduce the number of possible isomeric metal complexes, as well as the number of different reaction pathways when compared with a nonsymmetrical ligand.³ This consequence can have a beneficial effect not only on the enantioselectivity of the reaction because the competing less-selective pathways can be eliminated, but

also on the mechanistic studies because fewer reaction intermediates are taken into account, and thus it simplifies analysis of the ligand–substrate interactions that may be responsible for the optimal asymmetric induction.

For example, in an effort to alkylate cyclohexanone enamines enantioselectively using proline esters as chiral auxiliaries, Yamada⁴ observed low *ee*'s (10-30% *ee*) in the alkylation products. However, when a *C*₂-symmetrical 2,5-dimethylpyrrolidine was applied in the same reaction, Whitesell⁵ achieved much higher enantioselectivities (80-90% *ee*, Scheme 1.1).

Scheme 1.1 Asymmetric alkylation of cyclohexanone^{4,5}

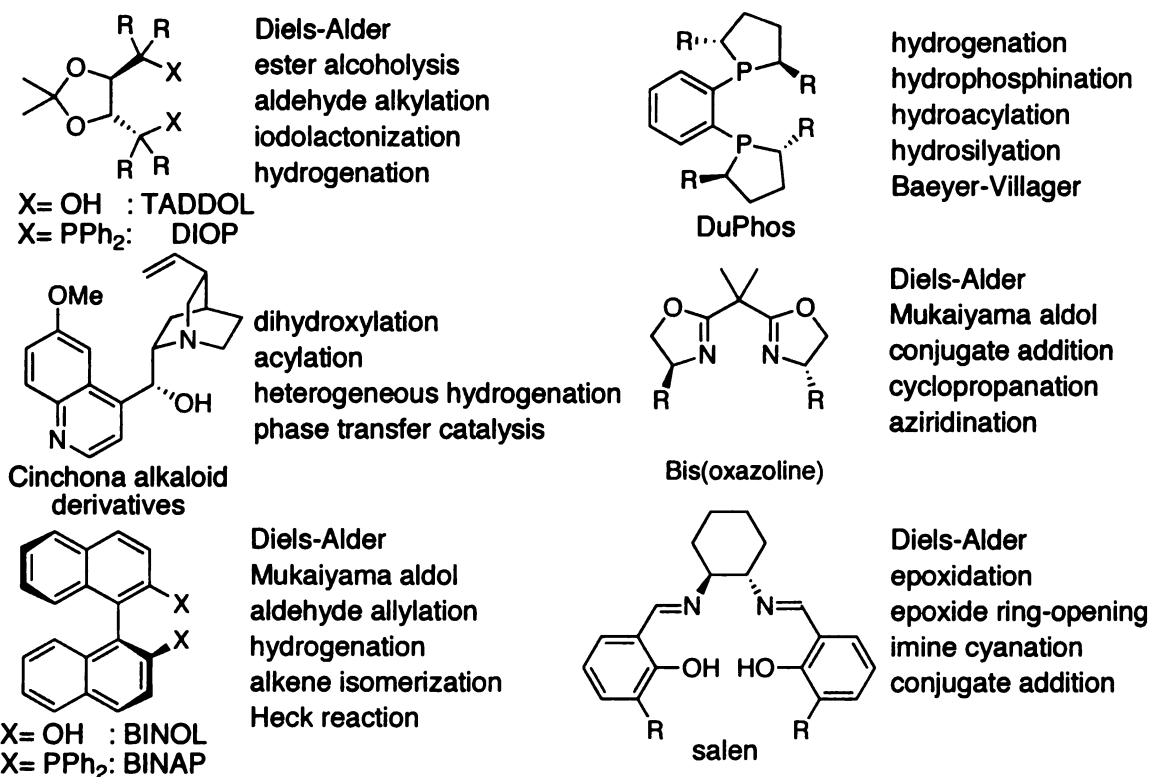


Clearly, there are two possible distinct conformations (**1a** and **1b**) for enamine **1** formed by cyclohexanone and (*S*)-methyl proline, which results in four possible diastereomeric transition states in the alkylation reaction and only one of them is disfavored due to steric hindrance. The three favored transition states then lead to the formation of the final product in both *R* and *S* forms; accordingly, low enantioselectivities are observed. On the other hand, when 2,5-dimethylpyrrolidine is adopted, only two diastereomeric transition states are possible and one of them is disfavored. Consequently, the only favored transition

state gives the alkylated product in high enantioselectivity (Scheme 1.1).

Armed with this idea, Kagan and co-workers⁶ developed and applied the chiral ligand DIOP possessing C_2 symmetry, one of the simplest symmetry elements that can be incorporated into chiral ligands, for asymmetric hydrogenation reactions. The design principles that led Kagan to DIOP had a marked impact on the course of research in asymmetric catalysis. Many ligands bearing C_2 axes of symmetry were subsequently prepared and tested, among which only a few classes were found to have a general scope. These ligands have come to be called the “privileged” ligands,⁷ and the important members are depicted in Figure 1.1. To date, most of the successes in asymmetric synthesis have been obtained with catalysts made from these ligands (Figure 1.1).

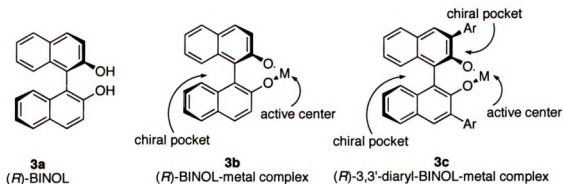
Figure 1.1 Examples of privileged ligands⁷



1.2 BINOL: A versatile chiral ligand

First synthesized by Pummerer in 1926,⁸ the enantiopure 1,1'-bi-2-naphthol (BINOL, **3a**, Figure 1.2) has become one of the most widely used ligands in asymmetric synthesis, although its potential as a chiral ligand was not recognized until Noyori used it for the reduction of aromatic ketones and aldehydes in 1979.⁹ Conformationally, BINOL and its derivatives are relatively flexible, allowing them to accommodate a number of metals, and this results in skeletally rigid complexes owing to their bidentate nature (**3b**, Figure 1.2). Benefiting from these characteristics, BINOL and its derivatives have demonstrated excellent chiral inductions, either as ligands or as chiral auxiliaries, in a remarkable number of organic transformations ranging from Diels–Alder cycloadditions to polymerization reactions.^{9b}

Figure 1.2 BINOL complexes



In spite of BINOL's efficacy in asymmetric synthesis, a limitation of the BINOL design is that the chiral pocket formed by the two naphthyl rings is remote from the chelation site. Therefore, upon coordination with a metal, the active center is isolated from the chiral environment (**3b**, Figure 1.2). Consequently, asymmetric steric shielding of certain coordinated substrates might be compromised. Since

the molecular architecture of BINOL fails to offer a direct communication between the chiral environment (i.e. the binaphthyl system) and the reaction center, the enantioselection often requires additional assistance.¹⁰ One of the ways to gain this assistance is the introduction of substituents at the 3,3'-positions of BINOL.¹⁰ The effects of such 3,3'-substituents can be clearly seen from the Lewis acid-mediated catalytic asymmetric aziridination reaction¹¹ (AZ reaction, Scheme 1.2).¹²

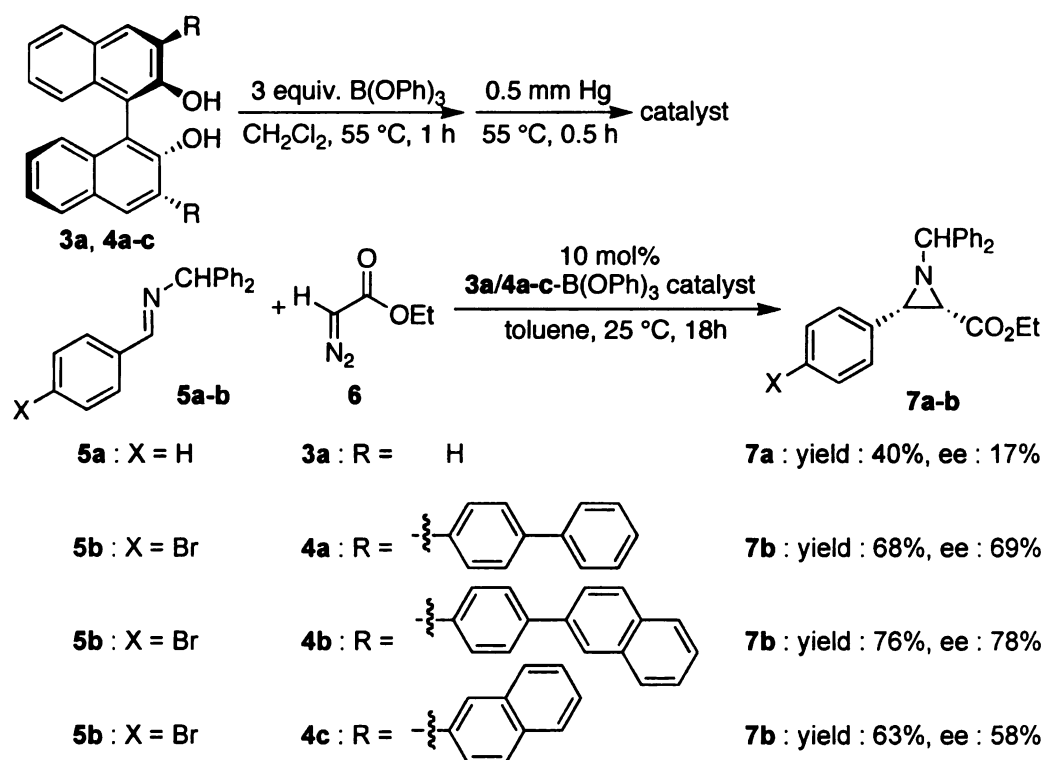
1.2.1 Asymmetric AZ reaction using BINOL and derivatives as ligand

Aziridines have been used as a starting point for the synthesis of a number of drugs^{12c} including L-DOPA^{12b} and the LFA-1 antagonist BIRT-377.¹³ One way to synthesize enantiomerically enriched aziridines is the Lewis acid catalyzed AZ reaction, which generally involves the reaction of a carbenoid with a suitably *N*-substituted imine that is activated by a chiral Lewis acid. A number of ligands have been employed for this AZ reaction with limited success as indicated by the observed low asymmetric inductions.^{11b,c} For example, when the catalyst complex derived from 1 equiv. of BINOL (**3a**) and 3 equiv. of B(OPh)₃ was used, the *cis*-aziridine **7a** could be produced in moderate yields with only 17% ee from imine **5a** (Scheme 1.2).^{12a}

Upon consideration of what changes could be readily made to the parent BINOL ligand to render it more effective, Wipf and Lyon^{12d} sought to apply various 3,3'-diaryl-BINOLs (**4a-c**, Scheme 1.2) as ligands in the AZ reaction via the same protocol as described in Scheme 1.2. Introduction of such 3,3'-substituents is believed to be able to extend the stereochemical environment of

the BINOL ligand and restrict the orientation of the substrates around the active center while still maintaining the C_2 axes. Thus, the reactants can be directed to adopt certain conformations to produce aziridines with improved optical outcome. This claim can be supported by the immediate observation of a jump in the enantiomeric excess value of the product **7b** (58-78% ee vs. 17% ee for **7a**) upon using these bulkier ligands (**4a-c**, Scheme 1.2).

Scheme 1.2 Asymmetric AZ reaction promoted by chiral Lewis acids^{12a,d}



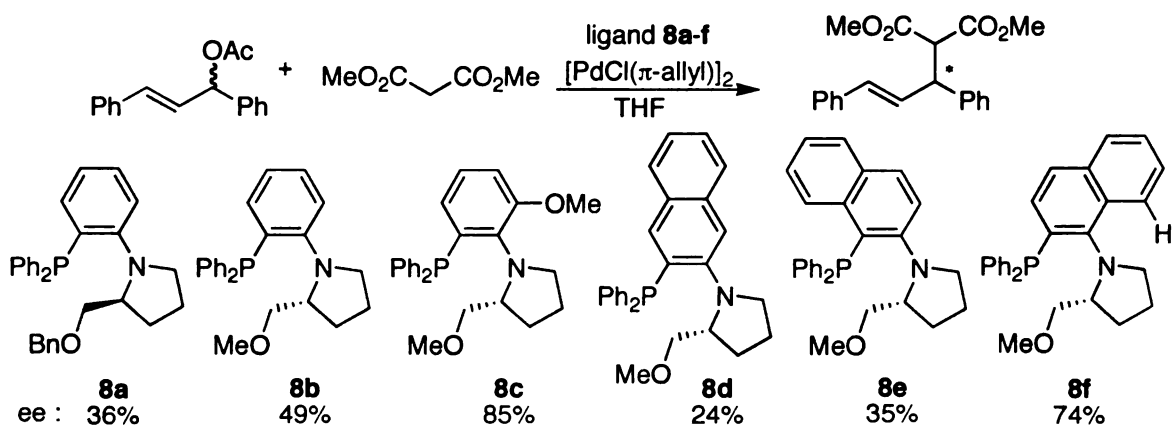
1.2.2 Limitations in the 3,3'-disubstituted BINOL design

Evidently, such extended barriers around the chiral pocket of BINOL are the determining factors in their effectiveness in asymmetric catalytic reactions.¹⁴ In fact, the importance of subtle structural changes in these catalysts is highlighted by the remarkable differences in enantioselectivity, reported by numerous research groups, depending on the size of the 3,3'-substituents in their catalyst

optimization studies.^{10,15} In spite of this, an inherent drawback of such ligand design is the presence of the C-C single bonds between the 3,3'-substituents and the binaphthyl unit, which increases the flexibility of the skeletal backbone. It is usually desirable to avoid such flexibility in chiral ligands since it is commonly believed that good enantioselectivity is necessitated by the spatial fixation of bulky groups of ligands to form the chiral environment around the active center.² In this respect, it is reasonable to believe that the reaction will display good enantioselectivity only if a stable and rigid position of the substituents in the catalyst are maintained.

For example, ligands **8a-f** (Scheme 1.3) have been used for a Pd-catalyzed asymmetric allylation reaction,¹⁶ and each ligand has a chiral centre in the pyrrolidine ring that can rotate around the C-N bond. Among them, only two ligands (**8c** and **8f**) possess substituents that confine the conformational rigidity, and it is exactly the palladium catalysts formed by these two ligands and Pd complexes that lead to a sharp increase in enantioselectivity (85% ee for **8c** and 74% ee for **8f**, respectively; Scheme 1.3).

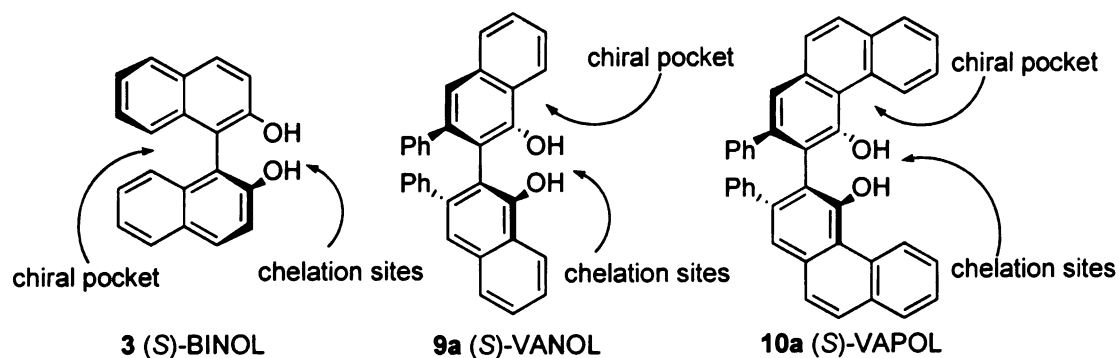
Scheme 1.3 Pd-catalyzed asymmetric allylation reactions with ligands **8a-f**¹⁶



1.3 VANOL and VAPOL: A new high performance ligand platform

To move the chiral pocket closer to the active center while still maintaining the rigidity of the catalyst, the Wulff's group developed the "vaulted biaryl" ligands, VANOL (**9a**, 3,3'-diphenyl-[2,2'-binaphthalene]-1,1'-diol, Figure 1.3) and VAPOL (**10a**, 2,2'-diphenyl-[3,3'-biphenanthrene]-4,4'-diol, Figure 1.3).¹⁷ The goal was to extend the ring system in the direction of the phenolic hydroxyls, forming a stereochemical environment around the active site that is much deeper than BINOL, which would offer a direct interaction of the chiral core of the ligand skeleton with the reactants. Like BINOL, the two-point binding of the two hydroxyl groups in VANOL and VAPOL affords better organization about the metal center. Meanwhile, the C_2 symmetry of these ligands renders such coordination sites homotopic, which introduces less ambiguity in understanding the nature of the catalyst-substrate complexation. Another significant feature of VANOL and VAPOL is that the rotation about the single bond uniting the two naphthol moieties is constrained by the bulk of the adjacent phenyl substituents, which not only increases the rigidity of the skeleton but also prevents these ligands from racemization under the conditions used for catalytic transformations. In addition to their structural steric bulk, these all-aromatic compounds feature relatively high chemical stability and enhanced Lewis acidity. Their aryl walls also provide a highly polarizable surface with the potential of associating in π - π and CH- π interactions with substrates.

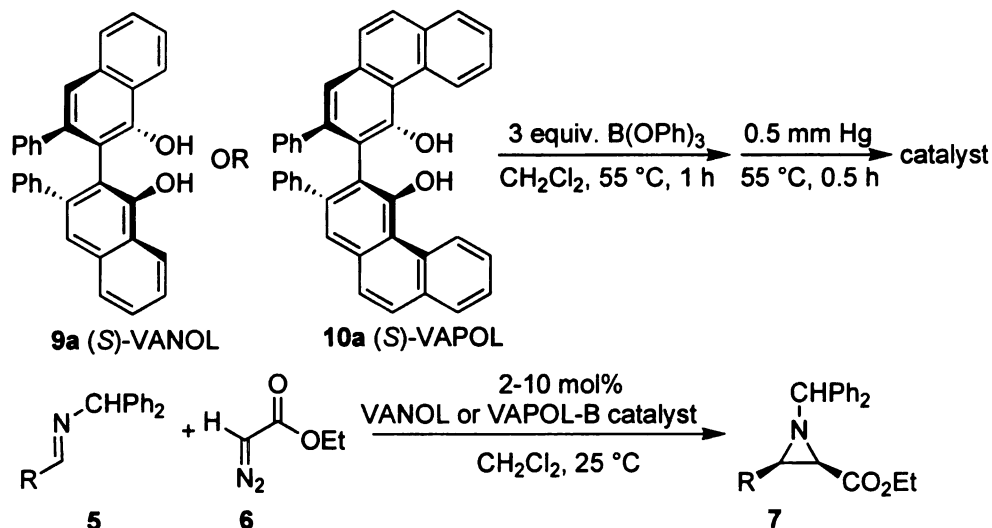
Figure 1.3 BINOL, VANOL and VAPOL ligands



1.4 VAPOL / VANOL ligands in asymmetric catalysis – a brief introduction

The Wulff's group described the Lewis acid-mediated catalytic asymmetric aziridination reaction^{11,12a-b} using the catalyst derived from 1 equiv. of VANOL or VAPOL and 3 equiv. of B(OPh)₃ (Scheme 1.4).

Scheme 1.4 Aziridination reactions using VANOL/VAPOL as ligands¹²

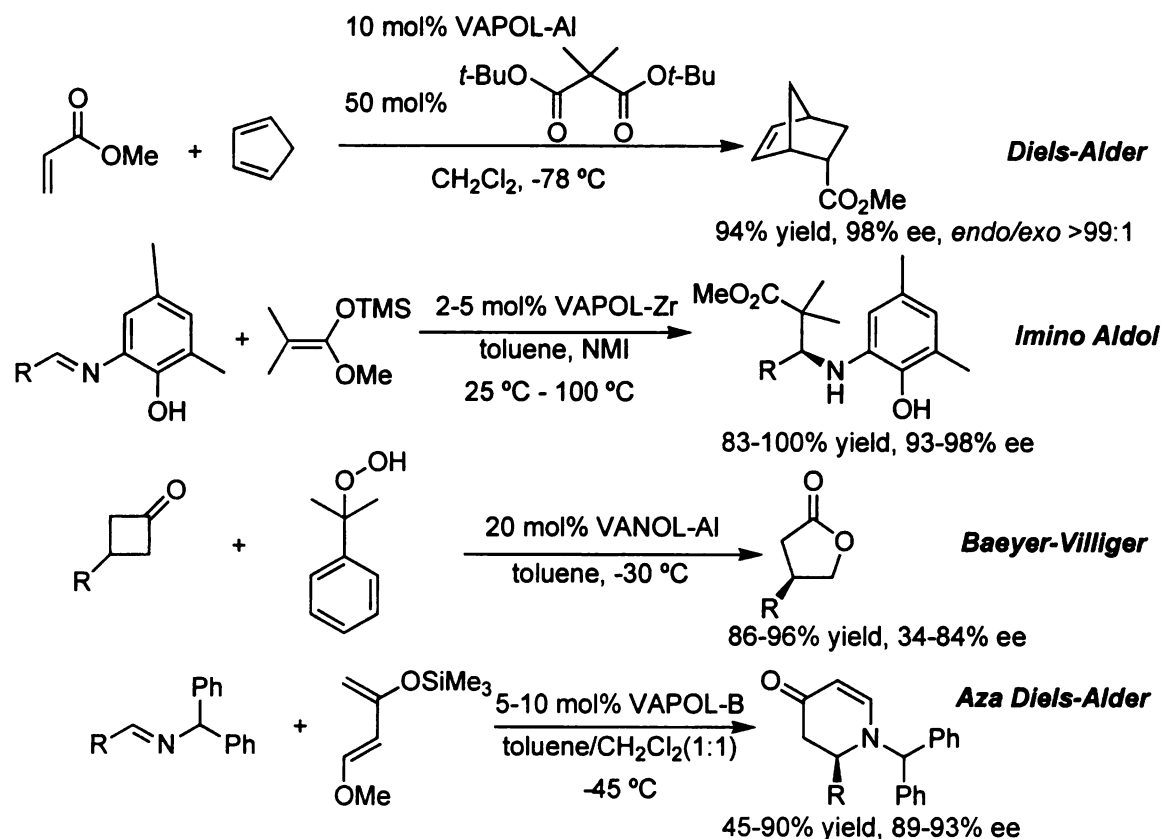


Thus, in the presence of 2 – 10 mol% of this catalyst, *N*-benzhydryl imines (**5**) were successfully reacted with ethyl diazoacetate **6** to produce aziridines **7** with high *cis* diastereoselectivity (> 25:1) and up to 98% ee (Scheme 1.4). In addition to the extraordinary selectivity, it was found that this reaction was general for both aryl and alkyl aldimines. This truly groundbreaking research, together with

the fact that much lower enantioselectivity was obtained from the same reaction using corresponding catalysts prepared from BINOL and its derivatives (**3a**, **4a-c**, Scheme 1.2), clearly highlight the unique features of this class of ligands for asymmetric catalysis.

The aforementioned catalytic asymmetric aziridination protocol represents an attractive route to enantioenriched heterocycles from an abundant and inexpensive feedstock,^{12,18} and the phenomenally high efficiency it exhibits to selectively install two consecutive stereogenic centers quickly triggered an extensive search for more applications of the VAPOL/VANOL ligands (Scheme 1.5).¹⁹

Scheme 1.5 Examples of asymmetric reactions using VANOL/VAPOL ligands¹⁹



Early examples of the applications of VANOL/VAPOL ligands include Diels-Alder^{17a, 19b-d} and imino-aldol reactions by former group members (Scheme 1.5);^{19f} in both cases, the yields and ee's were obtained on a very high level. For the Diels-Alder reaction, VANOL did not work as efficiently as VAPOL, which was in contrast to the Baeyer-Villiger reaction on cyclobutanone derivatives for which VANOL offered a better stereochemical outcome than VAPOL.^{19a} Inspired by the successful applications of the VAPOL/VANOL ligands in the aziridination reaction, Dr Newman, a former group member, employed a similar protocol to activate various *N*-benzhydryl imines for the aza Diels-Alder reaction with the Danishefsky's diene. Good to excellent yields of the Diels-Alder adduct were obtained with excellent enantioselectivities.^{19e}

Early work mainly focused on VAPOL/VANOL-metal complexes as chiral catalysts for organic reactions. Undoubtedly, the most convenient alternative to the metal-based Lewis acids is the proton. Akiyama and Terada pioneered the development of BINOL based²⁰ chiral phosphoric acids (**3d**, Scheme 1.6) which subsequently have been extended by others to a wide range of asymmetric reactions.²¹ These chiral organocatalysts generally exhibit catalytic activity by themselves without aid of any metals, and they have emerged as a novel catalyst family. Being the active center, the phosphoric acid activates substrates electrophilically either by protonation or H-bonding. The seminal studies by various research teams based on **3d** highlight the strong potential of VANOL-**(11)** and VAPOL-phosphoric acid (**12**) for various asymmetric transformations (Scheme 1.6).²² With this insightful idea in mind, Antilla and co-workers have

examined the coordination chemistry of these ligands by the synthesis and characterization of the complexes (dppe)Pt(S-VANOL) and (dppe)Pt(S-VAPOL), which have quite different features from the complexes of VAPOL or VANOL with early transition metals and with main group metals.²³ The crystallographic properties of the uncomplexed VANOL and VAPOL ligands were investigated by Matzger and co-workers.²⁴ With all of the data now available, it is likely that interest in the applications of VAPOL/VANOL will blossom given that concise and cheap pathways to access these ligands from easily available starting materials are now available as a consequence of the work of this thesis.

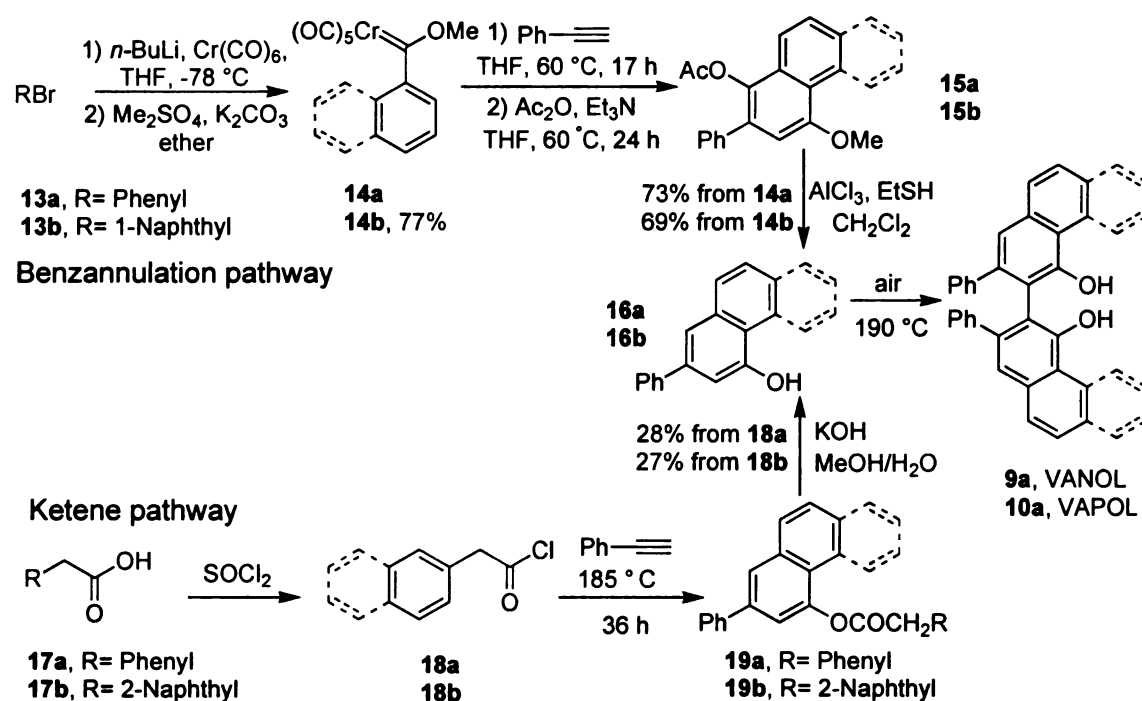
1.5 Preparation of the VANOL/VAPOL ligands: precedent methods

While the launch of VANOL and VAPOL ligands has had a tremendous impact on asymmetric synthesis, gaining fast and inexpensive access to these compounds remains a challenge to synthetic chemists. These unique polyphenolic compounds exhibit an unusual array of structural features, including a biaryl axis that unites two identical aromatic units flanked by a hydroxyl functionality and a phenyl group, with which the hydroxyl group has a *meta*-relationship. The vicinal phenyl groups lead to restricted rotation about the biaryl axis that imparts chirality to the molecule. Naturally, the syntheses of both ligands share a common step in the oxidation coupling of monomeric precursors.

Enticed by the structural distinctions of VANOL and VAPOL and in their unique catalytic activities, the Wulff group developed several different synthetic routes to the VANOL/VAPOL ligands. Organometallic approaches to the monomers received special attention due to the group's long-standing interest in

the chemistry of carbene complexes. Hence, formation of the intermediates **15a** and **15b** (Scheme 1.7) was achieved *via* the benzannulation reaction of aryl carbene complex as **14a** and **14b** with phenylacetylene.^{17b} Subsequently, **15a** and **15b** were converted to the desired monomers **16a** and **16b** upon exposure to EtSH in the presence of AlCl₃. Good yields of both monomers were furnished after three steps in this synthetic route.

Scheme 1.7 Preparation of VANOL or VAPOL ligands



Another approach explored by our group involved formation of the phenol nucleus *via* a thermally induced ring expansion of cyclobutenones that were generated by a [2+2] cycloaddition of an *in situ* produced ketene with an alkyne (Scheme 1.7).^{17b} Reaction of the resultant naphthol with excess ketene then led to the 1-naphthol esters (**19a-b**) as the final products. Upon hydrolysis, these esters **19a-b** were converted to **16a** and **16b** in low yields.

1.6 Main goals of this thesis work

While the abovementioned synthetic methods^{17b} (Scheme 1.7) were adequate for providing small quantities of the racemic VANOL and VAPOL ligands, it became immediately obvious that a scale-up of this chemistry would not provide a viable long-term option for securing large quantities of these ligands for academic/commercial purposes. The discovery preparation using Wulff's benzannulation chemistry was costly since it relies heavily on carbene complexes. The cost of the starting chromium hexacarbonyl ($\text{Cr}(\text{CO})_6$, \$ 5/g)²⁵ may not be an issue on small scale, but it could become prohibitive for large-scale synthesis. The thermal ketene [2+2] cycloaddition method, on the other hand, exhibits notable efficiency owing to the single-step nature from inexpensive starting material; however, it routinely afforded only low yields of products contaminated with tarry materials, which usually required extensive and tedious chromatographic columns for purification. Thus, it does not yet represent a practical tool for the synthesis of VANOL/ VAPOL on large scale.^{17b}

Plans have also been formulated to expand the applications of VANOL/VAPOL by incorporating various substituents bearing different steric and electronic properties into the ligands. Such modified VANOL/VAPOL ligands are crucial to scrutinize the mechanism of Wulff's catalytic asymmetric aziridination.^{18c,f} In this regard, it would be instructive to evaluate the activities of various analogues of these ligands on the aziridination reaction in order to elucidate structural features that contribute to the selectivities, as it was found that subtle alterations in the steric and electronic properties of VANOL/VAPOL

led to dramatic variations of both their chemical and optical outcome.^{18c,f} In addition, the resultant conformationally rigid yet tunable ligands could offer a great advantage for optimizing the enantioselectivity of the aziridination reaction. Thus, development of various pathways to access both VANOL and VAPOL ligands is indispensable to prepare these ligands themselves in the most efficient manner. More importantly, these pathways enhance the chances to find the best method to tolerate a variety of substituents which will allow us to maximize the structural diversity of the VANOL/VAPOL ligands.^{18f} Finally, a part of the research goals was to develop solid supported VANOL and VAPOL ligands

1.7 Conclusion

Given the fact that the unique properties of VANOL and VAPOL in asymmetric catalysis have drawn much attention from the chemical community, and that demand from other research teams and commercial suppliers was constantly increasing, this research program was initiated to devise a modular synthetic strategy that would allow us to construct not only both the parent ligands themselves, but also a number of derivatives not readily accessible by their simple chemical modifications. For practical reasons, such a strategy must be “scalable”— it must be able to deliver the VANOL/VAPOL ligands rapidly and cheaply from easily accessible starting materials. This is an extremely challenging task since we have to translate the scale from milligrams to hundreds of grams while maintaining high quality, reproducibility and minimum cost. Meanwhile, it was hoped that such pathways would tolerate different substituent patterns on the starting materials to meet the needs of our research program.

In the following chapters, the studies towards access to VANOL monomers *via* different pathways will be discussed (chapter two), as will investigations toward the construction of 2-phenyl-4-phenanthrol as monomer for the VAPOL synthesis (chapter three). The development and optimization of the oxidative coupling protocol to dimerize both VANOL/VAPOL monomers will be addressed (chapter four), which will be followed by exploration of resolution conditions of the resultant racemic ligands (chapter five). The detailed study to evolve the VANOL derived catalysts for asymmetric aziridination reaction, together with the attempted syntheses of solid supported ligands will be addressed in chapter six.

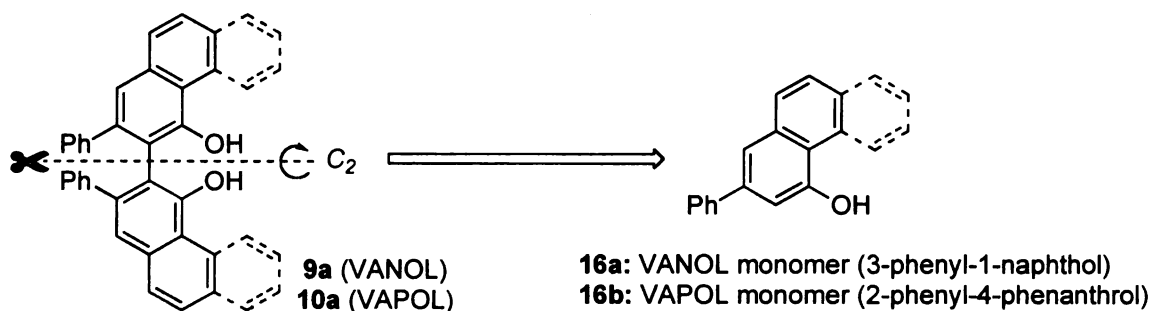
CHAPTER TWO

SYNTHESIS OF 3-PHENYL-1-NAPHTHOL AS VANOL MONOMER

Being new members of the set of “privileged” ligands,⁷ catalysts made from VANOL and/or VAPOL have demonstrated high efficacy toward various synthetic transformations,^{18,19} although what ultimately determines high asymmetric inductions for these reactions can be quite different. With this in mind, VANOL and VAPOL can be regarded as useful platforms for the discovery of new catalysts and reactions. Naturally, the availability of these ligands becomes a very important issue for their applications.

Though not required,² incorporation of C_2 symmetry in a ligand not only halves the number of possible transition state geometries in a given reaction, but also greatly simplifies the preparation strategy (Scheme 2.1). Therefore, for VANOL and VAPOL, disconnection along the C_2 axis results in two identical units, or monomers²⁶ (**16a** and **16b**, Scheme 2.1). Attention was thus turned to the VANOL monomer **16a** as the starting point for the synthesis, which was anticipated to be instructive to establish some general methods for both VANOL and VAPOL synthesis.

Scheme 2.1 General strategies for synthesis of the VANOL and VAPOL ligands



Arene groups are key units in organic chemistry. From a synthetic standpoint, the regiospecific preparation of poly-functionalized aromatic compounds is quite a formidable challenge, particularly for complex substitution patterns. Conventional methodologies to modify a given aromatic material, such as electrophilic or nucleophilic substitutions and coupling reactions, are often inconvenient due to different activating properties and orientating effects of the substituents. Taking this into account, along with the associated multistep reaction sequence, as well as the difficulties in regioselectively achieving specific substitution architectures, it appeared to be strategically sound to consider preparation of **16a** from benzene precursors in a linear fashion. This strategy would complement or even be superior to pathways based on chemical modification of pre-existing aryl cores in terms of chemical feasibility, practicality, and regiochemical outcome.

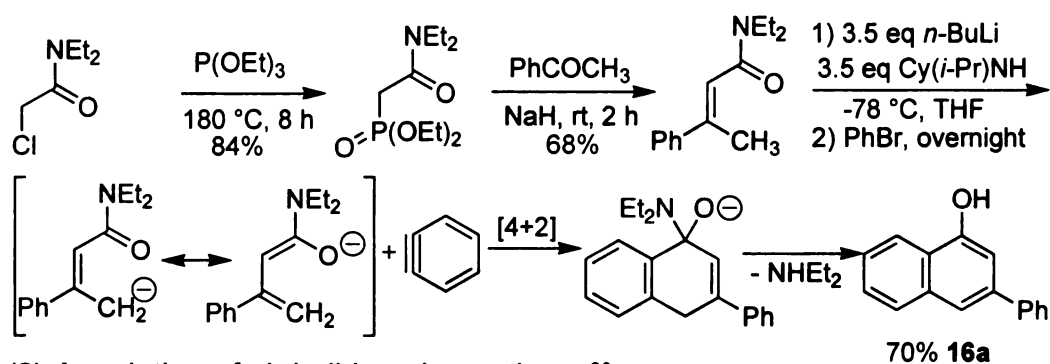
2.1 Introduction

The monomeric intermediate to VANOL, the *meta*-substituted 1-naphthol (**16a**, Scheme 2.1) is structurally simple; yet its preparation is challenging to install a phenyl group *meta*- to the hydroxyl functionality, which is a well-known *ortho/para* director in conventional electrophilic aromatic substitutions. To circumvent this regiochemical problem, we sought to synthesize the VANOL monomer *via* linear (or *de novo*) pathways, in which the desired substitution pattern of the aromatic product is determined by the structure of the starting materials. They were subsequently subjected to evaluation for large-scale production.

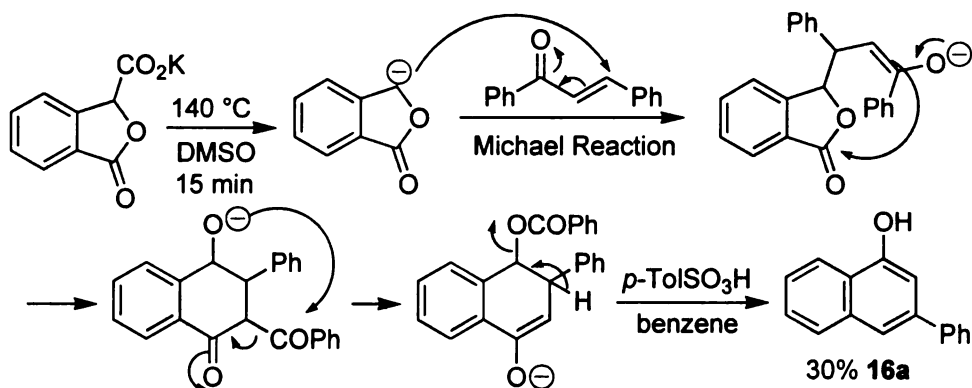
While the methods described in Chapter One for the synthesis of VANOL & VAPOL are impressive (Scheme 1.7), their drawbacks and limitations become apparent when performed on large scales. On revisiting the literature to find a reliable, efficient, and scalable route to **16a**, we found that the linear syntheses of the VANOL monomer are limited to the following methods (Scheme 2.2).

Scheme 2.2 Other linear syntheses of the VANOL monomer **16a**

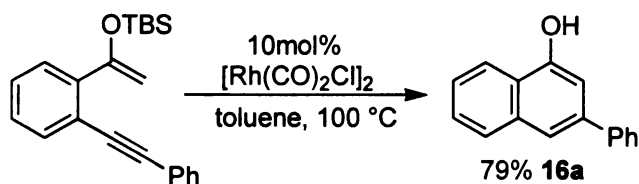
(1) Carbanion-induced condensation pathway²⁷



(2) Annulation of phthalide anion pathway²⁸



(3) Metal mediated cyclization pathway^{29a}



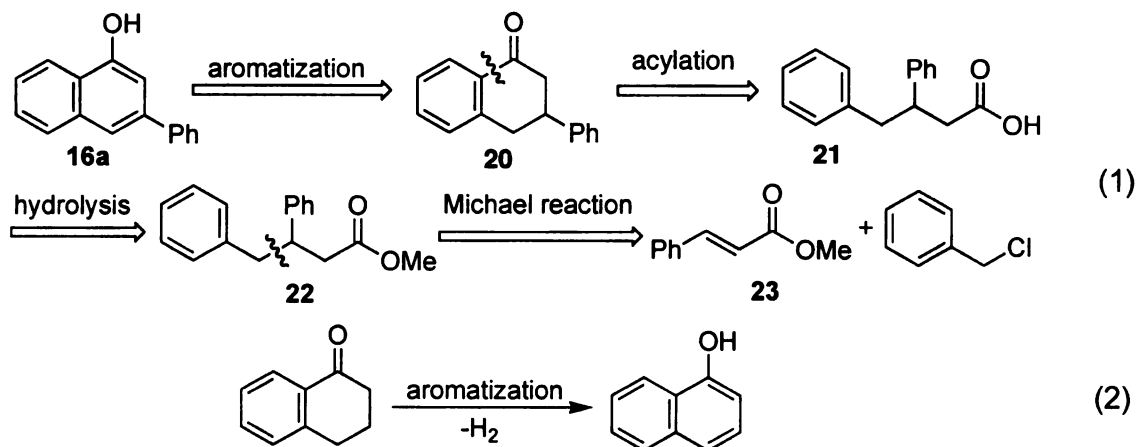
As shown above in Scheme 2.2, a number of methods and a wide variety of reactions are available for the synthesis of monomer **16a**. Method (1) is not

easily accessible as a result of the multiple-step preparation process and the strong bases required. Method (2), on the other hand, suffers from low yield, as the desired compound **16a** is the minor product of the reaction. The metal catalyzed cyclization (Method (3)) usually requires a precious metal to get reasonable yields from starting materials that are not commercially available. Thus, looking for an improved and more general access to this target, we thought of a different strategy that enabled access to **16a** from more readily available starting materials.

2.2 Synthesis of **16a** by dehydrogenation of 3-phenyl-1-tetralone

Strategically, a good starting point to develop a synthesis sequence that is potentially scalable is to apply the well-established methods that have been developed for analogs of the target molecule. Specifically, we planned our new strategy for **16a** via dehydrogenation of the corresponding 3-phenyl-1-tetralone (**20**, equation 1, Scheme 2.3) to furnish the 1-naphthol moiety in **16a**, since one of the major industrial pathways for the synthesis of 1-naphthols involves the aromatization of 1-tetralone (equation 1, Scheme 2.3).^{29b,c}

Scheme 2.3 Industrial method for preparation of 1-naphthol



Retrosynthetic analysis of the target compound leads to **20** (equation 1, Scheme 2.4), which in turn can be derived from ester **22**. We envisioned **22** as a β -substituted propionate derivative, which could be directly obtained by the Michael reaction to the inexpensive cinnamate ester **23**.³⁰ The striking feature of this strategy is the ready availability of the starting materials and its conciseness. Moreover, the reactions involved in each step have been extensively studied, which should help ensure its viability for bulk manufacture. Additionally, it is important that this route proceeds through intermediate **21** since, as an acid, this should be easily crystallizable. Thus, its purification could be easily carried out thereby avoiding chromatography that might impede throughput on large scales.

2.2.1 Considerations for large-scale synthesis

The simple translation of a description of a laboratory synthetic processes into operations on a large quantity of material often proves to be problematic; thus, the focus of large-scale syntheses differs from routine organic chemistry. It emphasizes the optimization of the process and defines the factors to make a sequence of reactions amenable to scale up. Meanwhile, a good process should reliably yield product of high purity with the minimum number of isolated intermediates. In this regard, however, the reported procedures of the above-described syntheses of the VANOL monomer **16a** are straight out of the academic laboratory with little optimization of the individual steps to be adaptable to scale up (e.g. extended cooling time, vast quantity of solvents for highly diluted reactions, stoichiometric amount of reagents and chromatographic column

purifications). Hence, all of these procedures would likely need further optimization before scale-up could be realized.

Collectively, during the literature study of the synthetic process for **16a**, we detected a lack of critical information on parameters influencing several key steps of the approach, which relies on seemingly well-established transformations. Among the issues encountered for the tetralone approach (Scheme 2.3) were the following: developing a protocol for the conjugate addition of a highly reactive benzylic nucleophile to the Michael receptor **23**; developing a practical protocol for the selective cyclization reaction of **21**, and determining critical parameters affecting the conversion of tetralone **20** to **16a** reproducibly. With this in mind, we then initiated our studies on scale-up of the tetralone route to **16a** with optimization of the Michael addition.

2.2.2 Optimization of the Michael addition to ester **23 on small scales**

First described by Komnenos and then extensively studied by Michael,³¹ the Michael addition is now a vital part of many synthetic methods on which organic chemists depend for their access to a variety of compounds.³² Following the pioneering work of Gilman,³³ the conjugation addition of organocopper reagents to α, β -unsaturated carbonyl compounds, a powerful tool to transfer carbon nucleophiles to Michael acceptors, is both a classic and a contemporary³⁴ reaction in organic synthesis. Hence, methodology to improve the overall efficiency and specificity of these reactions is still of current interest. For example, Corey³⁵ noted that TMSCl was capable of enhancing the rate of addition of cuprates to enones, and later Johnson³⁶ reported their studies of

With these improvements in hand, the major concerns for this reaction then moved to how to transfer highly reactive nucleophiles such as the benzylic anion to Michael receptors. Thus, Ferreira³⁰ successfully reacted enoates with various benzylic copper reagents, and the corresponding saturated esters were isolated in low to excellent yields (Scheme 2.4).

[illegible]

At outset of this research, the Grignard reaction was first optimized. Thus, instead of performing the reaction at room temperature, a THF (5 mL) solution of

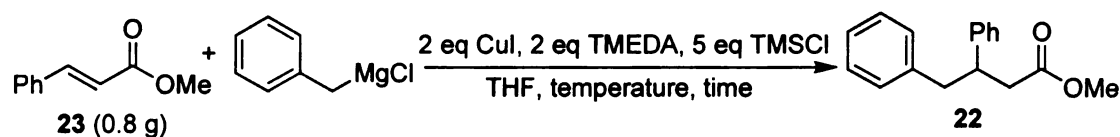
benzyl chloride (10 mmol) was slowly added to Mg (8 eq) over one hour at 0 °C, followed by warming up to ambient temperature for another hour. The strongly exergonic nature of the reaction was clearly reflected in the rapid melting of ice in the cooling bath. These optimal conditions were employed for the rest of the small-scale optimization studies on the Michael reaction.

With optimal conditions for the generation of the Grignard reagent in hand, attention was next turned to the Michael reaction, which required 2 equiv of freshly purified Cul as called for on the literature procedure.³⁰ To circumvent tedious steps in the purification of Cul,³⁷ the influence of the quality of the Cul was investigated by running two reactions under identical conditions using purified and unpurified Cul (commercially available from Aldrich) as shown in Table 2.1. Whereas the use of carefully purified Cul in the reaction of benzyl cuprate with **23** gave an 88% yield (entry 1, Table 2.1), much to our surprise, unpurified Cul produced **22** with even better yields (100%, entry 2). This was of course a much-welcomed result since solvation of Cul in aqueous KI was required for its purification,³⁷ and the resulting solution was fairly sensitive to air, and additionally, the purified Cul had to be dried thoroughly before it was subjected to the reaction. This discovery clearly indicated that these fussy steps could be eliminated from the process. Thus, unpurified Cul was used throughout the study.

In the original paper,³⁰ the reaction was started at -78°C followed by warming up to -30°C and held there for 24h. However, it would be inconvenient to have large reactors capable of maintaining such low temperature at scale. The

operation involves generating the CuI-TMEDA solution and BnMgBr in separate reaction vessels before the Grignard reagent was transferred to the CuI-TMEDA complex. Reaction mixtures can be transferred in the span of minutes on small scale, but more attention should be paid to this aspect for scale-up. To address these issues, it was reasoned that the procedure could be modified accordingly along two lines: (1) run the reaction at higher temperatures,³⁸ and 2) reduce the amount of the solvent.

Table 2.1 Optimization of the amount of solvent in the Michael addition



Entry	THF (mL) ^a	CuI	Conditions	22 (%) ^b
1	45	Purified ^c	-78 to -30 °C /24 h	88
2	45	Crude ^e	-78 to -30 °C /24 h	100
3	35		-78 to -30 °C /24 h	85.7 ^d
4	45		0 °C /21 h	76.2 ^d
5	45		-78 °C /6 h, then 0 °C /15 h	89
6	40		-78 to 25 °C /22 h	33.3 ^d
7	35		-78 °C /3 h, then 25 °C/ 21 h	54.0 ^d

^a For experimental details, see Section 7.2.1.1 of Chapter Seven. ^b Isolated yields by column chromatography. ^c Purified as in reference 37. ^d Conversion is based on crude ¹H-NMR spectrum by using α-olefinic proton of **23** and γ-proton of **22**. ^e Dried under vacuum (5 mmHg) at 90 °C.

Unfortunately, incomplete conversion was observed when the reaction was performed at higher concentration (entry 3, 6, 7, table 2.1) as indicated by the existence of an olefinic proton doublet for **23** in the ¹H-NMR spectrum of crude reaction mixture. Similar results were obtained when the reaction was carried out at 0 °C (entry 4).³⁸ To account for this observation, it was proposed that the incomplete conversion at higher temperature was due to decomposition of the

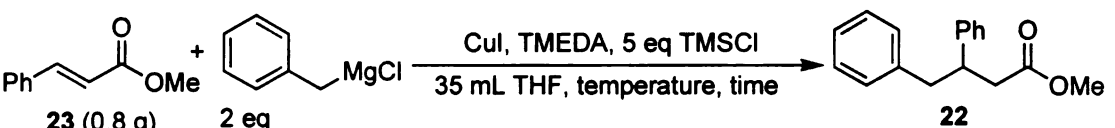
cuprate reagent and support for this can be found in the literature.³⁹ It has been reported³⁰ that the organocopper reagents are not reactive towards enoates at $-78\text{ }^{\circ}\text{C}$ but are at higher temperature ($-30\text{ }^{\circ}\text{C}$). Thus, it was wondered if the reaction could be further simplified by starting the reaction at -78°C followed by warming up to $0\text{ }^{\circ}\text{C}$.⁴⁰ Much to our delight, a good yield of **22** was afforded after the reaction mixture was maintained at a final temperature of $0\text{ }^{\circ}\text{C}$ for 15 h (entry 5). This was an encouraging result since it was generally believed that simple alkylcopper compounds decompose below $0\text{ }^{\circ}\text{C}$.^{30,39} Thus, to establish a successful addition, it seemed crucial to carefully control the temperatures to achieve a balance between the reactivity and stability of organocuprate reagent.

Clearly, the Michael addition of stoichiometric organocopper reagents is highly sensitive to various reaction conditions including the concentration. Concentration effects have been noted in only a few isolated instances,⁴¹ and these findings that higher yields were obtained with more dilute conditions is in agreement with our results.

At this point, a reasonable explanation for this concentration-dependent effect is not evident. It is known the cuprates can have complex aggregation states,⁴² and their reactivity is usually depended on the state of aggregation.⁴³ Therefore, such effects are tentatively attributed to the aggregation changes when the concentration of reagent is varied. The incomplete conversion at higher concentrations might be due to the formation of kinetically less reactive cuprate species. It is also possible that the formation of bibenzyl byproduct was accelerated at higher concentrations.

In the light of the comments above, it was speculated if the loading of CuI was reduced, the reaction could be run at higher concentrations of **23**. In preliminary experiments, the conjugate addition of 1.1 equiv of CuI and 1.4 equiv of TMEDA to acceptor **23** gave an 82% yield of **22** (Table 2.2, entry 1). Encouraged by this lead result, a thorough investigation of the reaction stoichiometry was undertaken. It was pleasing to find that the use of lower loadings of CuI and TMEDA as well as THF led to improved yield (91%, entry 2). However, when the reaction was performed with 10mol % of CuI and TMEDA (entry 3), incomplete conversion was observed presumably owing to the insufficient amount of the copper salt.

Table 2.2 Optimization of the reagent stoichiometry of the Michael addition

				
Entry	CuI (eq) ^a	TMEDA (eq)	Conditions	22 (%) ^b
1	1.1	1.4	-78 °C /3 h, then 25 °C/ 21 h	82
2	0.55	0.66	-78 to 0 °C/ 24 h	90.9
3	0.12	0.13	-78 to 25 °C/ 22 h	51.0 ^c
4	0.11	0.20	-78 to 25 °C/ 24 h	64.5 ^c
5	0.13	0.40	-78 to 25 °C/ 24 h	83.3 ^c

^a Dried under vacuum (5 mmHg) at 90 °C overnight. For experimental details, see Section 7.2.1.1 of Chapter Seven. ^b Isolated yields by column chromatography. ^c Conversion determined by the ¹H-NMR spectrum of the crude reaction mixture using α-olefinic proton of **23** and γ-proton of **22**.

In contrast to the above observations, the Michael addition using substoichiometric amount of copper salts is a well-established procedure. However, copper-catalyzed conjugate additions with the highly reactive benzyl Grignard reagent have never been documented to the best of our knowledge.⁴⁴ It

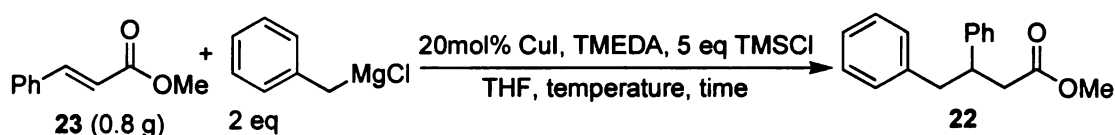
was reasoned that the catalytic process failed to turnover because decomposition of the organocuprate was faster than the delivery of benzyl group to **23** during warmup.⁴⁵ Therefore, to make the catalytic reaction proceed, the resulting 'cuprate complex' must necessarily be "picked up" and stabilized immediately, suggesting that an excess of TMEDA might be necessary. This diamine ligand was expected to bind copper *via* the nitrogen atoms, which could bring about a number of advantages. First of all, such chelation could result in the effective solvation of the copper reagent, whereby the electron density on copper would be increased *via* electron donation and lead to more reactive nucleophiles. The strong coordinating property of TMEDA might also be capable of breaking down the aggregation of the (less reactive) polymeric organocopper reagents,^{43c} which might also improve its reactivity. Finally, excess TMEDA might lead to stabilization of the benzylcopper reagents. This stabilization may result from chelating by the occupation of the vacant orbitals on copper,⁴⁶ which may prevent the Wurtz-like degradation.³⁰ Thus, the reactive copper species could remain stable above the required activation temperatures to permit the fast transfer of the benzyl groups.

To test such a hypothesis, we first examined the reaction with 2.0 equiv of TMEDA relative to CuI (Table 2.2, entry 4). In contrast to anticipation, the reaction was not complete after 24h, and employment of more TMEDA (4 eq relative to CuI, entry 5) also failed to completely transfer the benzyl group to **23**.

Clearly, the loading of CuI used above was too low. More catalyst was then included in the reaction (entry 1, Table 2.3). To our delight, the reaction

proceeded smoothly; upon warming up to ambient temperature, compound **23** was completely consumed after 24 h as indicated by $^1\text{H-NMR}$ analysis. However, these conditions were highly unreliable and sensitive to the quality of reagents (entry 1 to 4). In addition, these conditions were not viable at higher concentrations (entry 5 to 7). It is possible that this represents the bottommost level of CuI needed to allow the reaction to consistently turnover. To make it more practically feasible, the reaction was attempted using a large excess of TMEDA. To our delight, in the presence of 7.2 equiv of TMEDA (relatively to CuI, entry 8), ester **22** was isolated with excellent yield after 7 h.

Table 2.3 Optimization of the amount of TMEDA and THF in the Michael addition



Entry	THF ^a (mL)	TMEDA (eq) ^b	Conditions	Conversion (%) ^c
1	35	2	-78 to 25 °C/ 24 h	100
2				64.1
3				70.4
4				100 ^d
5	20	2	-78 to 25 °C/ 24 h	66.7 ^d
6			-78 °C/ 4 h, then 25 °C/ 20 h	81.3 ^d
7			-78 °C/ 10 h, then 25 °C/ 14 h	60.6 ^d
8		7.2	-78 to 25 °C/ 7 h	83 ^{d,e}
9			-78 to 25 °C/ 17 h	55 ^{d,f}

^a For experimental details, see Section 7.2.1.1 of Chapter Seven. ^b Relative to CuI. ^c Based on crude $^1\text{H-NMR}$ spectrum. ^d New bottle of CuI from Aldrich was used. ^e Isolated yield of **22** by column chromatography. ^f Isolated yield of **21** *via* base extraction using hexanes.

Another synthetically important feature of these reaction conditions (entry 8, Table 2.3) is the fact that the Michael reaction was complete upon warming up to 25 °C. This simple operational maneuver paid off handsomely: not only was the

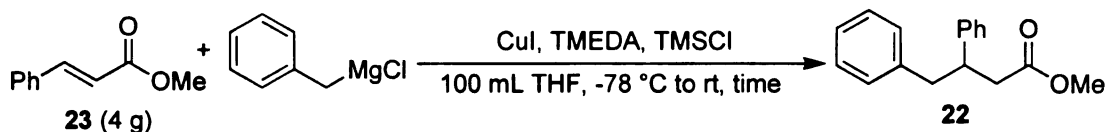
reaction accelerated significantly as indicated by the much shorter reaction time, it also allowed the elimination of the cumbersome cooling system required by the original protocol.

The only byproduct detectable from the reaction was bibenzyl which was resulted from the Würtz reaction.⁴⁷ To separate this compound more efficiently, alternative procedures were explored; it was found that the acid **21** could be prepared in a 'one-pot' protocol by hydrolysis of crude product of the Michael reaction using KOH in boiling water. Taking advantage of the insolubility of bibenzyl in such a highly alkaline solution, this side-product was removed by washing with hexanes. The solution of the potassium salt of acid **21** was then treated with hydrochloric acid followed by ether extraction and evaporation to yield acid **21** (entry 9, Table 2.3). This acid was pure enough for the next step. These changes not only led to simplified procedures, but also avoided the cumbersome column chromatographic purification, since further purification of acid **21** can be easily achieved by crystallization.

In an effort to mitigate this Würtz reaction, the idea was examined if it was viable to generate and react the benzyl organocopper reagent using less-than-reported amount of materials in the Grignard reaction (Table 2.4). It was found that as little as 1.4 equiv of the Grignard reagent was necessary to promote the reaction and gave a comparable yield of **22** after workup (entry 1 and 2). It was anticipated that the facile benzyl transfer with less than 2 equiv of the benzyl group would be of considerable advantage for further synthetic transformations including the cost minimization from both material waste and product isolation. In

another experiment, the loading of TMSCl was halved without loss in yield (entry 3).

Table 2.4 Optimization of the Grignard reagent stoichiometry in the Michael addition

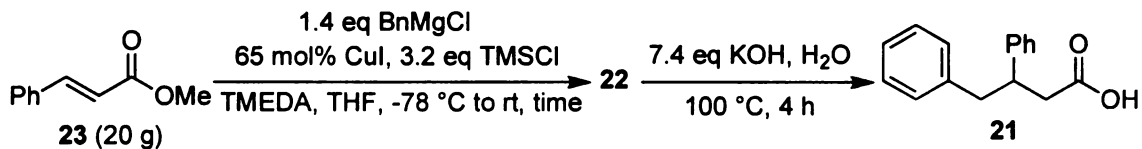


Entry ^a	PhCH ₂ Cl (eq)	CuI (eq)	TMEDA (eq)	TMSCl (eq)	Time (h)	22 (%) ^b
1	2	0.25	1.73	5.0	16	60.6
2	1.4	0.25	1.72	5.0	10	68.7
3				2.5	5	56.0
4		0.64	1.33	2.3	9	95.0

^a The equivalent of all the reagents were based on methyl cinnamate (**23**). For details, see Section 7.2.1.1 of Chapter Seven. ^b Isolated yields by column chromatography.

The CuI-TMEDA catalyst system described above gave a decent yield (56-68%) of **22** at 25mol% catalyst loading. However, this yield was significantly lower than the reaction using 66mol% CuI (91%, entry 2, Table 2.2). Thus, the Michael reaction was repeated by using 66mol% CuI with 2.3 eq of TMSCl (instead of 5 eq). Gratifyingly, the yield could be recovered (95%, entry 4, table 2.4). Furthermore, these conditions could be successfully scaled up to 20 g of **23** (Table 2.5).

Table 2.5 The Michael reaction using 20 grams of methyl cinnamate (**23**)



Entry ^a	THF (mL)	TMEDA (eq)	Time (h)	22 (%) ^b	21 (%) ^c
1	500	1.30	9	95.3	-
2		1.32	10	-	100

^a The equivalents of all the reagents were based on methyl cinnamate (**23**). ^b Isolated by silica gel chromatography. ^c Isolated by extraction using aqueous KOH.

2.2.3 Summary of optimizations of the Michael addition on small scales

An efficient protocol for the efficient Michael addition was established in the preliminary optimization studies described above. This study gave the lowest catalyst loadings (20 mol% of CuI) that has been reported for a Michael addition to enoates using highly reactive benzylic cuprate reagents. Investigation of the CuI:TMEDA ratios in this catalysis indicated that the catalyst made with a 1:2 ratio of these two reagents was usable but highly inconsistent, whereas the catalyst derived from a 1:7 ratio of CuI:TMEDA (20 mol% of CuI) produced **22** with consistently moderate yields. While such results might be acceptable on small scale, the 65 mol% loading of the CuI catalyst with a CuI/TMEDA ratio of 1:1 generally gave much higher yields and was the catalyst of choice. Thus, it will be used throughout the subsequent scaleup studies.

In this section, it also demonstrated how the original procedure could be adapted to one that was expedient for scaleup as summarized in Table 2.6 (4 grams of **23**). Entries 1 and 2 of Table 2.6 indicate the reagent loading for the original and new procedures for scale-up, respectively. Additionally, the new conditions do not require any special cooling protocol that maintains an intermediate temperature and the reaction time was dramatically reduced. Furthermore, it was found that the column chromatography purification of the conjugate addition product could be avoided by base extraction of the crude product followed by acidification.

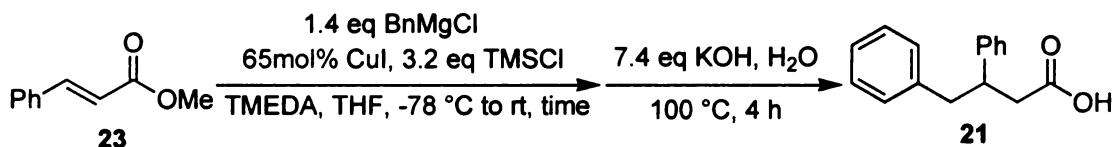
Table 2.6 Comparison of different conditions for the Michael reaction^a

Entry	THF (mL)	CuI (eq)	TMEDA (eq)	TMSCl (eq)	BnCl (eq)	Mg (eq)	Conditions	22 (%) ^d
1	45	2 ^b	2.2	5	2	8	-78 to -30 °C/ 24 h	88
2	20	0.65	0.64	2.3-5 ^c	1.4	3.5	-78 to 25 °C/ 5 h	95

^a The equivalents of all the reagents were based on methyl cinnamate (**23**). ^b Purified according reference 37. ^c As low as 2.3 eq of TMSCl could be used. Further optimizations needed. ^d Isolated yields by column chromatography.

2.2.4 Scale up of the Michael addition reaction

Under the optimized conditions, the Michael addition to produce **22** was then investigated on 100 g scale and the results are summarized in Table 2.7.

Table 2.7 Large-scale preparation of **21** via the Michael reaction

Entry ^a	23 (g)	THF (mL)	TMEDA (eq)	Time ^b (h)	21 (%) ^c
1	100	2500	0.70	9	96.8
2				3	100
3				18	100

^a The equivalent of all the reagents were based on methyl cinnamate (**23**); For experimental details, see Section 7.2.1.1 of Chapter seven. ^b Time was variable due to different amount of cooling agent was used. ^c Isolated yields by base extraction.

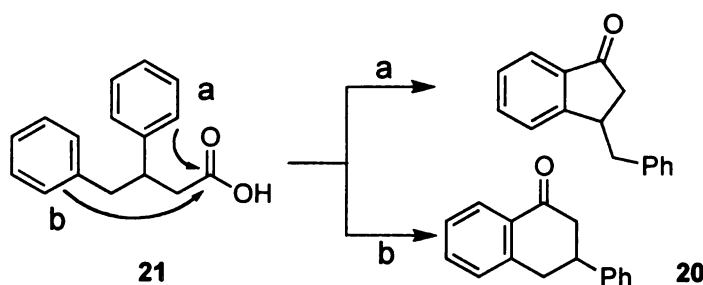
Thus, the best conditions on small scale were reproduced successfully on 100 g scale using 65mol% of catalyst where **23** was completely consumed as indicated by crude ¹H-NMR spectrum. Because the ester **22** was not readily crystallizable, it was imperative that the hydrolysis provided acid **21** as pure as possible so as not to introduce any byproducts that would necessitate the use of chromatographic purification. A simple workup procedure involving basic

hydrolysis and hexanes extractions reliably afforded >96.8% yields of the **21**. The high conversion at low catalyst loading not only enabled the high yield of the product, but also facilitated simpler workup procedures to handle large amount of insoluble copper salts.

2.2.5 Intramolecular Freidel-Crafts reaction to generate tetralone **20**

Following the successful large-scale preparation of acid **21**, attention was next focused on how to construct 3-phenyl-1-tetralone (**20**, Scheme 2.3) in an efficient and practical manner. An acid induced intramolecular Freidel-Crafts reaction⁴⁸ (cycloacylation) was envisioned for such a cyclization process. This reaction leads to a cyclic ketone by using various acids. One of the concerns about this reaction, however, is that in the case of acid **21**, two aromatic rings are accessible, and thus cyclization can occur either through pathway a or b (Scheme 2.5). This leads to either a hydrindone (pathway a) or a tetralone (pathway b, **20**).^{48a,52,53}

Scheme 2.5 Tetralone versus hydrindone products in cycloacylations of **21**



Fortunately, cycloacylation of substrate **21** has been successfully accomplished using H_2SO_4 ⁵⁰ and PPA.⁵¹ In fact, for our purpose, the acid of choice for the preparation of the VANOL monomer **16a** is polyphosphoric acid (PPA),^{49,50} since it is effective but less corrosive. A small-scale reaction in PPA at

100 °C (entry 1, Table 2.8) was first conducted, and the structure of the product was established to be corresponding tetralone by its spectroscopic data.⁵¹

Having established the profile of the reaction, it was then repeated on different scales, and the results are collected in Table 2.8. It was found that the yields of the reaction could be reproduced independent of the scale. When more than 100 grams of acid **21** was used (entry 4 to 6), however, vacuum distillation was employed to remove water produced in the reaction to drive the reaction to completion. Not knowing if the impurities⁵⁴ in the crude product would have any adverse effects on the next step, **20** was purified by crystallizations (entry 6) and an excellent yield of **20** was obtained after three sequential steps (from BnCl) without purification of any of the intermediates.

Table 2.8 Cycloacylations of **21** on different scales

Reaction scheme: **21** (2-phenyl-3-phenylpropanoic acid) $\xrightarrow[\text{time}]{\text{PPA, temperature}}$ **20** (1-phenyl-2,3-dihydro-1H-benzo[b][1,4]dioxin-6-one)

Entry	21 (g)	PPA (g)	Temperature (°C) ^a	Time (h)	20 (%) ^b
1	1.20	7.24	100	2.5	87.7
2	5.00	15.6	115	2	89.8
3	20.0	37.7	120	2.5	96.4
4	101	194	120	2 h, vacuum 2 h ^c	98.1
5	153	301	120	4.5 h, vacuum 3 h ^c	95.8
6	157	301	120	4.5 h, vacuum 3 h ^c	85.4 ^d

^a Temperatures of oil bath. For experimental details, see Section 7.2.1.2 of Chapter Seven. ^b

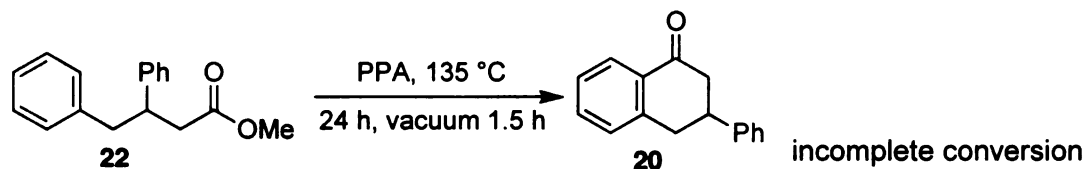
Unless otherwise mentioned, the crude product was used for the next step without further purifications. ^c Vacuum (3 to 5 mmHg) was applied at the indicated temperature. ^d Yield based on

23 after crystallization and 2 chromatographic columns on the mother liquor.

Concerns with the conciseness of process motivated an effort to seek to minimize the steps by employing the ester **22** directly in the cyclization step

(Scheme 2.6). Yet, although Freidel-Crafts acylation on esters can be achieved⁵⁵ in some cases, cyclization of **22** was fairly sluggish under similar cyclization conditions as indicated by the long reaction time. Moreover, it was even harder to purify the resultant **20** from this reaction and thus this approach was put on hold.

Scheme 2.6 Direct cycloacylation of ester **22** to generate tetralone **20**



2.2.6 Generation of the VANOL monomer 16a via dehydrogenation of 20

The conversion of the tetralone **20** to the target molecule **16a** via dehydrogenation should be straightforward.⁵⁶ Nobel metals are well precedented²⁹ reagents for the oxidative aromatization of tetralone derivatives; palladium-carbon,⁵⁷ in particular, functions well under heterogeneous conditions. This would ensure its easy removal *via* filtration and thus simplify the procedure. Therefore, it was decided to carry out the dehydrogenation of **20** with this method using palladium-carbon as the catalyst.

While numerous examples of this type of reaction could be found in the literature,⁵⁶ at the time this work was pursued, however, no examples were found using **20** as substrate. Thus, the exploration was begun with the treatment of **20** by Pd/C (6.6 mol% of Pd) in refluxing toluene (entry 1, Table 2.9). However, no reaction was observed after two hours based on TLC. Happily, **20** was smoothly consumed upon shifting the solvent to mesitylene⁵⁷ (entry 2). After refluxing for four hours, the phenol **16a** could be detected by TLC, together with trace amounts of the starting ketone **20**. Surprisingly, at least three side-products were

observed if it was heated for six hours (entry 3). This result cautioned against the use of extended reaction time heating the reaction mixture for too long period.

Table 2.9 Solvent effects on the dehydrogenation of **20**

O=C1C(=O)C2=CC=CC=C2C1Cc3ccccc3
 $\xrightarrow[\text{solvent, time, reflux}]{\text{Pd/C}}$
Oc1c2ccccc2c(c1)Cc3ccccc3

20 **16a**

Entry	20 (g)	Solvent ^a	Pd/C ^b (g)	Temp. (°C)	Time (h)	16a (%)
1	0.95	toluene ^c	0.3	110	2	Nd ^d
2	0.95	mesitylene	0.3	166	4	Incomplete ^d
3	0.95	mesitylene	0.3	166	6	Overreacted ^d
4	0.55	diglyme	0.04	162	4	Incomplete ^d
5	0.51	pseudocumene ^e	0.13	170	5	Trace ^d
6	0.51	<i>p</i> -cymene	0.15	177	5	75.2 ^f

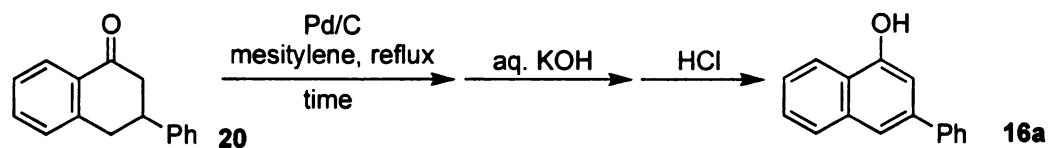
^a Unless otherwise specified, all reactions were performed in 30 mL solvent. ^b The ratio of palladium to carbon was 10%. ^c The volume was 40 mL. ^d Not detected based on crude TLC. ^e 1,2,4-trimethylbenzene. ^f Isolated yield by column chromatography.

Apparently the reactivity of Pd/C towards dehydrogenation in mesitylene is a consequence of the higher temperature attainable with this solvent. Dilemmatically, this solvent was hard to remove due to its high boiling point. As a result, a solvent with a high boiling point as well as one that is easy to remove during workup was desired. Diglyme⁵⁸ (entry 4) was then tried since it is easy to get rid of by virtue of its miscibility with water. However, the reaction gave incomplete conversion of **20** after heating for four hours. This observation and the fact that diglyme is relatively expensive (\$49.5/ 500 mL)⁵⁹ should limit the large-scale utility of this solvent. Cheaper solvents such as pseudocumene (i.e. 1,2,4-trimethylbenzene, \$24.8/ 500 mL versus \$51.3/ 500 mL for mesitylene),⁵⁹ on the other hand, only gave trace amounts of the desired phenol **16a** as

detected by TLC (entry 5). Much to our delight, *p*-cymene (entry 6) provided a hospitable medium for the reaction, and successful transformation of **20** to **16a** was evident by the fact that only aromatic protons were observed in the ^1H -NMR spectrum on the crude reaction mixture. Although the dehydrogenation worked well in this solvent, the potential to form explosive peroxides upon exposure to air⁶⁰ presented safety concerns, and thus this solvent was abandoned.

Attention then returned to mesitylene as solvent with alternative isolation strategies. Considering that the product bears an phenolic hydroxyl functionality (pK_a : 10)⁶¹ and that the starting ketone does not (pK_a of α -H: 20),⁶¹ the two compounds should be easily separable by careful controlling the pH during workup. As a matter of fact, the desired VANOL monomer **16a** was obtained in good yield by extracting the crude organic solution with aqueous KOH (entry 1, Table 2.10). This protocol allowed for a complete extraction of the product from the organic layer as indicated by TLC. Both TLC and ^1H -NMR analysis of the extracted material confirmed it was pure monomer **16a**. The screening reaction was carried out on small scale (entry 1), and encouraged by its success, the reaction was then repeated on larger scales using mesitylene as solvent.

Table 2.10 The dehydrogenation of **20** in mesitylene

					
Entry	20 ^a (g)	Solvent (mL)	Pd/C ^b (g)	Time ^c (h)	16a (%) ^d
1	1.0	30	0.27	4	77
2	5.1	50	0.30	20	38.2
3	5.1	100	0.32	20	49.5
4	18.7	200	0.98	8	21.6
5	92	1000	6.1	113	67
6	136	1500	10.8	192	54.3 ^e

^a Crude **20** was used. For experimental details, see Section 7.2.1.3 of Chapter Seven. ^b The ratio of Pd to C was 10:1. ^c The reaction was stopped at the indicated time. ^d Isolated yields by column chromatography. ^e Yield was based on **23**.

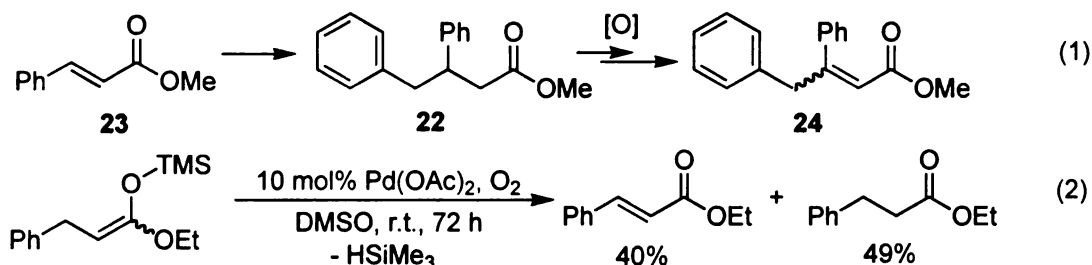
The concentration profile of the reaction was first investigated by employing two reactions in different volumes of solvent (entry 2 and 3, Table 2.10). It was found that a higher yield of **16a** was afforded in the more dilute solution, which might be problematic on large scales because this would lead to generation of substantial quantities of waste solvent and the requirement of larger vessels. Furthermore, attempts to reduce the amount of costly catalyst (\$99.5/ 10g,⁵⁹ entry 1 vs. entry 4) proved unproductive, since a reasonable conversion of the dehydrogenation of **20** required longer reaction time, and on even larger scale to an unacceptable level (up to 8 days, entries 5 and 6). In addition to the long reaction times, the overall yield of **16a** varied considerably from batch to batch (75-21%), and despite much effort, it was not possible to further optimize this reaction.

Plausibly, the highly capricious nature of the dehydrogenation of **20** was due to the existence of unknown impurities in the starting materials, since the crude form of **20** was used in most of the cases in the cycloacylation step. Efforts to purify **20** by crystallization proved not to be profitable, as exhibited by facile formation of oily materials. Chromatography and distillation were considered less attractive options. These impurities adversely affected the dehydrogenation reaction, and this motivated a search for alternative routes that did not include an oxidative aromatization step.

2.2.7 Modified methods to synthesize 16a by reconstruction of double bond

The tetralone dehydrogenation route was ultimately deemed impractical for large-scale manufacture chiefly due to the relatively low efficiency of the dehydrogenation step. Notably, this step involves oxidation state adjustment (oxidation) and it was the bottleneck in terms of yield. Therefore, shifting such an adjustment to the early stage of the synthesis was deemed important to avoid wasting material and effort. Thus, oxidation of the Michael addition product by regeneration the double bond that exists in the starting enoate **23** (Scheme 2.7, equation 1) was examined.

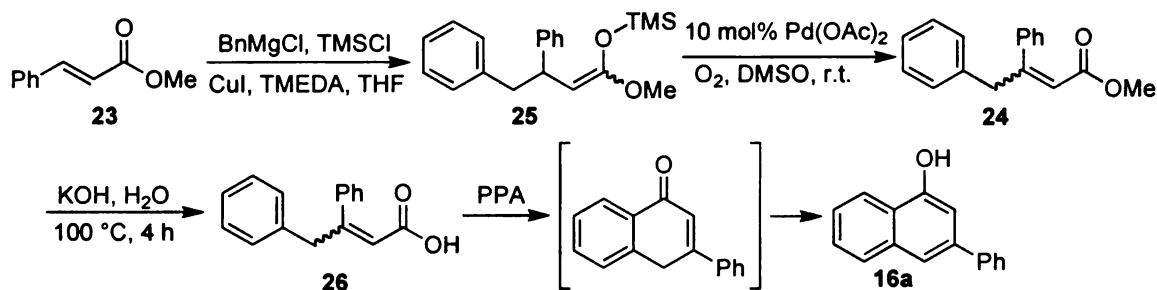
Scheme 2.7 Synthesis of enoates by dehydrosilylation of silyl enol ether



After a survey of the literature,⁶² the dehydrosilylation reaction pioneered by Saegusa⁶³ and later by Larock⁶⁴ (equation 2) was opted for as the most suitable method for three reasons: 1) It can be done catalytically with cheap oxidants such as O₂ or even air;⁶⁴ 2) the reagents involved are non-toxic, non-hazardous and environmentally friendly; 3) most importantly, the direct product of the Michael addition reaction is the silyl enol ether **25**, which is a suitable substrate for the Saegusa dehydrosilylation reaction (Scheme 2.8).⁶⁴

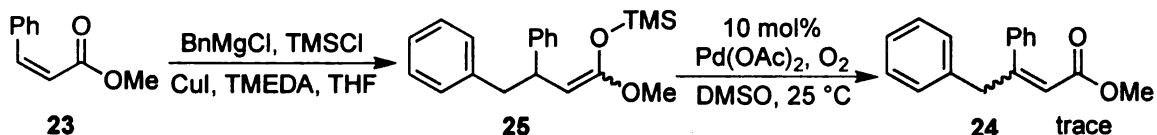
Therefore, instead of treatment with mild acid, the arrival of the initial product of Michael reaction (e.g. the silyl enol ether **25**) will be met with Larock's condition to effect the rebuilding of the C-C double-bond (Scheme 2.8).⁶⁴

Scheme 2.8 Revised synthetic plan using Saegusa's dehydrosilylation reaction⁶⁴



Unfortunately, while enol silanes could be effectively converted to enones and enals by Pd-catalyzed oxidation,⁶⁴ the reaction of **25** was sluggish. Only a trace of **24** was detected in the ¹H-NMR spectrum (Scheme 2.9), a result that has yet to be adequately explained. No further effort was made to optimize this reaction due to time constraints, and it should not necessarily be concluded that such a pathway is impracticable.^{63b} Nonetheless, the advantages inherent in this sequence as a shorter, more efficient approach could justify a return to this approach.

Scheme 2.9 Dehydrosilylation of **25** (See Section 7.2.1.4 of Chapter Seven)

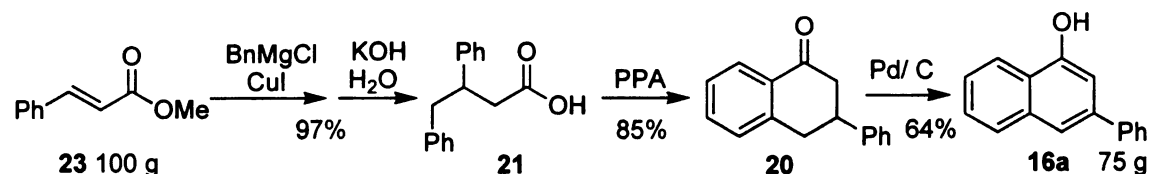


2.2.8 Summary of route involving dehydrogenation of tetralone 20

In total then, the overall route as outlined in Scheme 2.10 to 3-phenyl-1-naphthol (**16a**) constitutes a straightforward and efficient process from easily accessible starting materials as outlined in Scheme 2.10. Most promisingly, it can be scaled up. The overall yield of **16a** is 54.3% (5 steps) starting with 100 g of methyl cinnamate (**23**), from which 75 g of **16a** could be obtained. Operationally, the whole process involves just two isolated intermediates, and no

chromatographic columns were necessary to obtain pure product. Accordingly, it proved possible to optimize the Michael reaction to be compatible with a large-scale synthesis in terms of reagent loading, reaction conditions as well as workup procedures.

Scheme 2.10 Overview of the synthesis of **16a** from **23**

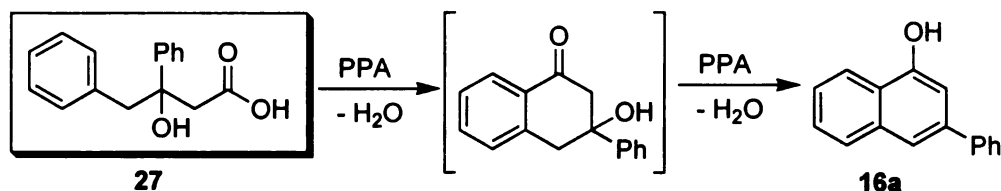


This process was expected to compete favorably with known methods for the preparation of VANOL, but it did not meet the criteria for a practical large-scale preparation. First of all, monomer **16a** was afforded in only mediocre overall yield, which was no better than the yield *via* the benzannulation reaction (Scheme 1.7).^{17b} The multiple-step character of this process weighs it down, which is in contrast to the CAEC approach as a virtually one-step process (Scheme 1.7).^{17b} Moreover, there are a number of inherent limitations for this methodology: drastic conditions required by the conjugate addition reaction involving highly sensitive reagents and the difficulty in purifying tetralone **20**, which is presumably the cause of the sporadic consistency of the dehydrogenation reaction. The involvement of costly precious metals in the dehydrogenation entailed unacceptably long reaction times. Thus, in light of the attendant inefficiencies, attention returned to revise the aforementioned route in Scheme 2.10 and to examine alternative and more efficient methods for VANOL synthesis.

2.3 Synthesis of 16a through the Reformatsky-cycloacylation pathway

As illustrated by the dehydrogenation of tetralone **20** (Table 2.10), adjusting oxidation levels in the synthetic sequence resulted in loss of efficiency,⁶⁵ so it became necessary to introduce the proper oxidation level as early as possible. It was then reasoned if the oxidation state was suitably “set” in the starting materials or in an early intermediate, such steps could be possibly avoided. With this in mind, the idea of structure **27** came to the fore (Scheme 2.11),⁶⁶ which featured an “oxidized” β -carbon. Under acidic conditions, it was anticipated that the hydroxyl group could be readily eliminated during the acid facilitated cycloacylation reaction, and therefore the aromatic moiety could be furnished in one step.

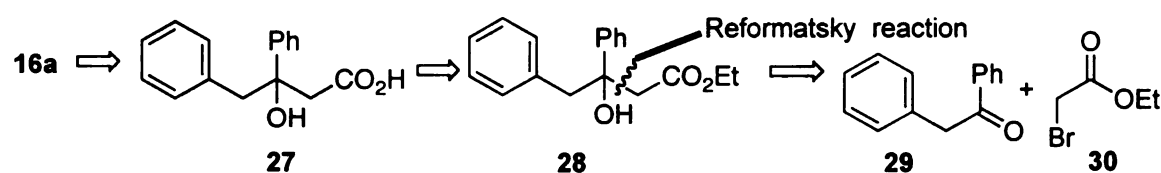
Scheme 2.11 The structure of the proposed precursor (**27**) to **16a**



2.3.1 Retrosynthetic strategy for the Reformatsky-cycloacylation pathway

By careful analysis of acid **27**, which has the correct oxidation state of the final product, it was envisioned that **27** could arise from the Reformatsky reaction between commercially available deoxybenzoin (**29**, scheme 2.12) and ethyl bromoacetate (**30**) followed by hydrolysis. Subsequent cyclization to the tetralone intermediate was expected to be ultimately driven by aromatization to VANOL monomer **16a**, which could occur by an elimination of H₂O.

Scheme 2.12 The retrosynthetic analysis to **16a** via Reformatsky reaction route



This retrosynthetic strategy enjoys not only a shorter pathway relative to the dehydrogenation of tetralone method, but also eliminates the hard-to-purify tetralone intermediate **20**. From an economical point of view, this pathway was very appealing compared to dehydrogenation of tetralone route: it offers the replacement of the unstable organocuprate reagents requiring cryogenic conditions with room-temperature stable organozinc reagents. An additional attractive feature of this methodology is that the feasibility of the cycloacylation step using PPA had been studied during the course of the tetralone route (section 2.2). Thereby, at the outset this new strategy had promise to provide a superior source for the VANOL ligand.

2.3.2 Optimizations of the Reformatsky reaction

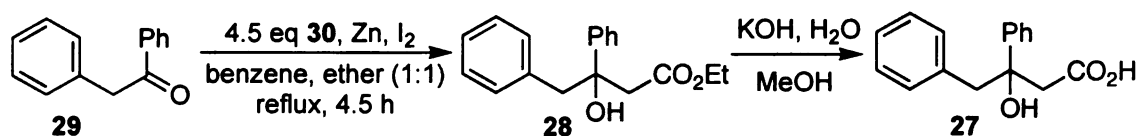
The metal-mediated addition of α -halogenated esters to ketones (Reformatsky reaction) plays an important role in the formation of C-C bonds; it manages to produce synthetically very useful β -hydroxyl esters. As a result, it has been reported in the literature quite extensively⁶⁷ and the key features of the reaction have been well studied.

The preparation of **28** has been reported *via* Reformatsky reaction of **29** with **30**,⁵⁰ and a slightly revised procedure^{66b} was employed (Table 2.11). Therefore, ester **28** could be easily obtained in the presence of Zn after refluxing in a mixture of benzene and ether (1:1) for 4.5 h (entry 1). The reaction was very

clean, with no side products detected. A simple flash silica gel column purification of the crude product was sufficient to produce **28** in excellent yield. Upon exposure to base, the corresponding acid **27** could be isolated in 90.7% yield.

Next, a search was begun for optimum conditions aiming at scaling down the amount of reagents and circumventing chromatographic purifications. Happily, it was found that the reaction proceeded equally well using lower loading of zinc (entry 2, Table 2.11). The yields of **28** and **27** were found to be reproducible under these conditions (entries 2, 3 and 4). Some effort was spent on simplifying the procedures by hydrolyzing the crude Reformatsky product with base without purification of the intermediary ester **28**. This procedure involved simply refluxing the crude products with aqueous KOH in MeOH for 0.5-2 h, followed by hexane extraction to remove less polar byproducts. However, this direct procedure afforded diminished yield of **27** (entry 5). Fortunately, upon scaling up, the yield was recovered under the same one-pot protocol (entries 6 and 7); excellent yields were obtained in both instances. In addition, the acid **27** was readily crystallizable, which allowed for greater efficacy and ease in purification.

Table 2.11 Optimization of the Reformatsky reaction of **29** and **30**



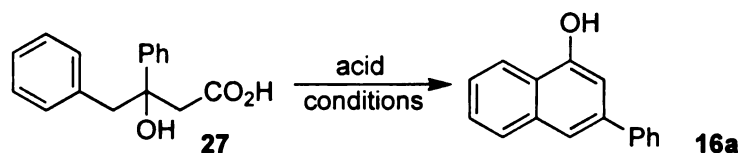
Entry	29 (mmol)	Zinc ^a (mmol)	28 ^b (%)	27 ^b (%)
1	10	14.2	88.7	90.7
2	5	7.6	97.3	91.5
3	10	8.1	90.0	Not determined
4	10	8.4	81.7	93.9
5	10	7.7	Not determined	36.3 ^c
6	22.2	6.9	Not determined	60.0 ^{c,d}
7	20	7.7	Not determined	82.2 ^c

^a Zinc was activated; See Section 7.2.2.1 and 7.2.2.2 of Chapter Seven for details. ^b After flash silica gel column. ^c Yield over two steps. ^d After crystallization.

2.3.3 Development and optimization of the cycloacylation reaction of **27**

Construction of the phenol functionality of the VANOL monomer **16a** by the cycloacylation of **27**⁴⁸ was critical to the success of the synthesis *via* the Reformatsky reaction. The synthesis of **16a** from **27** was strategically more economical than dehydrogenation route from the tetralone **20** since the installation of the double bond *via* dehydrogenation would become unnecessary. The major concern, though, in the cycloacylation of such compounds having tertiary alcoholic moieties lie in their high vulnerability to degradations under acidic conditions: it is well known that, upon elimination of a H₂O molecule, the resultant carbocation is stabilized by alkyl substituents attached directly to the positively charged carbon, and therefore they can be readily formed and undergo various transformations.^{66g}

The initial experiment of the acid-catalyzed cycloacylation of **27** was conducted using PPA since it had been successfully performed on acid **21** (Section 2.2). Contrary to cyclization of **21** (Section 2.25), however, difficulties were encountered in the conversion of **27** to **16a**. Elimination of H₂O took place smoothly upon exposure of **27** to excess PPA at 120 °C, with TLC analysis indicating complete consumption within 5 h (entry 1, Table 2.12). Regular workup and purification then resulted in **16a** with 21.6% yield that was identified by its characteristic odor and mobility on TLC, and further confirmed by subsequent separation on silica gel chromatography.

Table 2.12 The acid facilitated cycloacylation reaction of **27**

Entry	27 (mmol)	Acid (mmol)	Solvent (mL)	Conditions ^a	16a ^b (%)
1	8.0	PPA (20 g)	-	120 °C, 5 h	21.6
2	1.35	BF ₃ •OEt ₂ (47.8)	-	0 °C to rt 24 h; Then reflux 1.5 h	0 19.0
3	1.64	BF ₃ •OEt ₂ (3.98)	CH ₂ Cl ₂ (20) ^c	0 °C to rt 17 h; Then reflux 36 h	0 29.2
4 ^d	1.28	BF ₃ •OEt ₂ (3.98)	CH ₂ Cl ₂ (20)	0 °C to rt 15 h; Then reflux 36 h	0 0
5	1.3	SnCl ₄ (21.8)	-	110 °C, overnight	6.6
6	0.51	TiCl ₄ (20.0)	-	Reflux, 13 h	15.4
7	1.26	TiCl ₄ (2.74)	CH ₂ Cl ₂ (10)	0 °C, 3 h then rt 15 h	0
8	1.31	TiCl ₄ (2.74)	CH ₂ Cl ₂ (10)	-78 °C, 5 h; rt, 16 h	0
9	1.26	AlCl ₃ (9.75)	Toluene (20) CH ₂ Cl ₂ (5) ^e	0 °C to rt overnight	0

^a Conditions were not optimized, and the reaction was tracked by TLC. See Section 7.2.2.3 of Chapter 7. ^b After flash silica gel column. ^c Solvent evaporated after refluxing. ^d Reaction of entry 3 was repeated with care to prevent solvent from escaping. ^e CH₂Cl₂ was used to dissolve AlCl₃.

It was speculated that the low yield was possibly the result of the harsh conditions required by PPA; therefore Lewis acids were examined in the cyclization of **27** since that lower temperatures could be employed. However, the reaction was not operative when BF₃ etherate was used at 0 °C (entry 2), and **27** was largely unchanged even after stirring the reaction mixture for 24h at ambient temperature. A low yield (19.0%) of **16a** was obtained after heating the same reaction mixture to reflux for 1.5 h under solvent-free conditions (entry 2). Upon heating in CH₂Cl₂ for 36 h, on the other hand, acid **27** underwent intramolecular acylation and dehydration reaction and gave a 29.2% yield of **16a** (entry 3). It was noticed that the solvent had completely evaporated in this case; so a more

carefully controlled reaction was performed to allow for a minimal loss of solvent (entry 4). Surprisingly, no product was detected under the same conditions.

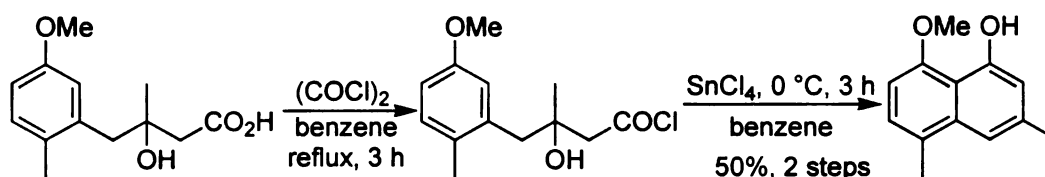
This beneficial effect of solvent-free conditions was partially supported by the reaction using SnCl_4 (entry 5) and TiCl_4 (entries 6-8) as promoters under neat conditions. Thus, while low yields of **16a** were afforded from the reactions at elevated temperatures under neat conditions (entries 5 and 6), no **16a** was detected when the reaction was carried out in CH_2Cl_2 with TiCl_4 (entries 7 and 8). Stronger Lewis acids like AlCl_3 were shown to be totally unsuitable for this transformation (entry 9); a complex mixture of unidentifiable compounds was obtained when the reaction mixture was maintained at 0 °C followed by warming up to ambient temperature.

To date, It is difficult to offer a plausible hypothesis as to why **27** is inferior in the Friedel-Crafts reaction; maybe in this case the need for the disruption of aromaticity during the electrophilic ring closure may tip the balance in favor of alternative processes, therefore accounting for the array of byproducts produced from the reaction of acid **27**. Such an argument could be supported by the observation that forcing conditions were usually required to promote the reaction. We reasoned that if acid **27** was converted to its acid chloride, the electrophilicity and reactivity could be enhanced and then the reaction might be more selective.

Although a literature survey revealed only a few reports⁶⁶ on the chemoselective cyclization of such β -hydroxyl acid chlorides, a promising report^{66c} described the use of a mild Lewis acid, more specifically, SnCl_4 to promote this transformation in moderate yields (Scheme 2.13). The application of the reported reaction protocol gave, in our case, **16a** as the major product in

moderate yield (entry 1, Table 2.13). One distinctive aspect of this reaction was the presence of various byproducts detected by TLC analysis. Notably, it was necessary to use an excess of Lewis acids to achieve reasonable yields of **16a**, and it was important to operate the reaction at low temperatures to minimize production of these byproducts.^{66c}

Scheme 2.13 The results of the cycloacylation reaction by Pakrashi^{66c}



The successful reaction with SnCl_4 prompted the exploration of more conditions for this reaction. Since PPA was workable for the cycloacylation of acid **27**, it was natural to employ it in this reaction in the presence of POCl_3 (entry 2, Table 2.13). This compound functioned as solvent as well as reagent to generate the acid chloride *in situ*. Unfortunately, only trace **16a** was detected by TLC together with a complex mixture of unidentifiable byproducts. $\text{BF}_3 \cdot \text{OEt}_2$, on the other hand, facilitated the reaction to produce **16a** in modest yield (entry 3).

Table 2.13 The Lewis acid facilitated cycloacylation of the acid chloride from **27**

Entry	27 (mmol) ^a	Lewis acid	Solvent ^b	Conditions ^c	16a ^d (%)
1	4.7	SnCl_4	Benzene	0 °C, 3 h	51.2
2	0.66	POCl_3 ^e	PPA ^f	Reflux for 1 h	Trace ^g
3	2.37	BF_3	CH_2Cl_2	0 °C, 3 h	38.8
4	2.35	AlCl_3	CH_2Cl_2	0 °C, 3 h; rt overnight	6.84
5	2.50	ZnCl_2	CH_2Cl_2	0 °C to rt, 12 h; reflux 4 h	6.4
6	2.5	FeCl_3	CH_2Cl_2	0 °C to rt, 12h; reflux 0.5 h	Trace ^g
7	2.5	TiCl_4	CH_2Cl_2	0 °C, 3 h; rt overnight	47.3

^a To prepare the acid chloride, (COCl)₂ (12.4 eq) in 40 mL benzene was used. For experimental details, see Section 7.2.2.3 of Chapter Seven. ^b Unless otherwise mentioned, 40 mL of solvent was used. ^c Conditions were not optimized, and the reaction was monitored by TLC. ^d Isolated yields after flash silica gel column. ^e 25 eq was used. ^f 20 grams. ^g Based on TLC.

Other Lewis acids were much less active in this reaction (entry 4-6, Table 2.13), and the FeCl₃-mediated reaction was not productive at all (entry 6). However, the most propitious results were obtained using TiCl₄ as promoter (entry 7). This reaction offered **16a** in a yield comparable to SnCl₄, and TLC inspection indicated that the starting material **27** was the only compound other than **16a** in the crude mixture. Evidently, the relatively low yield was due to incomplete conversion with TiCl₄; therefore these results suggest that this is promising for making further improvements to effectively deliver the VANOL monomer *via* this methodology.

2.3.4 Summary

To summarize, acid **27** was easily synthesized by the Reformatsky reaction with high efficiency from readily available starting materials. The cyclization of acid **27** and its corresponding acid chloride was effected by various Lewis acids to form the VANOL monomer **16a**. While this new synthetic strategy was evolved to make the original cycloacylation more efficient, the yields of the key step were routinely lower than anticipated. Furthermore, because of the potential downstream problems in the separation and purification of the desired **16a**, as well as cost and disposal concerns raised by the fact that the reaction appears likely to require the use of large amounts of Lewis acids, this approach lost its

simple appeal and was eventually abandoned. Nonetheless, this approach is viable and should be kept in mind for future applications and analog synthesis.

2.4 Concluding remarks on the linear (*de novo*) approaches to 16a

The synthetic strategies for the monomeric **16a** were initiated *via* condensation chemistry of a linear precursor to construct the fused aromatic ring system. They were not restricted to generating the substitution patterns dictated by directing groups on the aromatic ring. These routes were originally designed to make the synthesis of **16a** more efficient and adaptable to the large-scale preparation of VANOL. Indeed, most of the above processes were simple and high yielding. However, quite opposite to our anticipations, they were still not ideal for scaleup investigations, as they were relatively long (up to 5 steps), required special conditions like a large cooling bath. They needed an excess acid as well as expensive reagents (Pd/C). In the end, all of these *de novo* approaches were put on hold in favor of a radically redesigned and more modular preparation sequence described below.

2.5 Synthesis of 16a through carbocation rearrangement (Part I)

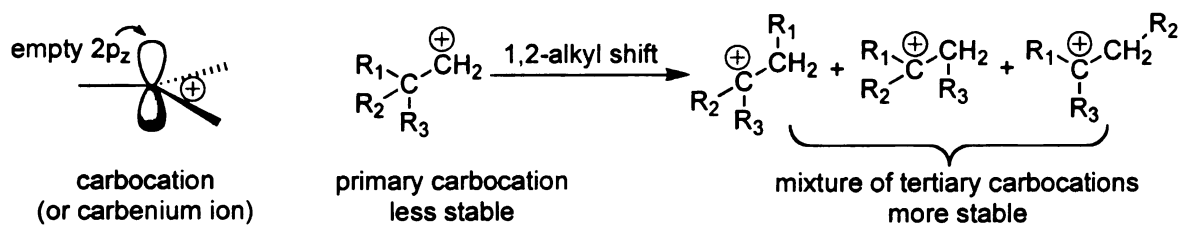
The examples presented above mainly focus on those methods that convert single ring benzene precursors into naphthalenes. They were generally efficient enough to provide the VANOL monomer **16a** with acceptable overall yields. More importantly, since the substitution pattern of the aromatic product was determined by the structure of the starting materials, these *de novo* approaches circumvented the problems of regiochemical control of the conventional electrophilic aromatic substitution reaction.

However, these sequences involve cyclization steps that generally require forcing conditions and the oxidation states of the intermediates need to be adjusted to form the phenol functionality. Thus, if **16a** could be synthesized by the modification of a pre-existing naphthalene core *via* carbocation triggered rearrangement to install the desired *meta* relationship between the phenyl and hydroxyl groups,⁶⁹ then these undesirable steps could be eliminated from the synthesis once and for all. In addition, this would advantage to be taken of the great diversity of commercially available naphthalene derivatives in the preparation of VANOL in more concise synthetic routes.

2.5.1 Introduction to carbocation rearrangements

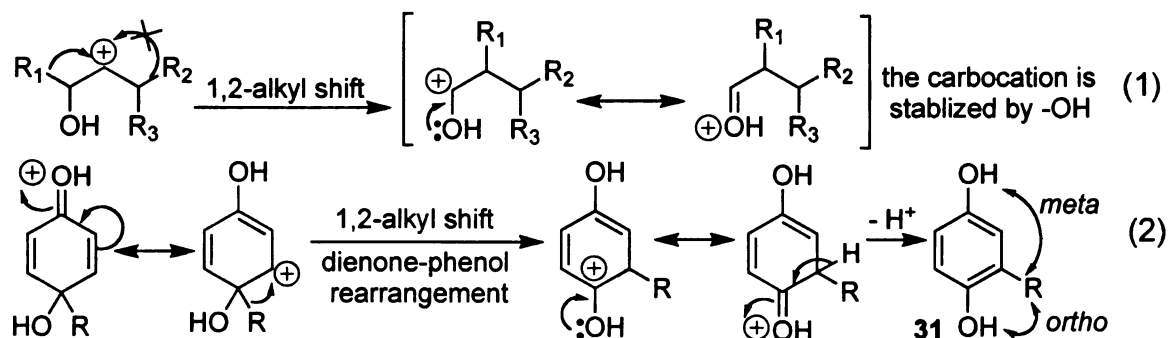
Carbocations are arguably the most important intermediates in organic chemistry,⁷⁰ which are generally credited to Norris^{70b} and Kehrman^{70b} for their discovery. Carbocations have an incomplete octet at carbon because it has only three shared electron pairs, which makes it very unstable and very reactive. Non-stabilized carbenium ions such as primary carbocations (Scheme 2.14) feature a large number of structural rearrangements that are triggered by their relatively high energies, which can be quickly released by migration of a group to form other more thermodynamically stable isomers. However, increasing the stability of carbocation intermediates is not the only driving force that leads to molecular rearrangement. If angle strain, steric crowding or even torsional strain in the reactant can be relieved by shifting certain groups to a carbocation site, such a rearrangement is commonly observed⁷¹ that may generate products with structures remarkably different from the starting compounds.

Scheme 2.14 Carbocation and rearrangement of carbocations



However, rearrangements involving carbocations can be complicated by various competing pathways (Scheme 2.14). This is because the differences in the barriers between migratory groups are usually low⁷¹ unless the structural situation favors a particular way. A good example of this is the rearrangement of a carbocation with a -OH group adjacent to it (Equation 1, Scheme 2.15). In this case the migration is particularly facile and selective since it generates a carbocation stabilized by the hydroxyl group. Such structural features can also be found in a cyclohexadienone system (Equation 2, Scheme 2.15), and the 1,2-shift in this case is referred to as 'dienone-phenol rearrangement'.⁷² This reaction has an additional driving force due to formation of a very stable aromatic system with the shift of a group to a position *meta* to one of the hydroxyl groups and *ortho* to the other (**31**, Scheme 15).

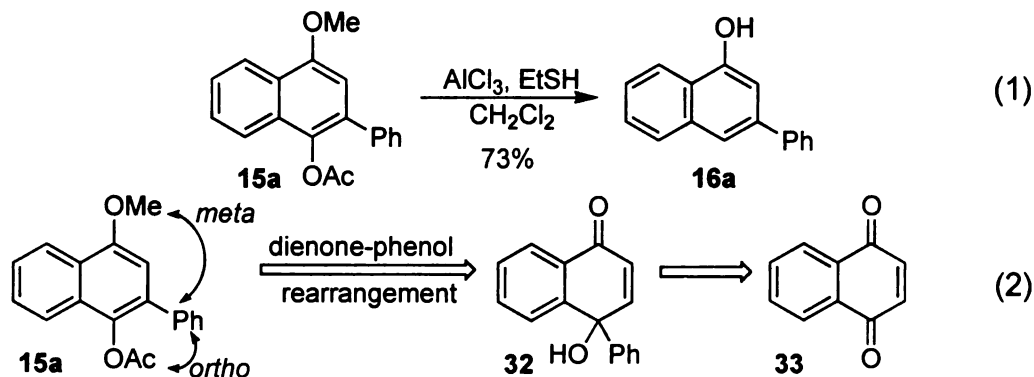
Scheme 2.15 Examples of selective carbocationic rearrangements



2.5.2 Synthesis of 16a by dienone-phenol rearrangement – retrosynthetic analysis

As illustrated in Scheme 1.7 in Chapter One, the VANOL monomer **16a** could be prepared by reduction of **15a** (equation 1, Scheme 2.16),^{17b} which was produced by the benzannulation of a carbene complex with phenylacetylene. Inspired by this process, a natural question that arose is whether other methods could be used to make intermediate **15a** more economically (Indeed, methods that could make ANY of the intermediates in these processes more efficiently should be considered!). Inspection of the structure of **15a** revealed that, as a 3-substituted naphthol, **15a** features a phenyl moiety *meta*- to one of the phenolic hydroxyl groups with another one *ortho*- to it (Equation 2, Scheme 2.16). As previously discussed (Scheme 2.15), this class of compounds could be easily accessed by a dienone-phenol rearrangement of a *para*-naphthoquinol derivative (i.e. **32**). The preparation of **32** was in turn envisioned as arising *via* addition of a suitable phenyl nucleophile to the naphthoquinone **33**.

Scheme 2.16 Retrosynthetic analysis of **16a** by dienone-phenol rearrangement



2.5.3 Introduction to dienone-phenol rearrangement

The acid and base catalyzed or photochemically induced migration of alkyl (or aryl)^{73a} groups in cyclohexadienones to give phenols (i.e. dienone-phenol rearrangement, Equation 2, Scheme 2.15) is an important reaction, used frequently for the aromatization of steroid derivatives.^{73b} The reaction is considerably exothermic due to the formation of very stable aromatic compounds.

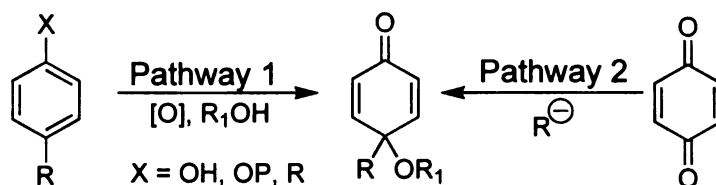
Mechanistically, the dienone-phenol rearrangement is typically acid catalyzed and therefore involves carbocation intermediates. Rearrangements of *para*-quinols occur under unusually mild conditions, since the hydroxyl group can stabilize a positive charge at C-4 owing to its electron-releasing property of its π -interactions. Due to the presence of a fused benzene ring, the rearrangements of 1,4-naphthoquinols only furnish 2-substituted-4-hydroxynaphthols *via* the migration of the geminal R residue to the vicinal carbon without perturbing the aromaticity of the fused ring. These effects make this pathway to **15a** appealing since it is anticipated to be a facile and selective process, free from harsh conditions and possible byproducts.

However, problems still exist. For example, the two hydroxy groups in the product have to be differentiated in order to selectively remove one of them in the following reduction reaction.^{17b,74} Success will also be highly dependent on the way the *p*-naphthoquinol is prepared, and this issue will be the subject of later discussion.

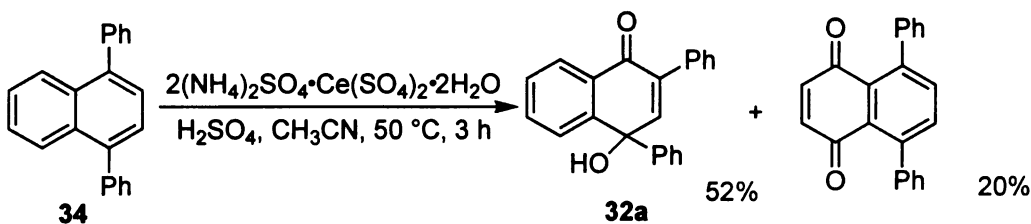
2.5.4 Synthesis of *p*-quinols: an overview

Having established the working hypothesis, it was then endeavored to synthesize 4-phenyl-1,4-naphthoquinol **32**.⁷⁵ There were two major pathways to generate *p*-quinols (Scheme 2.17), and the most common method involves the oxidation of a 1,4-disubstituted benzene species (pathway 1).⁷⁶ Singlet oxygen had been used extensively for this purpose, and in some cases, these reactions could be adapted to metal catalysis with hydroperoxide as the sacrificial oxidant. Other metal based oxidants have been used for this transformation including $\text{Pb}(\text{OAc})_4$, $\text{PhI}(\text{OAc})_2$ and $\text{Ti}(\text{NO}_3)_3 \cdot 3\text{H}_2\text{O}$. For instance, the synthesis of **32a** by oxidation of **34** using Ce(IV) species has been reported in moderate yield (Scheme 2.18).^{75a}

Scheme 2.17 General methodologies to prepare *p*-quinols



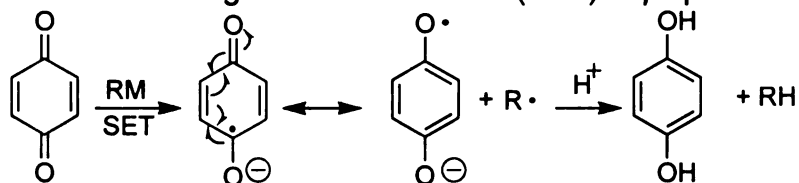
Scheme 2.18 Synthesis of **32** via oxidation of 1,4-diphenylnaphthalene (**34**)



The oxidative approach (Scheme 2.18) generally suffers from overoxidation owing to the destructive reagents that are used and thus this method is often complicated by various side reactions. In addition, analysis of the literature suggests that methods for the preparation of the requisite starting materials for

the synthesis of **32** are limited. Luckily, there are several other strategies for the preparation of *p*-quinols.^{76a} Among these, 1,2-addition to *p*-quinones (pathway 2, Scheme 2.17) is of great importance. This method involves the nucleophilic attack on one of the carbonyls of a *p*-quinone. While this reaction eliminates the need to install an oxygen atom *para* to the phenol, the desired addition of the carbon nucleophiles are normally overshadowed by the proclivity toward aromatization through reductive single electron-transfer (SET) process (Scheme 2.19),⁷⁷ particularly when bulky nucleophiles such as hindered organolithiums^{77b,c} or Grignard reagents^{77d} are used.

Scheme 2.19 Reductive single electron-transfer (SET) of *p*-quinone

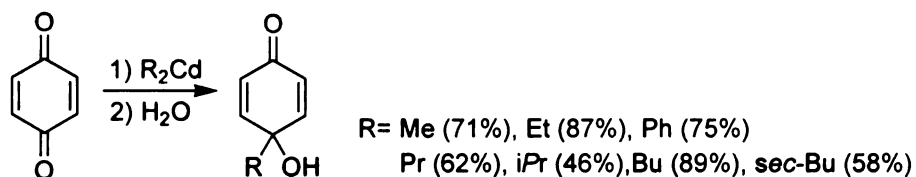


Therefore, other more circuitous methods have been developed to alleviate these problems, the most notable of which are cerium-mediated⁷⁸ additions and the employment of “masked quinones”^{79,76a} (quinone monoketals^{79a} and silylcyanohydrins^{79b,75b}) as methods for quinone alkylation. These methods require multistep procedures with less readily available starting materials, and this makes these protocols economically undesirable for the synthesis of VANOL.

One breakthrough in this field was the successfully employment of organocadmium reagents (Scheme 2.20).^{80d,e} Unlike their Grignard or organolithium counterparts, organocadmium reagents (R_2Cd) are known as mild yet efficient alkylation reagents capable of transferring both of alkyl and aryl

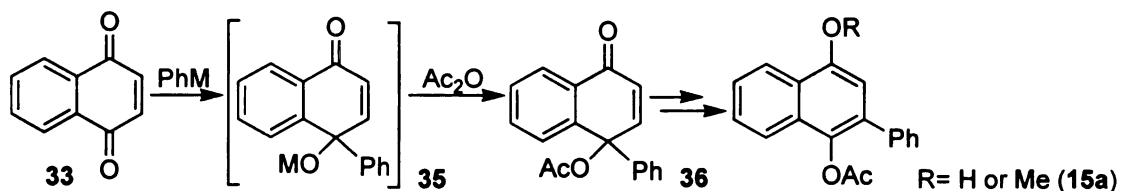
groups to quinone substrates with greater chemoselectivity^{80a,b} and regioselectivity.^{80c}

Scheme 2.20 Synthesis of quinols *via* quinone alkylation using R₂Cd reagents



To access the VANOL monomer **16a** *via* this strategy (Scheme 2.16), direct alkylation of 1,4-naphthoquinone (**33**) provides the most straightforward method. The major concern with this synthesis is the lack of methods to distinguish appropriately between the two resultant hydroxyl groups.^{17b} It was sensed that upon formation of the intermediary *p*-naphthoquinol **35**, it should be possible to intercept the hydroxyl to form acetyl ester **36**.^{61e} This should make it possible to effect the proper downstream functionality conversions (such as **15a**) to allow selective removal the hydroxyl vicinal to the phenyl group. These aspects prompted a study of the preparation of VANOL through this dienone-phenol rearrangement pathway (Scheme 2.21).

Scheme 2.21 Proposed synthesis of **36** *via* alkylation of quinone **33**



2.5.5 Synthesis of **37** *via* nucleophilic 1, 2-addition to **33**

Although the addition of PhLi to a mono protected naphthoquinone is known,⁷⁹ no reports of the direct addition of PhLi or PhMgX to 1,4-naphthoquinone was found from a SciFinder search. The fact that a variety of

alkyl groups had been effectively transferred to this substrate by organocadmium reagents^{80d,e} encouraged an examination of the addition of a phenyl group to 1,4-naphthoquinone **33** (Scheme 2.21) under similar conditions and the results are summarized in Table 2.14.

The viability of this process was first examined by reacting **33** with PhMgBr since PhMgBr is directly accessible from commercial vendors. This reaction was performed at $-78\text{ }^{\circ}\text{C}$ since hydroquinones have been reported to be the primary product at elevated temperatures.^{77d} Aqueous work-up gave a dark blue solution which quickly turned into an insoluble black complex mixture upon exposure to air (entry 1, Table 2.14). Several products were detected by TLC and one of them was later confirmed to be biphenyl. All attempts to completely separate and purify the byproducts failed. Some of the products seemed very sensitive to oxidation as they quickly changed to a dark-colored material that was insoluble in ether. Exposing **33** to the Ph_2Cd under the same conditions as described by Wigal^{80d} for alkyl cadmium reagents did not result in any appreciable addition product **32** (entry 2, Table 2.14).

Table 2.14 Synthesis of **32** by nucleophilic addition to 1,4-naphthoquinone

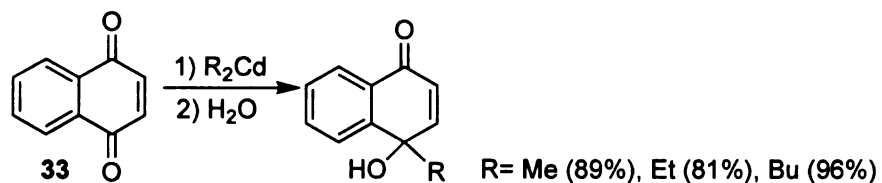
The reaction scheme shows 1,4-naphthoquinone (**33**) reacting with PhMX to form an intermediate in brackets, which is then treated with H₂O to yield product **32**.

Entry	PhMgBr (eq)	CdCl ₂ (eq)	Conditions ^a	32 ^b (%)
1	I ^c (1.0)	0	$-78\text{ }^{\circ}\text{C}$, 30 min	nd
2	I ^c (2.0)	1.0	$-10\text{ }^{\circ}\text{C}$, 1 h; $50\text{ }^{\circ}\text{C}$, 1 h; $25\text{ }^{\circ}\text{C}$, 12 h	nd
3	II ^d (1.0)	0	$-78\text{ }^{\circ}\text{C}$, 30 min	nd
4	II ^d (2.5)	1.4	$-10\text{ }^{\circ}\text{C}$, 1 h, reflux 12 h	nd

^a Not optimized; For experimental details, see Section 7.2.3 of Chapter Seven. ^b nd= not detected. ^c PhMgBr in ether solution (3M, not titrated) was bought from Sigma-Aldrich Company. ^d Made from PhBr and Mg in THF.

The results in entry 2 of Table 2.14 was different to the observations made by the Wigal, who claimed that various dialkylcadmium reagents had been successfully added to naphthoquinone with high yields (Scheme 2.22). The reaction in entry 2 was not complete even after extended time at elevated temperature as indicated by existence of **33** on TLC. Not knowing the quality of the commercial Grignard reagent,²⁵ PhMgBr freshly prepared from PhBr and Mg was subjected to the same conditions as entry 1 (entry 3, Table 2.14). However, the reaction failed to produce a detectable product according to TLC analysis. Next, Ph₂Cd generated from the freshly made Grignard reagent was examined (entry 4, Table 2.14), but this reaction only resulted in a partial conversion of **33** as indicated by TLC. Much to our delight, complete consumption was observed after refluxing the reaction overnight; yet, all attempts to separate the product failed, and it was observed that upon chromatographic separation, the crude mixture did not elute through column (entry 4).

Scheme 2.22 Nucleophilic alkylation to 1,4-naphthoquinone **33** by R₂Cd

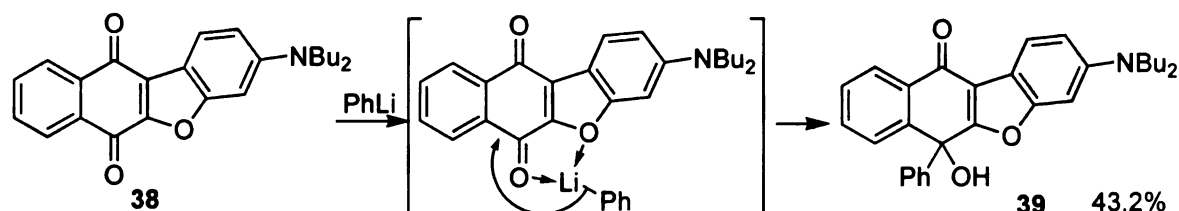


It is known that the addition of organometallic reagents to quinones produces not only quinols but also hydroquinone as a by-product which results from competitive reduction of the quinoid skeleton by organometallic reagents by

electron transfer processes.⁷⁷ Thus, the reaction of phenyl Grignard reagent with **33** gave a highly polar complex mixture, and this may have resulted from the decomposition of the electron-rich hydroquinone which in turn was produced by reductive single electron-transfer processes. The partial consumption of naphthoquinone using Ph_2Cd reagent, on the other hand, presumably resulted from the elevated steric hindrance, which prevented it from approaching 1,4-naphthoquinone and led to incomplete conversions.

Yoshida⁸¹ effectively transferred a phenyl group to the naphthoquinone derivative (**38**) using PhLi *via* 1,2-addition in the course of study of heterocyclic quinol-type fluorophores (Scheme 2.23). The major product was **39**, albeit in low yield. Hence, given proper control of the conditions, the formation of the VANOL monomer **16a** *via* this route can not be completely dismissed.

Scheme 2.23 Nucleophilic alkylation of PhLi to 1,4-naphthoquinone derivative **38**



2.5.6 Summary of dienone-phenol rearrangement

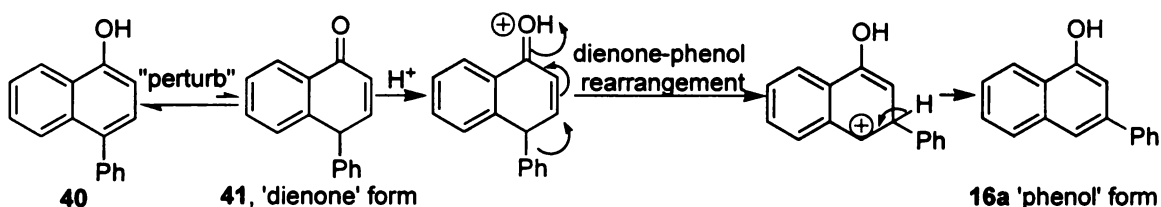
Alkylation of the quinone nucleus by organometallic reagents represented a direct route toward the synthesis of various quinols. Upon exposure to acid, these compounds would readily rearrange to 2-substituted-1, 4-dihydroxy aromatic compounds.⁷² In our hands, however, in contrast to the closely related alkyl analogues,^{80d} 1,2- addition of phenyl nucleophiles to naphthoquinone did

not proceed as anticipated, which was seriously deteriorated by side-reactions and incomplete conversions. While the reaction was potentially susceptible to various modifications for further improvement of its efficiency, these drawbacks together with high toxicity of organocadmium compounds demonstrated to us the unviability of this route to VANOL ligand. Therefore, this otherwise very promising method was given up and other modified routes were explored to prepare the VANOL monomer **16a**.

2.6 Synthesis of **16a** through carbocation rearrangement (Part II)

Although the above route involving a dienone-phenol rearrangement did not produce the desired monomer **16a**, it served to direct consideration to a related strategy. In the plan for the failed approach to **16a** using the dienone-phenol rearrangement, an interesting structural feature of the dienone was discerned. Thus, if it was possible to “perturb” 1-naphthol derivatives such as **40** into the “dienone” form **41** (i.e. keto form, Scheme 2.24),⁸² then in the presence of acid, in principle, a 1,2-shift could occur to furnish 3-phenyl-1-naphthol **16a** (“phenol form”, Scheme 2.24).

Scheme 2.24 Proposed dienone-phenol type rearrangement of “perturbed” **40**



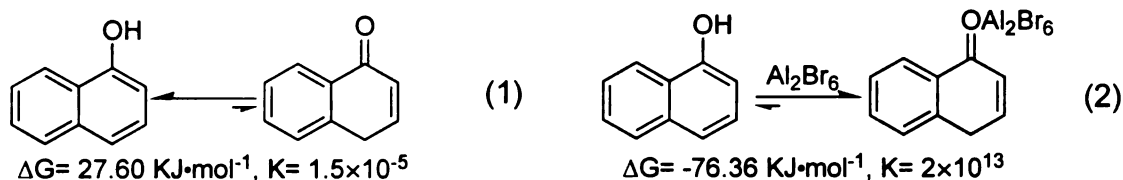
2.6.1 Preparation and rearrangement of 4-phenyl-1-naphthol: the ideas

Many mechanistic speculations have been advanced to explain the details of reactions based on the keto tautomers of phenols as reactive intermediates, and

examples include the Claisen rearrangement,⁷¹ the Kolbe-Schmitt⁷² and Reimer-Tiemann reactions.⁷²

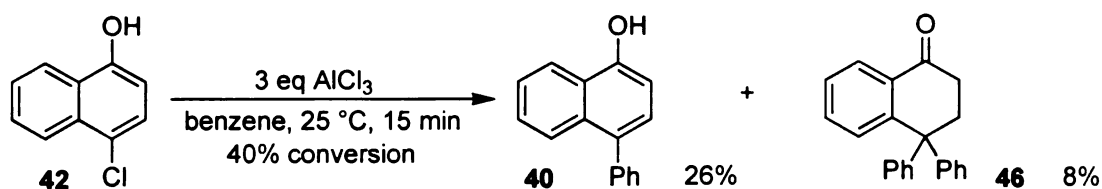
Owing to its extreme instability (Equation 1, Scheme 2.25), however, direct detection of this highly reactive species is rare. Important advances in this context have been accomplished in recent years by a number of research teams.⁸³ For instance, it has been suggested that when 1-naphthol is exposed to Lewis acids such as AlBr_3 , the tautomeric keto form will dominate the enol (Equation 2, Scheme 2.25).^{83a,b}

Scheme 2.25 Tautomerization of 1-naphthol with or without AlBr_3 ^{83b}



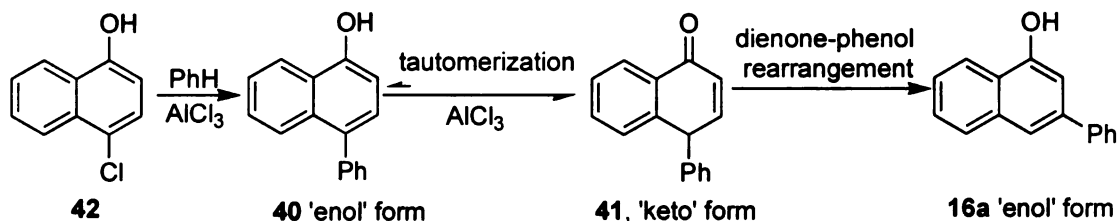
With known methodologies for the tautomerization of 1-naphthol into its dienone form, attention was then turned to the preparation of 4-phenyl-1-naphthol. *Para*-substitute phenols have been readily prepared by electrophilic aromatic substitution reaction.⁷¹ At the time this work was started, however, no convenient synthesis of 4-phenyl-1-naphthol was available. A survey of the literature turned up an interesting study by Koptug and coworkers,^{84,95b,c} who reported that 4-chloro-1-naphthol **42** reacted with benzene in the presence of acids to give **40** in low yields during the course of studies on trapping of protonated phenols by aromatics in the presence of acids (Scheme 2.26).

Scheme 2.26 Synthesis of **40** from **42** in the presence of AlCl_3 ⁸⁵



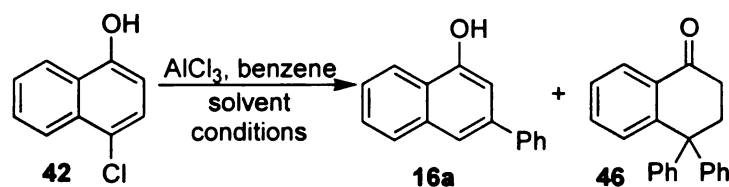
Based on these precedented observations, the VANOL monomer 3-phenyl-1-naphthol **16a** might be prepared by sequential alkylation-migration process (i.e. condensation, Scheme 2.27) of the easily accessible **42** because both steps required the mediation from strong Lewis acids such as AlCl_3 .^{85,88f}

Scheme 2.27 Synthetic plans of the VANOL monomer **16a** from **42**



2.6.2 Synthesis of 16a by condensation of 42 with benzene

At the outset, it was deemed essential to establish the general applicability of this single-step method. Thus, the reaction of 4-chloro-1-naphthol (**42**) was examined with 2.3 equiv of AlCl_3 using benzene as solvent (entry 1, Table 2.15).^{88e} We were pleased to find that at room temperature the reaction provided the desired naphthol **16a** in 57.2% yield, accompanied by a large amount of a byproduct that was later determined to be 4,4-diphenyl-1-tetralone (**46**). At this stage, it was considered that the formation of **16a** via this pathway was at least equally competitive to the methods described above, because it involved only one step from a commercially available starting material. More importantly, although the yield is moderate, this was only the first attempt.

Table 2.15 Optimization of the reaction of **42** with benzene

Entry	42 (mmol)	Solvent ^a (mL)	AlCl ₃ (eq)	Conditions	16a (%) ^g	46 (%) ^g
1	4	benzene	2.30	25 °C, 1 h	57.2	45.4
2	4	benzene	2.30	25 °C, 1 h with HCl	51.5	48.1
3	4	CH ₂ Cl ₂ , 15 ^b	2.47	25 °C, 1 h	Messy	- ^c
4	4	PhNO ₂ , 15 ^b	2.35	25 °C, 1 h	Messy	- ^c
5	4	benzene	2.41	0 to 25 °C, 1 h ^d	Mixture ^e	- ^c
6	3.2	benzene	3.07	80 °C, 1 h	89.9	nd ^f
7	5	benzene	2.02	80 °C, 1 h	90.1	nd ^f

^a Unless otherwise specified, all reactions were performed in 20 mL benzene. For experimental details, see Section 7.2.4.4 of Chapter Seven. ^b Volume of benzene was 1 mL. ^c Workup was not performed. ^d The reaction was kept at 0 °C for 30 min before warming up to 25 °C for another 30 min. ^e It was later isolated and then refluxed with benzene and 2.4 eq AlCl₃ for 1h, from which 86.7% of **16a** was obtained. ^f nd= not detected. ^g Isolated yields by column chromatography.

Having demonstrated the viability of the one-pot condensation process, the next goal became to improve the selectivity and the yield of naphthol **16a**. Based on the working hypothesis, it appeared that the acidic conditions were essential to ensure effective 1,2-alkyl migration;⁸⁴ therefore, the reaction was repeated with a continuous stream of dry HCl slowly infused into the flask to help drive the reaction to completion.⁸⁴ However, it was quite disappointing to find no improvement in yield (Table 2.15, entry 2). Another observation was that the mixture of **42** with AlCl₃ did not dissolve completely in benzene; it was conjectured that the poor solubility might sufficiently deteriorate the efficiency. Therefore, the reaction was performed using CH₂Cl₂ as co-solvent to address

this issue (entry 3). However, a complicated mixture formed as indicated by the $^1\text{H-NMR}$ spectrum. Switching the solvent to PhNO_2 (entry 4), a homogenous solution formed; but the $^1\text{H-NMR}$ and TLC analysis of the crude mixture confirmed the absence of desired product **16a**. This and the fact that PhNO_2 is toxic and hard to remove convinced us not to proceed with this solvent.

With these new data in hand, the initial reaction in entry 1 was re-examined for the effects that temperature would have when benzene was the solvent. The reaction failed to produce pure **16a** when it was started at $0\text{ }^\circ\text{C}$ followed by warming up to ambient temperature (entry 5, table 2.15). Instead, a mixture was obtained with a complex $^1\text{H-NMR}$ spectrum. It was thought that the formation of arenium ion intermediates requisite for migration results in the temporary loss of aromaticity and thus would generally requires a high activation energy.⁸⁶ In other words, a higher temperature might better promote the reaction. In congruence with this hypothesis, treatment of substrate **42** with 3.1 equiv of AlCl_3 in refluxing benzene followed by acid workup dramatically improved the outcome (entry 6), giving the VANOL monomer **16a** in 89.9% isolated yield. To test its reliability, the reaction was repeated under the same conditions and the identical yield of **16a** was afforded free of any detectable **46** (entry 7). Additionally, the mixture from the reaction in entry 4 was also converted to **16a** in high yield (see: note e).

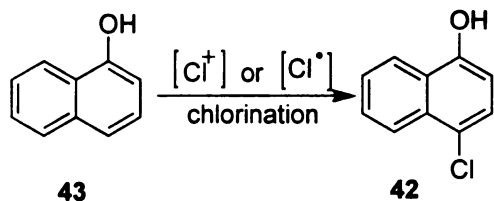
Fortuitously, the features of the condensation reaction made this methodology unexpectedly straightforward: First, all the starting materials could be obtained from inexpensive feedstocks; second, the reaction was performed in refluxing

benzene and was not particularly air and moisture sensitive. Finally, the phenomenally high yield of the reaction made isolation and purification very easy.

2.6.3 Optimization of the chlorination of 1-naphthol

Having established the feasibility of this fundamentally new route to VANOL summarized in Scheme 2.27, efforts were made to develop this into a large-scale synthesis. While **42** is commercially available, its cost is relatively expensive²⁵ and may be prohibitive for a large-scale synthesis. Thus a program was subsequently undertaken to investigate the preparation of compound **42** since very little has appeared in the modern literature on the synthesis of this compound (Scheme 2.28).⁸⁸

Scheme 2.28 Preparation of **42** by chlorination of 1-naphthol **43**



Chlorine substituted naphthols have been the subject of synthetic investigations for decades and some methods have been developed.⁸⁷ Exemplarily, Kast^{88a} reported the synthesis of **42** almost a century ago, but its potential in synthesis has remained unexplored to date. The straightforward method for the synthesis of this compound is chlorination of 1-naphthol by chlorinating agents (Scheme 2.28).⁸⁸ Examples of such agents that have been used include SO₂Cl₂,^{88a} 2,3,4,4,5,6-hexachloro-2,5-cyclohexadiene-1-one,^{88c} *N*-chlorosuccinimide (NCS),^{88d} and chlorine gas.^{88c,f} Preferably, the chlorinating agent of choice would be SO₂Cl₂ as it is effective,^{88a,b} cheap and convenient to handle owing to the easy removal of gaseous byproducts.⁸⁹ Since the

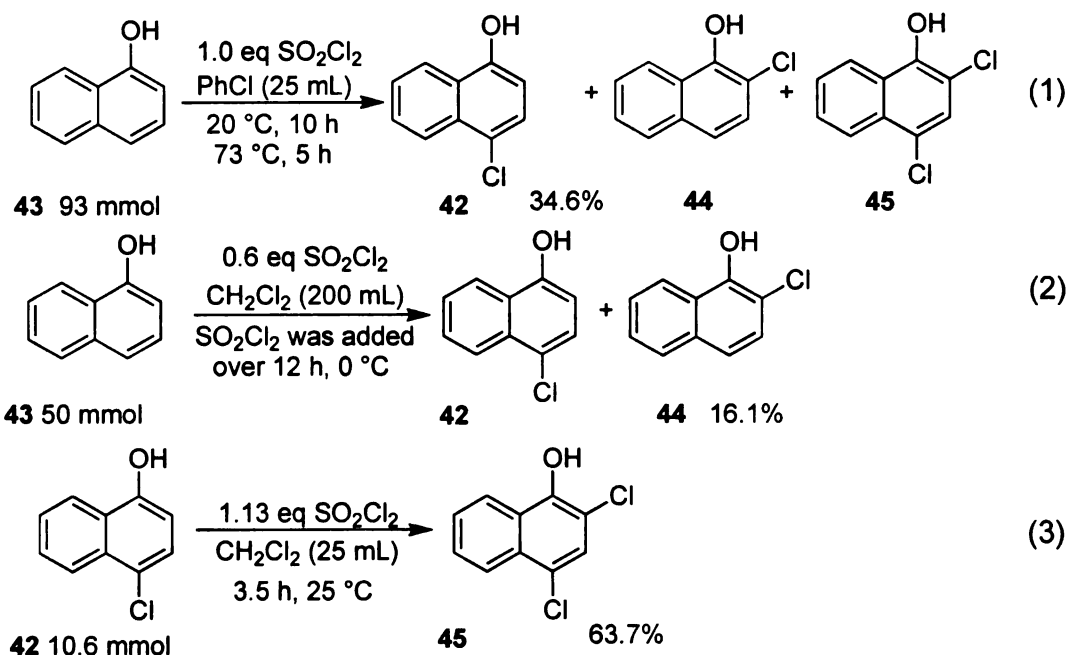
achievement of high material throughput in the synthesis of **42** is key to securing large quantities of VANOL, it was decided to investigate the syntheses of **42** by chlorination of 1-naphthol using SO_2Cl_2 .

The chlorination of **43** with SO_2Cl_2 has been carried out on industrial scales^{88e} under the conditions described in entry 1 of Table 2.16. This reaction was reported to prepare 250 kg of **42** by treatment of 500 kg of **43** in 1290 kg of PhCl with 470 kg (1 equiv) of SO_2Cl_2 . The reaction was repeated on 25 mmol scale under these conditions and the results are shown in entry 2, Table 2.16. Thus, a low yield of **42** was obtained as needle-like crystals, together with a small amount of 2-chloronaphth-1-ol **44** as isomeric byproduct and with 2,4-dichloronaphth-1-ol **45** as an overreacted byproduct (Equation 1, Scheme 2.29). However, these two byproducts were not described in the industrial procedures.^{88e} All attempts to completely separate these two byproducts from each other failed due to their extremely similar properties.

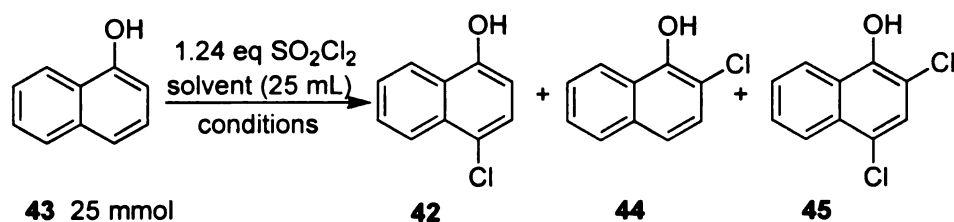
To confirm the identity of the three products from this reaction and to develop analytical methods for quantifying the amounts present in reaction mixtures, methods were developed for the selective synthesis of isomers **44** and **45**.^{88e} Isomer **44** was obtained in pure form by chlorination at low temperature with only 0.6 equiv of SO_2Cl_2 , which was added slowly to the highly diluted **43** in CH_2Cl_2 over 12 h (Equation 2, Scheme 2.29. For experimental details, see Section 7.2.4.2 of Chapter Seven). Under these conditions, the dichlorinated byproduct **45** could be successfully suppressed, and **44** was isolated in pure form in 16.1% yield. The dichlorinated byproduct **45** was prepared by reacting pure **42** with

SO₂Cl₂ (Equation 3, Scheme 2.29. For experimental details, see Section 7.2.4.3 of Chapter Seven).

Scheme 2.29 Preparation of **42**, **44** and **45** by chlorination reactions



Although the yield of **42** was essentially the same (entries 1 and 2, Table 2.16), the reaction was found not to go completion under the published conditions and the crude reaction mixture was found to be a 100:39:4 mixture of **42**, **44**, **45**, respectively. To speed it up and drive the reaction to full conversion, the reaction was run in different solvents under refluxing conditions with a slight excess of SO₂Cl₂. Refluxing chloroform^{88a} did not lead to an improved yield of **42** (entry 3). In contrast to the industrial conditions in chlorobenzene, the intended product **42** was produced in higher yield when CH₂Cl₂ was used as the solvent (entry 4), while in refluxing 1,2-dichloroethane (DCE, entry 5) a tarry mixture was obtained.

Table 2.16 Solvent effects on the syntheses of **42** by chlorination of **43**

Entry	Solvent	Conditions ^a	42 : 44 : 45 ^b	Conversion ^b (%)	42 ^c (%)
1 ^e	PhCl	20 °C, 10 h; 73 °C, 5 h	-	-	40
2	PhCl	20 °C, 10 h; 73 °C, 5 h	100: 39: 4	78.6	34.6
3	CHCl ₃	Reflux, 3.5 h	100: 65: 19	96	42.0
4	CH ₂ Cl ₂	Reflux, 3.5 h	100: 29: 21	96.7	53.0
5	DCE	Reflux, 3.5 h	100: 50: 10	92	- ^d
6	benzene	Reflux, 3.5 h	100: 128: 18	85	27.0
7	DMF	85 °C, 3.5 h	Messy ^d		
8	THF	25 °C, 3.5 h	Messy ^d		
9	Ether	25 °C, 3.5 h	Messy ^d		
10	CH ₃ CN	25 °C, 3.5 h	Messy ^d		

^a SO₂Cl₂ was added over 3 h. For experimental details, see Section 7.2.4.4 of Chapter Seven. ^b

Based on integration of the 2-H proton for **42** and **43**, and the OH proton for **44** and **45**. ^c Isolated yields by crystallization from hexanes and CH₂Cl₂. ^d A tarry crude product formed and no desired product was isolated. ^e Data from reference 88e.

Non-chlorinated solvents were also tested; they were either less effective (benzene, entry 6) or reacted with SO₂Cl₂ (entry 7 to 10). In the other chlorinated solvents tested (entry 2), the desired product was still formed, albeit in somewhat diminished yields compared to the optimal outcome in CH₂Cl₂.

Unexpectedly, the rate of addition of SO₂Cl₂ to the CH₂Cl₂ solution of 1-naphthol had an enormous impact on the selectivity for the desired 4-chloronaphth-1-ol product **42**. A significant increase in yield (from 46.9 to 64.6%, Table 2.17, entry 1 and 2, respectively) was observed when SO₂Cl₂ was added all at once.

The increase in selectivity might be attributed to kinetically favored attack at the α -position of the naphthalene nucleus, which reflects a preference for generating a cationic intermediate that maintains one intact benzene ring.⁷¹ This suggests that temperature may be important in controlling selectivity and this will be addressed below. It was found that the reaction could be scaled up under these conditions to give **42** without loss of yield (entry 3); however, the concomitant violent release of heat and gaseous waste discharge at this temperature made it practically unsuitable for large-scale preparation of **42** due to safety concerns alone.

Table 2.17 The effect of the rate of addition of SO₂Cl₂ on the chlorination of **43**

	43	42	44	45	
Entry	43 (mmol)	Conditions to add SO ₂ Cl ₂ ^a	42 : 44 : 45 ^b	Conversion ^b (%)	42 ^c (%)
1	25.0	Over 3 h	100: 76: 35	100	46.9
2	25.0	All at once	100: 36: 13	97.4	64.6
3	126.5	All at once	100: 32: 8	97.9	66.7
4	25.1	Over 3 h ^d	100: 28: 5	93.7	62.8

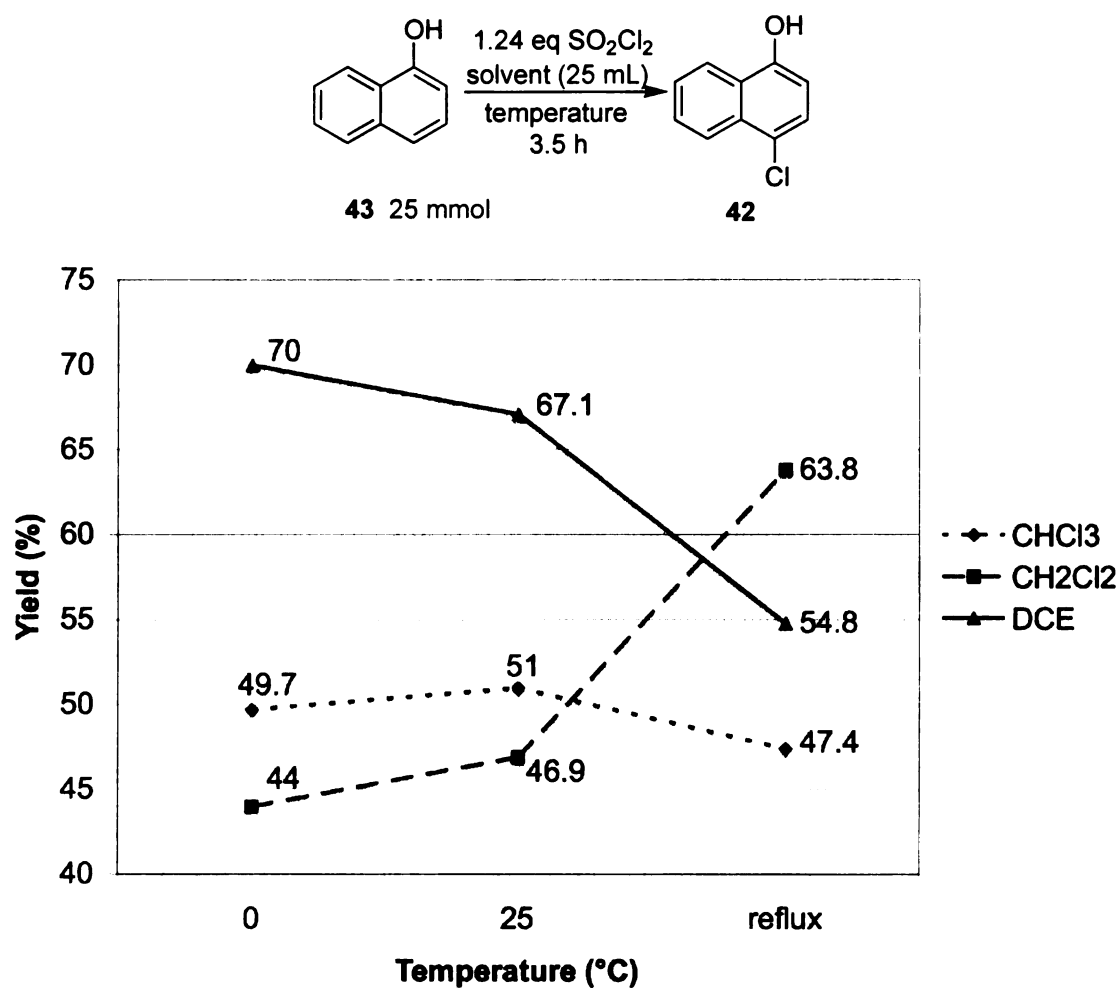
^a After addition of SO₂Cl₂, the reaction was held for 0.5 h. ^b Based on integration of the 2-H proton for **42** and **43**, and the OH proton for **44** and **45**. ^c Isolated yields by crystallization from hexanes and CH₂Cl₂. ^d Under reflux with 2 g of silica gel.

To enhance the reactivity, we also investigated the effects of additives on the reaction.^{89,90} Hojo and Masuda⁹¹ reported that when SO₂Cl₂ was used as chlorinating agent in refluxing CCl₄, anisole could only be chlorinated in conjunction with silica gel and did so in almost quantitative yield. Indeed, when

the reaction of SO_2Cl_2 with **43** was conducted in CH_2Cl_2 in the presence of silica gel, it was found the yield (62.8%, entry 4, Table 2.17) of **42** was improved from 46.9% in its absence (entry 1, Table 2.17). This was comparable to the yield achieved by the protocol of adding SO_2Cl_2 all at once (64.6%). At the present time, no tenable explanation is available for the enhancement of selectivity in the presence of silica gel. Perhaps the silica gel contributes to the polarization of SO_2Cl_2 and a heterolytic dissociation of SO_2Cl_2 into Cl^+ ,⁹² which interacts with **43** in an electrophilic substitution reaction with improved selectivity. Because zeolites are well-defined microporous materials with a large diversity of composition and structure, it may be useful in the future to examine their effects on the chlorination of **43**.

Next, the influence of temperature on the reaction was examined in different solvents.⁹⁰ The effects of these solvents were studied at reflux, 25 °C and at 0 °C. This survey of temperatures and solvents is illustrated graphically in Figure 2.1. It was discovered that while no significant change in yield of **42** occurred in CHCl_3 when the temperatures was varied, an increase in the temperature led to the formation of **42** in higher yields in CH_2Cl_2 . Interestingly, in 1,2-dichloroethane (DCE) the temperature effects were reversed from those in CH_2Cl_2 with the highest yield of **42** occurred at lower temperature, and DCE was superior to the other solvents at all temperatures tested.

Figure 2.1 Temperature effects on chlorination of **43** in different solvents



Entry	Solvent	Temperature (°C)	42 : 44 : 45 ^a	Conversion (%) ^a	42 (%) ^b
1	CHCl ₃	0	100: 76: 12	89.1	49.7
2		25	100: 70: 13	91.0	51.0
3		Reflux (61)	100: 44: 8	89.3	47.4
4	CH ₂ Cl ₂	0	100: 48: 13	99.0	44.0
5		25	100: 76: 35	100	46.9
6		Reflux (40)	100: 29: 21	96.7	63.8
7	DCE	0	100: 26: 7	93.4	70.0
8		25	100: 21: 7	93.0	67.1
9		Reflux (83)	100: 15: 5	91.1	54.8

^a Based on integration of the 2-H proton for **42** and **43**, and the OH proton for **44** and **45**. For experimental details, see Section 7.2.4.1 of Chapter Seven. ^b Isolated yields by crystallization from hexanes and CH₂Cl₂.

It was reported that at elevated temperatures, SO_2Cl_2 decomposes into SO_2 and Cl_2 , the latter being a much less *para*- / *ortho*- selective chlorinating^{88c} agent due to its high reactivity and smaller size.^{89b} Presumably, the high 4-Cl/2-Cl isomeric ratio observed in the chlorination of 1-naphthol in DCE could be attributed to the solvent's higher polarity⁹³ which may facilitate heterolytic dissociation of SO_2Cl_2 into Cl^+ and SO_2Cl^- , which may favor electrophilic substitution at the *para*- position in contrast to a less selective radical substitution process.^{93b}

Based on the observation that the yields were sensitive to the rate of addition of SO_2Cl_2 in CH_2Cl_2 where a greater rate favored higher yields (Table 2.17), the same protocol was subsequently employed in the reaction in DCE (Table 2.18).⁹⁰

Table 2.18 The effects of the rate of addition of SO_2Cl_2 to synthesize **42** in DCE

c1ccc2cc(O)ccc2cc1 (43, 25 mmol) $\xrightarrow[\text{temperature conditions}]{1.24 \text{ eq } \text{SO}_2\text{Cl}_2, \text{DCE (25 mL)}}$
Clc1ccc2cc(O)ccc2cc1 (42) + Clc1ccc2cc(O)ccc2cc1 (44) + Clc1ccc2cc(O)c(Cl)ccc2cc1 (45)

Entry	Temp. (°C)	Conditions to add SO_2Cl_2 ^a	42: 44: 45 ^b	Conversion ^b (%)	42 ^c (%)
1	0	Over 3.5 h	100: 20: 9	97	60.3
2		All at once	100: 19: 7	98.4	69.7
3	25	Over 3.5 h	100: 21: 7	93.4	67.1
4		All at once	100: 24: 18	99.3	66.2

^a After addition of SO_2Cl_2 , the reaction was held for 0.5 h. ^b Based on $^1\text{H-NMR}$ spectrum. ^c

Isolated yields by crystallization from hexanes and CH_2Cl_2 .

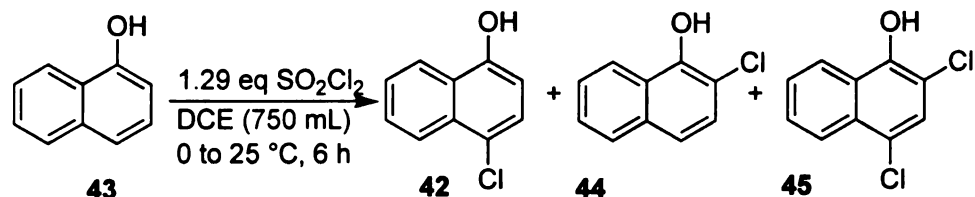
As a matter of fact, the yields did improve when the reaction was run at 0 °C if all of SO_2Cl_2 was added all at once (entry 1 versus entry 2, Table 2.18); yet the effect was not as substantial as in CH_2Cl_2 particularly at room temperature (entry 3 and 4, respectively). This might be the result of a compromise in different

selection factors during addition when DCE is solvent. As formerly mentioned, fast addition sets off a quick-release of gas and heat that raises safety concerns. Consequently, it was decided to go forward with the large-scale synthesis of **42** at 0 °C by slow addition of SO₂Cl₂ to a DCE solution of 1-naphthol.

2.6.4 Preparation of 4-chloro-1-naphthol **42** on large scale

With many of the crucial parameters defined, the chlorination reaction under conditions given in the entry 1 of Table 2.18 was then repeated on large scale to test the technical operability and chemical efficiency (Table 2.19). Clearly, the reaction is capable of reliably delivering **42** in good yields on up to 120 g of 1-naphthol **43** (entry 5).

Table 2.19 Preparation of 4-chloro-1-naphthol **42** on large scale in DCE



Entry	43 (g)	Conditions ^a	42 : 44 : 45 ^b	Conversion ^b (%)	42 (%) ^c
1	60.7	0 °C, 6 h; 25 °C, 1h	Not determined		62.8
2	100.4		100: 20: 5	100	75.5
3	100.4	0 °C, 3.5 h; 0 to 25 °C, 2 h; 25 °C, 0.5 h	100: 20: 6	96.2	71.8
4	102.0		Not determined		70.2
5	120.0 ^d		Not determined		73.0

^a SO₂Cl₂ was added over 3 h. For experimental details, see Section 7.2.4.1 of Chapter Seven. ^b

Based on ¹H-NMR spectrum. ^c Isolated yields by crystallization, and then column chromatography on the mother liquor. ^d 900 mL DCE was used.

2.6.5 Summary for chlorination of 1-naphthol

Naphthol **42** has been known in the literature for a century.^{88a} However, in practice the synthesis of this compound was not examined in detail, especially in regard to optimization of the regioselectivity. Conceptually, the most

straightforward method for the preparation of **42** was chlorination of the readily available 1-naphthol. To the best of our knowledge, this was the first systematic investigation of chlorination of 1-naphthol using SO_2Cl_2 .⁸⁸ Upon a detailed look at this reaction, it was discovered that solvent and temperature have a dramatic effect on the reaction profile with DCE being overwhelming solvent of choice. In most other solvents the reaction failed to yield **42** in close to the same yield. The best yield was obtained in DCE at 0 °C and it was this same temperature that provided the product in the greatest state of purity. These conditions proved to be reliable upon scale-up, and have been successfully applied to the large-scale preparation of VANOL and provided a cost-effective way to access this ligand.

2.6.6 Preparation of the VANOL monomer **16a** on large scale

With enough starting materials in hand and with the optimum conditions defined, the next phase was to explore the synthesis of **16a** on large scale and the isolated yields of **16a** are summarized in Table 2.20. The byproduct **46** was not isolated from these reactions, but it was obtained from small-scale reactions (Table 2.15).

Table 2.20 Synthesis of **16a** by condensation of **42** with benzene

Entry	42 (g)	AlCl_3 (eq)	16a (%) ^b	Purification methods
1	100.3	1.60	96.5	Crystallization and column ^a
2	100.2	1.75	94.3	
3	100.1	1.74	93.3	Crystallization and extraction ^a
4	100.3	1.74	93.5	

^a The crude product was crystallized once and the 1st crop was taken. The residue in the mother liquor was collected and then further purified by the methods described. For experimental details, see Section 7.2.4.4 of Chapter Seven. ^b Combined yields of **16a**.

The Lewis acid of choice was AlCl_3 as it is effective, inexpensive, and easily removed from the product mixture. Two to three equivalents of AlCl_3 were used for the optimization of the initial conditions, but as low as 1.6 equiv AlCl_3 proved to be equally effective. The reaction time was determined by monitoring by TLC and it was found that it took about 1 hour to gain complete conversion. More time was unnecessary and offered no additional advantage. The purified major product of chlorination of 1-naphthol (i.e. **42**) was used to prepare **16a** on large scale according to the best conditions mentioned above and the results are summed up in Table 2.20.

It has been reported^{17b,18d} that the dimerization of **16a** to VANOL is very sensitive to the quality of the starting monomer; therefore, reaching this strict specification on large scale of **42** (100 g) was a technical challenge that forced an examination of several different methods for product purification (Table 2.20). The crude product was first crystallized using CH_2Cl_2 (200 mL) and hexane (500 mL, entry 1) to get 89 grams of **16a**. The residue obtained from the mother liquor after stripping off the solvents was then put on a silica gel column to collect any remaining **16a**. It was found that a standard silica gel column with a 1:10 mixture of ethyl acetate and hexanes as eluent was optimal, from which an additional 30 grams of **16a** was afforded. The total yield of VANOL monomer **16a** was 119 g (96.5%).

Not surprisingly, while the purity of **16a** was very high, the purification by silica

gel chromatography had a direct impact on the throughput of this raw material. It was noticed that the only isolatable byproduct from the reaction on small scale was ketone **46**. It was observed that ketone **46** was less soluble in alkaline solution than **16a**. This solubility difference was attributed to their acidities.⁶¹ With this information in mind, the naphthol **16a** was purified by extraction as follows: the aforementioned residue from the mother liquor was dissolved in toluene and then extracted three times with aqueous KOH, and then the water layer was acidified. **16a** was then extracted back into ether. The resulting monomer was pure as evidenced by its ¹H-NMR spectrum; however, TLC analysis showed that there were two other faint spots present. These impurities could be easily removed by a quick silica gel column under the above-described conditions. This process provided another portion of **16a** (ca. 10 g) that was demonstrated to be of sufficient quality to use in the synthesis of VANOL (entry 2 to 4, Table 2.20).⁹⁴

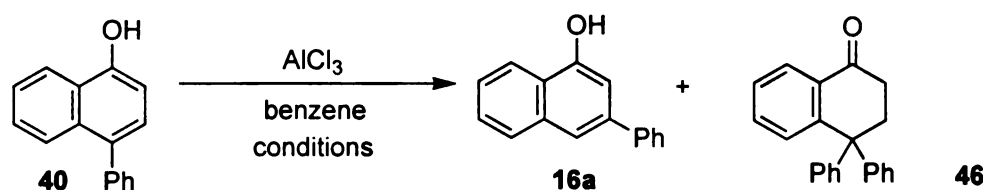
2.6.7 Mechanistic considerations and extension of the condensation reaction

While the studies described above led to a drastically different synthetic approach to VANOL monomer **16a**, the mechanism of the key step of this synthesis remains ambiguous.⁹⁵ Advances in understanding of the mechanism could facilitate the optimization of the reaction. More importantly, a deeper insight into the mechanism would possibly lead to an expansion of the scope of the reaction and to new classes of VANOL ligands bearing various functional groups.

It is believed that complex **50** (Scheme 2.30) is the key intermediate of the condensation reaction of **42** with benzene. This can be supported by the

following observations previously reported by Koptug: 1) It has been observed by $^1\text{H-NMR}$ spectroscopy,^{83f} 2) At low temperature with a short reaction time, naphthol **40** could be isolated as the major product from the reaction of **42** with benzene (Scheme 2.26),⁸⁵ which strongly suggests an intermediate of the type **50** is involved; 3) Compound **40** has been converted to the VANOL monomer **16a** as well (Table 2.21).⁸⁵

Table 2.21 Conversion of **40** to the VANOL monomer **16a**⁸⁵

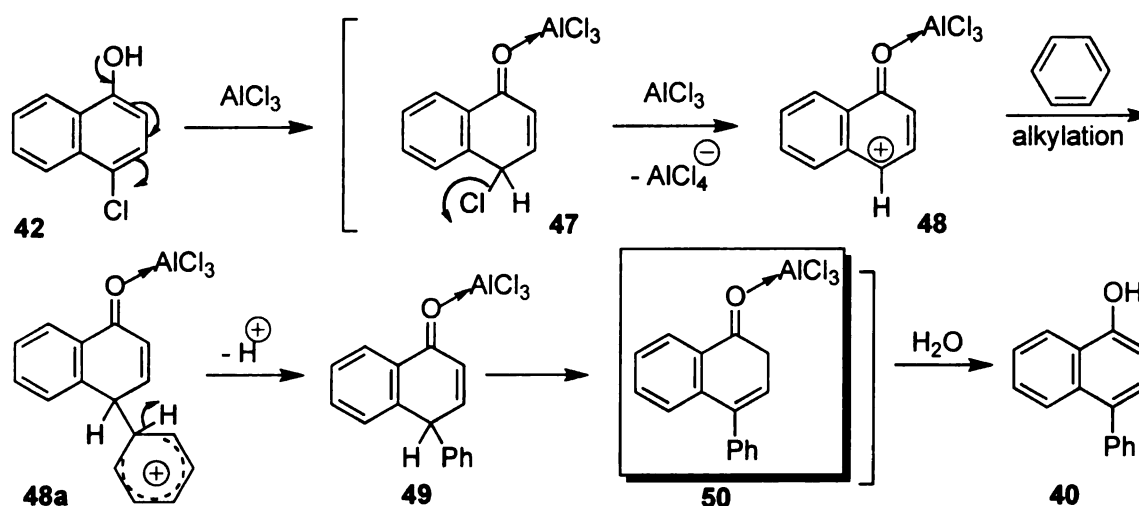


Entry	AlCl_3 (eq)	Conditions	Conversion ^a (%)	16a ^a (%)	46 ^a (%)
1	10	25 °C, 1 h	92	78	12
2	10	25 °C, 1 h, HCl (gas)	100	14	78
3	15	60 °C, 30 min	97	82	7
4	15	60 °C, 10 min, HCl (gas)	93	80	9

^a Determined by gas chromatography.

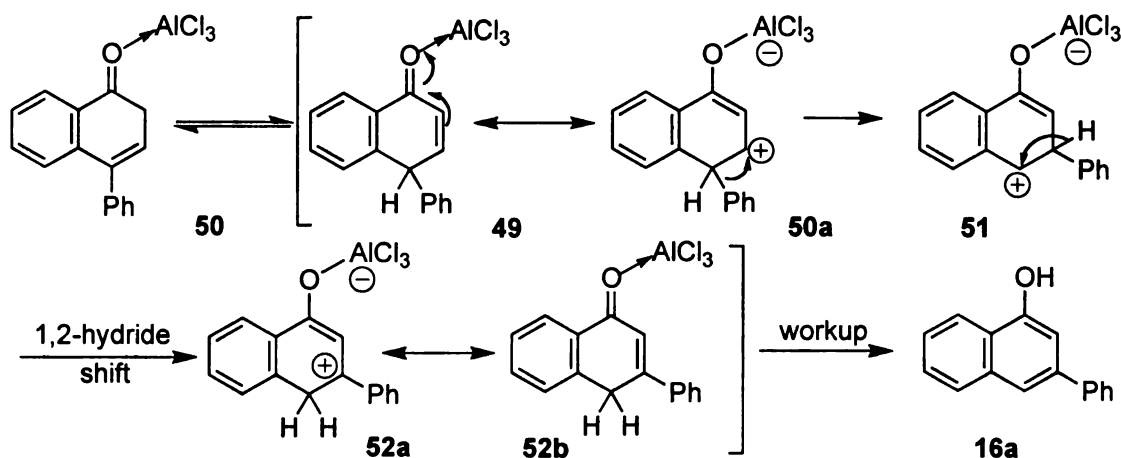
Therefore, the proposed mechanism to form **50** is outlined in Scheme 2.30. The initial coordination of AlCl_3 with the oxygen functionality of **42** is followed by the subsequent tautomerization.^{95c} Protonation of **47** should favor structure **48**,⁹⁶ since the resulting cation is stabilized by both the fused benzene ring (benzylic position) and the chlorine atom. Cation **48** then undergoes an alkylation reaction with benzene to give intermediate **49a** then to **49**, from which **50** can be generated after elimination of HCl. If the reaction is quenched at this stage, naphthol **40**, instead of **16a**, will be the major product of the condensation reaction.

Scheme 2.30 Proposed mechanism of the condensation of **42** with benzene



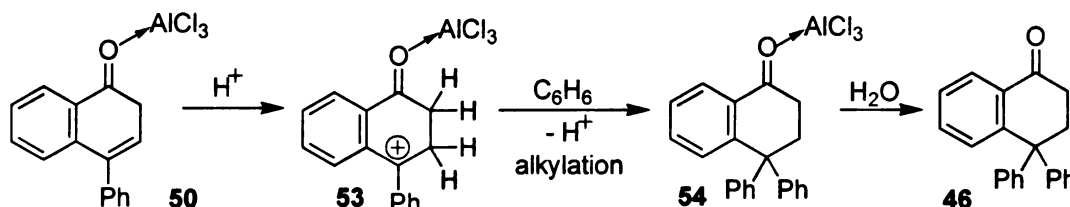
The formation of the *meta*-substituted phenol **16a** then begins with the tautomerization of intermediate **50** to give **49** (Scheme 2.31),^{83f} which leads to the intermediacy of cationic dienone-phenol precursor **50a**. A 1,2- shift of the phenyl group in **50a**^{95d} gives **51**, which is followed by a 1,2-hydride shift to generate intermediate **52**. Upon workup, **52** can be decomposed to form the desired VANOL monomer **16a**. The 1,2-phenyl migration is presumably favored by steric relief of the phenyl-*peri*-hydrogen repulsion,⁹⁷ and the greater stability of the cation in **51** relative to **50a**.

Scheme 2.31 A possible mechanism for the formation of **16a** from complex **50**



The formation of **46**, on the other hand, can be explained by the protonation of the key intermediate **50** (Scheme 2.32) in the same manner as the formation of **48** in Scheme 2.30. The subsequent alkylation of cation **53** by benzene gives rise to **54**, which in turn liberates the observed tetralone **46** after workup.

Scheme 2.32 A possible mechanism for the formation of **46** from intermediate **50**



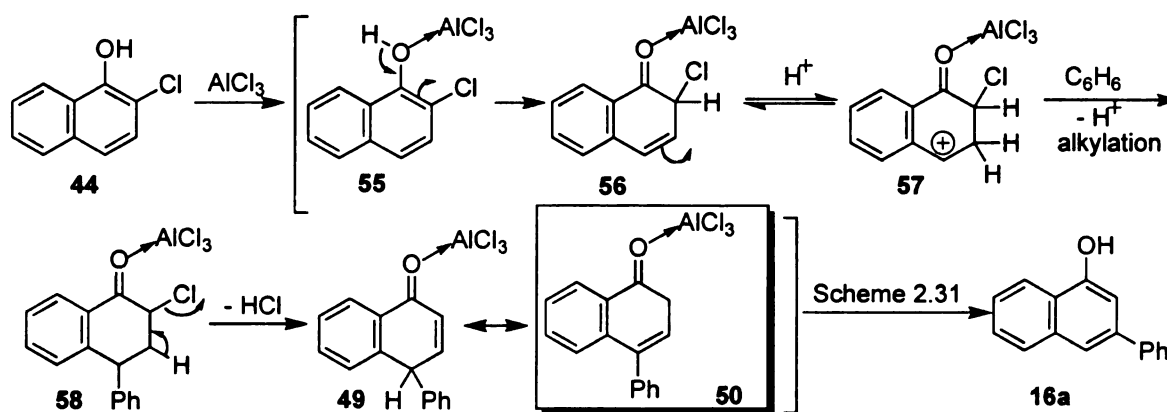
The highly acidic condition owing to the demanding cationic characters of the intermediates makes the presence of acid labile functionalities a concern. Even groups possessing basic proportions remain a concern, as a result of the strong coordinating ability of AlCl_3 as Lewis acid. These functional groups, either upon protonation or coordination with AlCl_3 , would substantially remove the electron density therefore retard and even shutdown the reaction, or induce byproducts. The electron neutral groups (such as methyl in toluene) might be tolerated. On this basis, it is predicted that the window for starting materials bearing different functional groups would be quite narrow.

It should be taken into account, however, that the Lewis acid does not necessarily participate directly in the isomerization process, and its role can be considered to increase the acidity of the medium and consequently to raise the equilibrium concentration of the protonated intermediates.^{85,95c} Accordingly, the condensation could proceed under the influence of the proton-donors rather than Lewis acids. In the later case, in order to gain a significant rate for the

transformation, higher temperatures might be required. In agreement with this suggestion, Zeolite catalysts bearing a quite high proton-donor ability have been successful utilized in the same reaction (see future work of this section).⁹⁸

Another noticeable feature from the mechanistic discussion was the role played by the chlorine atom in the reaction. Clearly, the overall oxidation state does not change by elimination of HCl during transformation of the intermediate **49** to **50** (Scheme 2.30); therefore it is envisioned that the participation and subsequent elimination of chlorine moiety from the substrate **49** is solely to maintain the overall oxidation state. It is then rationalized that: 1) it would not be a requirement for the chlorine atom to be *para* to the hydroxy group of 1-naphthol, and 2), other halogens should also be able to participate in the reaction (Scheme 2.34). In another words, 2-chloro-1-naphthol **44**, the major byproduct from chlorination of **43** that otherwise would be considered as hazardous waste, might be convertible to the VANOL monomer as well (Scheme 2.33). In fact, this has shown to be the case,⁹⁹ and 27% yield of **16a** could be obtained as shown in entry 1 of Table 2.22.

Scheme 2.33 A proposed mechanism for the condensation of **44** with benzene



Upon exposure to AlCl_3 in boiling benzene, naphthol **44** was smoothly converted to **16a** with decent yield (Table 2.22, entry 2); this paved the way for large-scale (100 g, entry 3) conversion of this material to phenol **16a**. Although very pleased with this outcome, it was found that at least three byproducts were present upon analysis of the crude reaction mixture. This made the purification very hard to perform. As a consequence, it appeared that we were dealing with, at most, a supplemental starting material with a complex reactivity profile, which complicated the condensation step by giving rise to side products.

Table 2.22 The condensation reaction of the mixture of **42** and **44** with benzene

Oc1ccc2cc(Cl)ccc2c1 (**42**) + Oc1ccc2cc(Cl)ccc2c1Cl (**44**) $\xrightarrow[\text{benzene, reflux, 1 h}]{\text{AlCl}_3}$ Oc1ccc2cc(Cc3ccccc3)ccc2c1 (**16a**)

Entry	42 (g)	44 ^a (g)	Benzene ^b (mL)	AlCl_3 (eq ^c)	16a (%) ^c
1	0	1.78	60	2.00	27.0 ^d
2	0	0.93	20	2.00	67.1 ^{e,f}
3	0	100	1700	1.60	78.2 ^{f,g}
4	0.46	0.48	20	1.92	82.3 ^e
5	4.75	4.75	200	1.88	78.2 ^e
6	25.0	22.1	800	1.71	79.1 ^g
7	50.7	50.2	2000	2.03	90.5 ^g

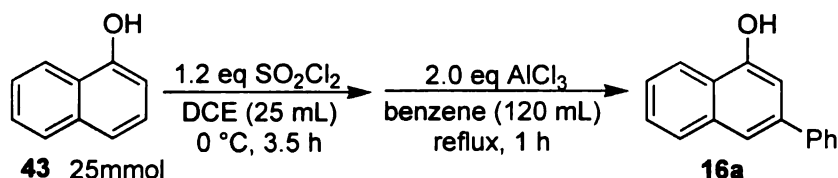
^a After purification by sublimation. On TLC, compound **44** was pure. For experimental details, see Section 7.2.4.4 of Chapter Seven. ^b Reagent grade. ^c Yield based on the sum of **42** and **44**. ^d Data from reference 99; reaction time is 240 h at 25 °C with HCl (g). ^e Purified by silica gel column. ^f Reaction time was 4 h. ^g Purified firstly by crystallization, and then column chromatography on the mother liquor.

The presence of the *ortho*-chlorine functionality in **44** represents a minor divergence mechanistically from **42** (Scheme 2.33), in such a way that loss of hydrogen chloride after alkylation produces **49** directly. As shown in Scheme

2.31, **49** is a common advanced intermediate for the rearrangement. It was also noticed the conversion of **44** to **16a** is more sluggish than **42** under the identical conditions. Thus, it took the reaction about 4 h to finish as indicated by TLC. Compared to **48** in Scheme 2.30, intermediate **57** in Scheme 2.33 is less stable therefore its formation is slower.

The fact that **44** can also be converted to **16a** was regarded as an extra bonus delivered by investigating the mechanism of the condensation reaction. Thus, motivated by the possibility of converting otherwise useless **44** to **16a**, the condensation reaction was run with a mixture of 1:1 of **42** and **44**.⁹⁹ The idea was that the presence of **42** might be able to 'attenuate' the reactivity of **44** by facilitating its protonation to form **57**. It was found that the reaction led to an improved yield of **16a** (Table 2.21, entry 4), and complete conversion was obtained in one hour. It could be repeated reliably on different scales (entries 5 to 7, Table 2.21).

Driven by the desire to avoid the isolation of **42**, it is natural that we became curious about the feasibility of the use of the crude mixture of products from the chlorination of 1-naphthol in the condensation reaction with benzene. If this hypothesis held true, the conversion of 1-naphthol **43** to **16a** should be able to be further improved since both **42** and **44** are applicable for the reaction. Thus, this would represent a chance to simplify the procedure and improve the yield at the same time.

Table 2.23 Condensation reaction of benzene with different starting materials

Entry	42 (%)	42: 44: 45 ^a	16a ^b (%)
1	nd ^c	100: 18: 4	62.7
2	60.3 ^b	100: 20: 9	54.7 ^d

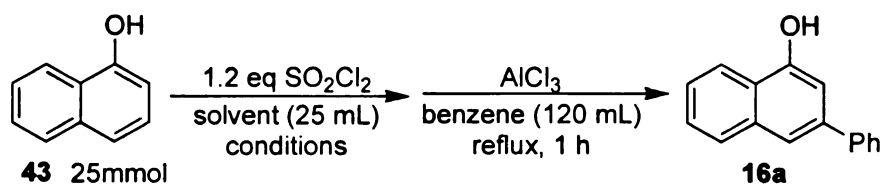
^a Based on ¹H-NMR spectrum. ^b Yields were based on **43** after column. ^c nd= not determined; the crude product was for condensation reaction. ^d The yield of condensation was 90.8% from **42**.

Accordingly, this hypothesis was tested by setting up two chlorination reactions under exactly the same conditions (Table 2.23). The crude products from the chlorination reaction in entry 1 were used without separation, whereas in entry 2, **42** was first isolated and purified *via* silica gel chromatography. Subsequently, the condensation reaction was conducted under standard conditions for both starting materials. Upon refluxing in benzene with AlCl₃, a gradual conversion of the crude mixture to **16a** was observed. The results in Table 2.22 clearly demonstrated that the reaction using the crude mixture of chlorination products furnished **16a** with higher yield (entry 1).

An effort was then set out to optimize this new protocol. In the first run, 2.7 equiv of AlCl₃ were required to achieve reasonable yields (Table 2.24, entry 1). Later, it was found that less AlCl₃ (1.6 equiv, entry 3) was needed upon further understanding of the reaction. (*vide infra*). This telescoping of two steps—chlorination and condensation—proved to be a highly efficient method for producing **16a** in typically > 60% over two steps. Additionally, it was found that the protocol was not sensitive to the conditions for the chlorination step and was

reproducible upon scale up (entry 3). The yield was higher on larger scale and this is probably due to a decreased loss of the product during isolation.

Table 2.24 Condensation of the crude product of chlorination reaction of **43**



Entry	Solvent ^a	Conditions ^a	42 : 44 : 45 ^b	AlCl ₃ (mmol)	16a (%) ^c
1	CHCl ₃	25 °C, 12 h; 61 °C, 0.5 h	100: 63: 0	2.7	67.7
2	DCE	0 °C, 3.5 h	100: 18: 4	2.0	62.7
3 ^d	CH ₂ Cl ₂ ^e	25 °C, 3.5 h	100: 28: 4	1.6	71.1

^a For chlorination. ^b Based on ¹H-NMR spectrum. ^c Yields were based on **43** over two steps, and the **16a** was isolated by column chromatography. ^d The scale of **43** was 40 g, and 800 mL of benzene was used for condensation step. ^e The volume was 300 mL.

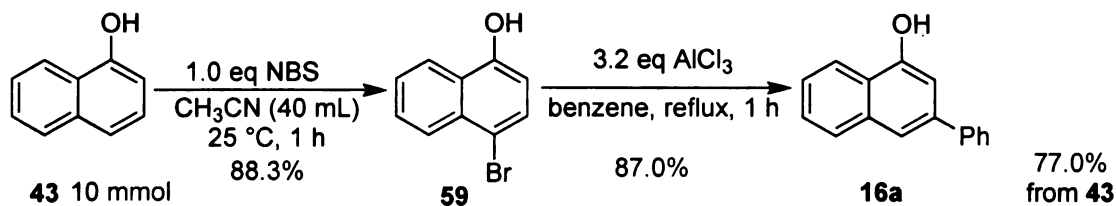
However, problems still remain for this new protocol. Foremost among them is that the quality of the crude product was worse than the reaction using pure **42**. Some colored impurities attended the formation of **16a**, which were not possible to remove without chromatographic separation.¹⁰⁰ While using chromatographic separation to remove these impurities may be the optimal technique on small scale, such a technique is unsuitable to prepare **16a** on large quantity due to cost considerations and equipment availability. Consequently, this new protocol was not examined for large-scale synthesis of the VANOL monomer **16a**.

2.6.8 Limitations and future work

The chlorination of 1-naphthol using SO₂Cl₂ provide for an inexpensive and scalable synthesis of the VANOL monomer **16b**. Nonetheless, there was room

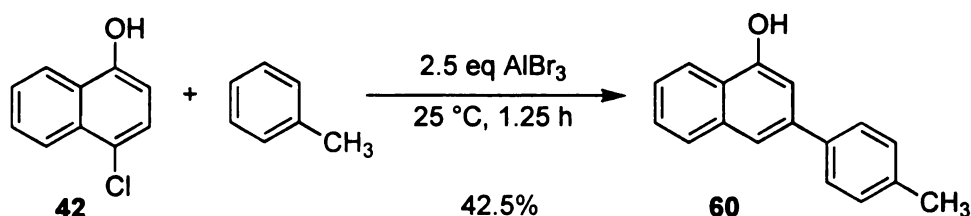
for improvement of this reaction as it produced a mixture of regioisomers that required separation and thus resulted in a loss of material. Additionally, two gaseous waste products, SO₂ and HCl, posed significant safety and environmental concerns. This prompted us to seek to resolve this problem by incorporating other halogens in the *para*-position of **43** (Scheme 2.34; for experimental details, see Section 7.2.4.5 of Chapter Seven). It was deduced that better *para*-selectivity could be achieved either if the reagents were milder, or the size of the halogen atom was larger.^{89a,88d} Thus, to pursue this possibility, the bromination reaction of **43** using NBS was investigated.^{101,88d} The preliminary results showed that, in acetonitrile, the reaction of **43** with NBS gave the desired regioisomer **59** with excellent yield under very mild conditions. The succinimide byproduct is non-hazardous and can be easily removed *via* a water wash. The question then arose as to whether or not the subsequent condensation with benzene was viable. The reaction of **59** was carried out in the same fashion as **42** (Table 2.20) and it did give **16a** in 87% yield. Undoubtedly, this result suggests that additional improvement of the efficiency of the already very impressive synthesis is possible, and it can be anticipated that such advances in this field would benefit all those interested in VANOL chemistry.

Scheme 2.34 Synthesis of **59** and its application in the synthesis of **16a**



However, the one major potential drawback for the approach involving either the 4-chloro or 4-bromo-1-naphthol (i.e. **42** or **59**) is that the reaction conditions required to obtain the best results might be too forceful to permit the presence of various functional groups. In an attempt to prepare solid supported VANOL (Chapter Six), this effect was tested with a range of Lewis acids (AlCl_3 and AlBr_3) on different substrates, but encouraging results were not obtained.^{95c} This is an example where the demanding conditions required for the condensation apparently are too harsh for functionalized systems. When toluene was employed in the reaction, a moderate yield (42.5%, Scheme 2.35) of **60** was obtained. These results indicate that there is indeed a narrow window to the scope of this reaction. A further disadvantage is that the use of AlCl_3 produces a corrosive acid by-product and presents a disposal problem. Hence, there was a considerable requisite to devise reactions that avoid such Lewis acids while maintaining good selectivity and involving much more environmentally benign processes.

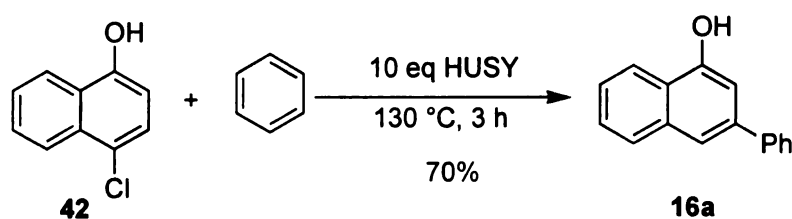
Scheme 2.35 Synthesis of **60** using toluene as alkylation agent



Zeolite catalysts are also known to promote many organic reactions much more efficiently and selectively than conventional Lewis acids,¹⁰² and they are promising for practical applications because the workup procedure is simplified. Furthermore, these solid acids could be reused. For instance, Zeolite HUSY

(ultra-stable Y zeolite, Scheme 2.36) can mediate the conversion of naphthol **42** to 3-phenyl-1-naphthol **16a** as well.⁹⁸ Accordingly, the fact that a zeolite can be used in place of AlCl_3 to effect the conversion of **42** to **16a** suggests that it may have enhanced functional group compatibility for this reaction. In turn this new protocol in hand may lead to more VANOL derivatives that will allow fine tuning of the properties of the ligand for various applications.

Scheme 2.36 Synthesis of **16a** using HUSY zeolite⁹⁸



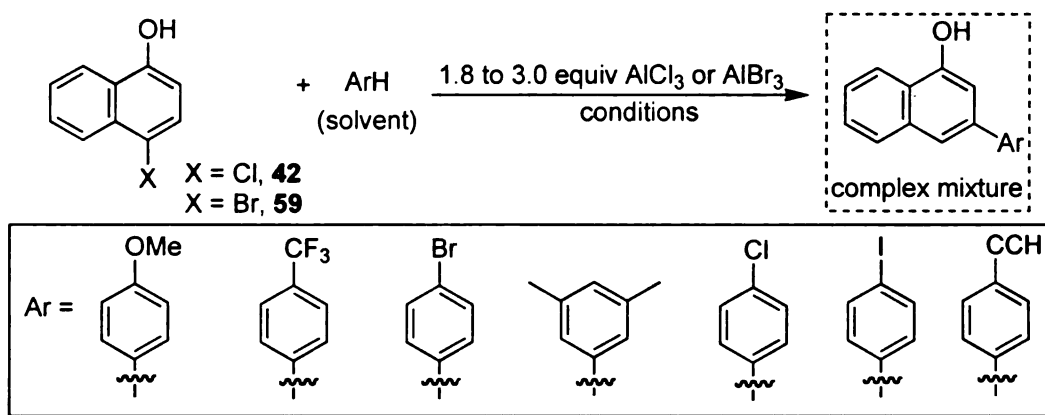
2.6.9 Summary

At elevated temperatures, 1-naphthols with a good leaving group in the 4-position of the phenolic ring undergo an intriguing reaction with benzene in the presence of acidic reagents, where loss of the leaving group at the 4-position occurs with introduction of a phenyl group in the 3-position. This structural reconstruction constitutes, in mechanistic terms, an electrophilic alkylation and 1,2-alkyl shift reaction sequence. When applied to 4-chloro-1-naphthol (**42**), this provides a direct and elegant access to the VANOL monomer from common starting materials. Although it cannot be said that the proposed mechanism has been overwhelmingly demonstrated, the improvements in overall efficiency can be attributed to a better understanding of the process as a consequence of the consideration of the likely mechanism.

Whereas this method afforded excellent yields of **16a**, it might not be as versatile as desired for the production of a range of derivatives bearing different

functional groups. This was revealed by the limited success to introduce more functional groups on the 3-substituted benzene ring. Attempts to do this led to either recovery of starting material or the formation of complex product mixtures when various functionalized benzenes were used (Scheme 2.37. See also: Chapter six for details).^{95c}

Scheme 2.37 Attempted preparation of the VANOL monomer derivatives



Meanwhile, in a study of the Wulff asymmetric aziridination reaction,^{12a,b} some efforts were directed to elucidating the mechanism of the reaction by using functionalized VANOL as ligands as a mechanistic probe with the ultimate goal to further optimize the aziridination reaction.^{18f} The fact that the above-described chemistry was not able to supply this class of materials clearly highlighted an urgent need for new methodologies that could. These new methods to be sought would be required to tolerate various functionalities as well as proceeding in significantly high overall yields from commercial starting materials.

2.7 Thermal rearrangement of 3,4-diphenylcyclobutenone to prepare 16a

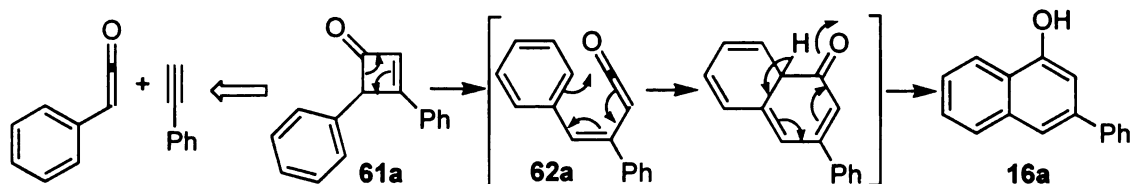
The reactions that have been successfully applied to the synthesis of the VANOL monomer **16a** encompass Friedel–Crafts cycloacylations (Scheme 2.11) and alkylations of 1-naphthol derivatives (Scheme 2.34), accompanied in the

latter case by cationic rearrangements. Both methods involve carbocations at a certain stage in the process. As a result, the structural features of the substrates are circumscribed by the highly electrophilic demands of these reactions, in such a way that the aromatic ring often has to be electron rich.

The driving force for the formation of naphthols *via* rearrangement of cyclobutenones (e.g. **61a**, Scheme 2.38),¹⁰³ on the other hand, is associated with the conversion of a strained rings to a stable aromatic system. Theoretically, this method should be much less sensitive to the electronic properties of the reactant since no ionogenic processes are involved. In fact, this methodology has been reported to afford aromatic products in relatively good yields with good tolerance for a wide variety of functional groups including halides, esters and amines.¹⁰⁴

Mechanistically, this reaction proceeds through the styryl ketene intermediate **62a** which results from the electrocyclic ring opening of cyclobutenone **61a**, followed by electrocyclization and tautomerization.¹⁰⁵ The precursor cyclobutenone can be generated by a [2+2] addition of an *in situ* generated ketene with an alkyne (i.e. [2+2] cycloaddition/ electrocyclization cascade reaction, or CAEC reaction).¹⁰⁵

Scheme 2.38 Mechanism for the rearrangement of cyclobutenone **61a** to **16a**



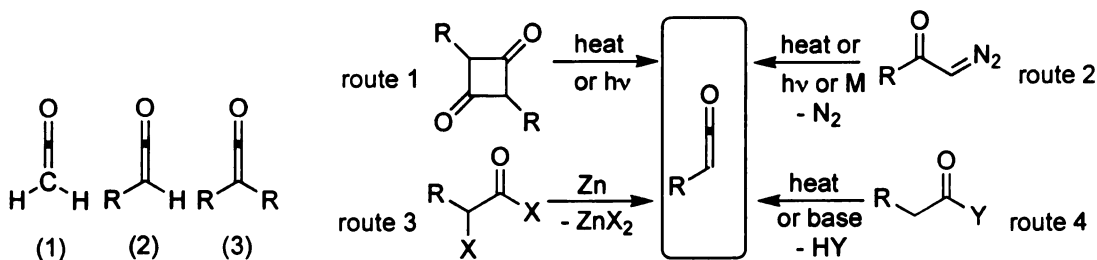
2.7.1 Introduction of ketenes

First introduced to the world a century ago by Hermann Staudinger,¹⁰⁶ ketenes are remarkable for the variety of ways in which they can be prepared, for their

high reactivity, and for the diversity of useful products resulting from their reactions.^{105a} The unique reactivity of ketenes that is expressed in [2+2] cycloaddition reactions has long been a renown and ready source of four member ring compounds, and this includes the distinctive characteristic of undergoing facile dimerization.

Structurally, ketenes can be categorized into three groups: non-, mono- and di-substituted ketenes (Figure 2.2, (1), (2) and (3), respectively. Mono-substituted ketenes bearing a hydrogen atom on the C-C double bond of the cumulene unit are usually deemed to be more reactive.¹⁰⁷ Therefore, they are more chemically challenging to prepare due to their strong tendency to polymerize, but their increased reactivity at the same time can make them more synthetically useful.

Figure 2.2 Overview of ketenes: types and methods to synthesize



There are many ways to synthesize ketenes, and most of them fall into the four categories shown in Figure 2.2.^{105a} When ketene dimers are readily available, pyrolysis or photolysis of such compounds provide a simple synthesis of ketenes (route 1). In contrast, Wolff rearrangement of α -diazo ketones triggered by light, heat or metal catalysts provides a method to access ketenes with relatively mild conditions (route 2). Ketene generation from α -halo acid chlorides by treatment of zinc (route 3), featuring inexpensive reagents and simple procedures, suffers from limited scope due partially to the vulnerability of

some substrates to cationic polymerization with the zinc salts (ZnX_2) formed in the reaction. Ketenes are most often produced from easily accessible carboxylic acids or their derivatives (route 4). Dehydrohalogenation reactions of acid chlorides with tertiary amines, in particular, gives rise to a large number of disubstituted ketenes.¹⁰⁸ This method is much less successful for mono-substituted ketenes.

Phenylketene,¹⁰⁹ a prototype of mono-substituted, non-persistent ketenes, has been extensively studied by spectroscopic methods and by trapping experiments. Since the discovery of this reactive compound, considerable effort has been made to understand its nature and as a result all of the methods indicated in Figure 2.2 have been used for its generation. For the generation of phenylketene employed in our previous VANOL synthesis, attention was focused on the thermal cleavage of phenylacetyl chloride.^{105b} This process offers the attraction that the starting material is low-cost and readily available from commercial suppliers in large quantities, and also that no additional reagents are involved which saves a lot of money and effort during purification. Most importantly, since the subsequent rearrangement of the cyclobutenone requires elevated temperature,^{105a} the generation of phenyl ketene and its [2+2] cycloaddition with phenylacetylene and the subsequent pericyclic process that lead to the formation of VANOL can be performed in one step.

2.7.2 Introduction to the [2+2] cycloaddition reaction of ketenes

While there are many known syntheses of highly strained 4-membered rings,^{103d} reaction of ketenes with compounds possessing carbon-carbon multiple

bonds (e.g. [2+2] cycloaddition) is widely accepted as one of the simplest methods. Although the mechanism is the source of some controversy,^{105a} this reaction offers an approach for the simultaneous formation of two C-C bonds, often without the need for solvent, catalyst, or high heat. With Staudinger's rigorous study as the foundation,^{109a} this class of reactions has been the subject of continuous research ever since and has been reviewed numerous times.¹¹⁰ It has been demonstrated that the reaction proceeds faster in polar solvents,^{110a} and substituent effect studies have shown that mono-substituted ketenes are generally more reactive than di-substituted ketenes and this has been attributed to steric effects.^{110a}

Acetylenes react with ketenes in a manner similar to that of olefins; this cycloaddition provides a major route for the preparation of cyclobutenones.¹¹¹ The resulting cycloadduct can undergo the previously mentioned rearrangement under thermal conditions to form 1-naphthol derivatives, which is a common and long established route for their syntheses.^{105b} Consequently, computational¹¹¹ and experimental^{105b} studies have been carried out on this process, and the process was found to be essentially thermo-neutral.^{110a}

2.7.3 Optimization of the CAEC cascade reaction to produce 16a

The original procedure by Kipping et al^{105b} for the preparation of naphthol **16a** involved thermal cracking of phenylacetyl chloride **18a** at 180 °C and *in situ* reaction with phenylacetylene under solvent-free conditions (entry 1, Table 2.25). This reaction was repeated under the identical conditions and the data is presented in entry 3 of Table 2.25. The desired product **16a** was isolated after

hydrolysis with yields consistent with published result (entry 3 vs entry 1). Variation of the amount of **18a** from the standard conditions led to no noticeable improvement in the yields (entry 1 vs entry 4 and 5).

Table 2.25 The thermal CAEC reaction to prepare **16a**

63a 45 mmol	18a 1.66 eq	temperature solvent 18 h	64
		KOH H ₂ O	16a
Entry	Solvent	Temperature (°C)	16a (%) ^a
1 ^b	None	180	29.3
2 ^c	Tetralin	190	48.6
3	None	180	30.1
4 ^d	None	180	30.8
5 ^e	None	180	24.0
6	1,2,4-trimethylbenzene ^f	168	1.3
7 ^g	Toluene ^f	110	0

^a Isolated yields by column chromatography; based on **18a**. For experimental details, see Sections 7.2.5.1 of Chapter Seven. ^b Results taken from reference 105b. ^c Results from the reference 112. ^d 2.5 eq of **18a** was used. ^e Reaction time was 21 h and 0.83 eq of **18a** was used. ^f Concentration of **18a** is 1.25 M. ^g Refluxed for 36 h.

Under the solvent-free conditions, aforementioned reactions produced a black tarry material. This process was highly complicated by side reactions and routinely gave yields of **16a** in the region of 20-30%. It was noticed that it became more difficult to stir as time went on. This led to the deduction that, apart from the thermally induced polymerization of the reactants, the low yields might be caused by the partial destruction of the substrates and products through their over exposure to heat under these harsh conditions. Thus, in an effort to explore methods to mitigate the impact of these drastic conditions, an efficient stirring

technique might be of great value to help conduct energy evenly to the reaction mixture.

Hence, solvents were considered for this reaction to improve the quality of the crude product although there are reports that cycloadditions of ketenes are generally run without solvent.^{110b} Nonetheless, it was envisioned that there was a potential tradeoff in the yields with the quality of the crude mixture. Much to our disappointment, the cycloaddition gave rise to a dramatic loss in yield under similar conditions in various solvents as shown in entries 6 and 7.^{110a} In toluene, the reaction failed to yield any detectable amount of **16a**; clearly, this happened because in this solvent the required temperature was unattainable at normal pressure. This hypothesis can be supported by the later-on discovery made by Schuster and coworkers that both the yield and the quality can be improved by using tetralin as solvent (entry 2).¹¹²

Having established the effect of solvent on the cycloaddition, attention was then turned to the possibility of the generation of the phenylketene at lower temperature with the help of triethylamine (i.e. NEt₃, Table 2.26). This approach was inspired by successful generation and isolation of this ketene by other chemists in the same manner.¹¹³ Contrary to our optimistic expectations, the reaction failed to give any desired **64**; instead a crude reaction mixture consisted of at least three compounds could be detected by TLC. The major one was isolated as a light yellow solid, which consisted of a mixture of unknown compounds (entry 1). Using ether or toluene as solvents, **64** was not detected by ¹H-NMR spectrum or TLC (entry 2 and 3). To control the rate of the formation of

the ketene, compound **18a** was added slowly to **63a** in refluxing toluene (entry 4), or without solvent (entry 5); despondently, the desired product **64** could not be isolated from the crude mixture after workup.

Table 2.26 The CAEC reaction of **18a** and **63a** in the presence of triethylamine

ClCC(=O)c1ccccc1 + c1ccccc1C#C $\xrightarrow[\text{solvent, temperature}]{1.2 \text{ eq NEt}_3}$ c1ccc2c(c1)c(c3ccccc32)OC(=O)Cc4ccccc4

18a **63a, 1.0 eq** **64**

Entry	Solvent ^a	Temperature (°C)	64 (%)
1	None	0	Not detected
2	ether	0	Not detected
3	toluene	110	Not detected
4 ^b	toluene	110	Not detected
5 ^b	None	25	Not detected

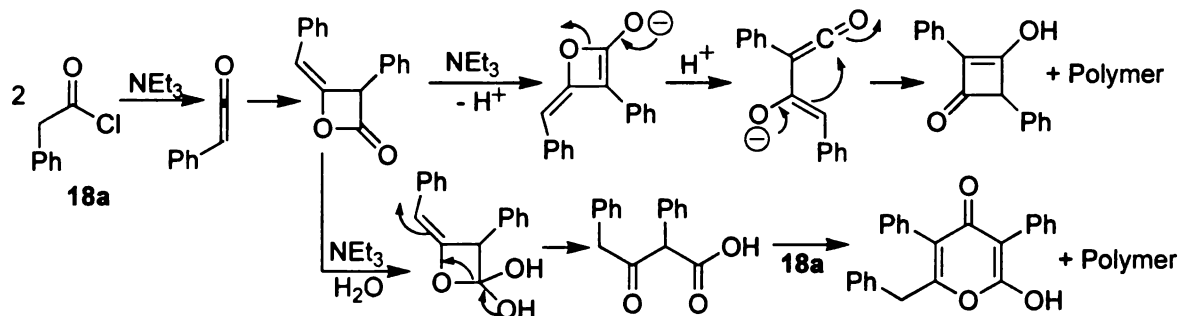
^a The concentration of **18a** was 0.3 M when solvent was used. The base was added last unless otherwise mentioned. For experimental details, see Sections 7.2.5.2 of Chapter Seven. ^b **18a** was added to **63a** and NEt₃ over 9 h.

As previously noted, the CAEC routes using **18a** and phenylacetylene **63a** suffered from the necessity of solvent-free conditions and with the liability of polymerization of mono-substituted ketenes. Structural elucidation of the major component of the crude mixtures generated by the reaction in Table 2.26 was not conclusive, but upon analyzing samples it was apparent that at least two carbonyl moieties were present in the ¹³C-NMR spectrum. Therefore, an assumption was made that we were dealing with a ketene polymer or oligomer or possibly a mixture of polymers or oligomers.^{105a}

It has been reported¹⁰⁷ that mono-substituted ketenes are more reactive than other ketenes; indeed, dimerization was reported to occur below 0 °C and could be catalyzed by R₃NHCl.¹¹⁴ Hence, these byproducts were tentatively assigned as mixtures of oligomers of phenylketene (Scheme 2.39). To test this hypothesis,

a control reaction was carried out by adding Et₃N (1.0 eq) to an ether solution of **18a**. The crude reaction mixture contained only one product with the same *R_f* value on TLC and the same ¹H-NMR spectrum (see Section 7.2.5.2 of Chapter Seven), which confirmed that the unknown mixture was solely **18a**.

Scheme 2.39 Possible products from the reaction of **18a** and Et₃N¹¹⁴



To eliminate this possible involvement of the ammonium salt in the reaction,¹¹⁵ Hunig's base (diisopropylethylamine, i.e. *i*-Pr₂NEt, Table 2.27) was used in favor of its enhanced steric hinderance over Et₃N.¹¹⁶ Unfortunately, this tertiary amine failed to generate **64** with phenylacetylene under all conditions examined (Table 2.27). Given the fact that such monosubstituted ketenes produced under similar conditions have been successfully trapped by a number of reactants,^{105a} we postulated that phenylacetylene was not reactive enough to cycloadduct to ketene under the conditions listed above. Thus, the observation of unwanted side products brought the project to a halt, and further development of this reaction with base induced ketene formation at low temperature was abandoned.

Table 2.27 Attempts at the CAEC cascade reaction using Hunig's base

18a 45 mmol	63a (0.67 eq)	1.4eq <i>i</i> -Pr ₂ NEt temperature solvent (50 mL)	64
Entry	Solvent	Temperature (°C)	64 (%)
1	Toluene	0 to 25 ^a	Not detected
2	CH ₂ Cl ₂	25	Not detected
3 ^b	CH ₂ Cl ₂	25	Not detected
4 ^c	Toluene	25 to 110 ^d	Not detected

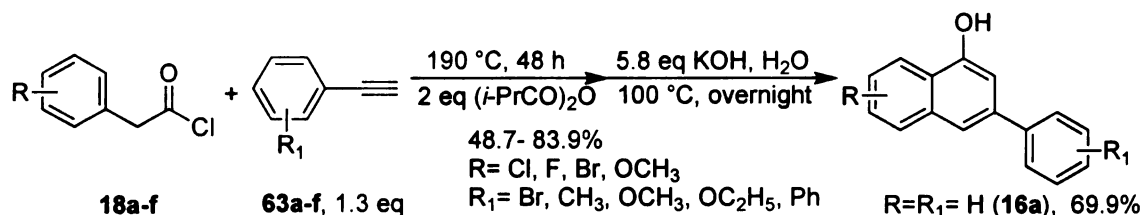
^a 0 °C for 30 min. For experimental details, see Sections 7.2.5.2 of Chapter Seven. ^b 10 mL of CH₂Cl₂ was used. ^c **18a** was added to a mixture of **63a** and *i*-Pr₂NEt over 8 h. ^d 25 °C for 38 h then refluxed for 3.5 h.

2.7.4 New conditions and future work

The indications from the work described above are that the CAEC route could potentially be used as the synthetic pathway to VANOL as well as its derivatives; but the low efficiency encouraged us to investigate other scenarios. Notably, excess phenylacetyl chloride (**18a**) was required to trap the naphthol functionality in the primary product to give ester **64** as the key intermediate. This presents a cost problem especially when the acid chloride partner is not readily available and thus quite precious. As the search for better conditions for the VANOL synthesis continued, it was found that the inclusion of isobutyric anhydride (i.e. *i*-PrCO)₂O) as solvent had a miraculous impact, which proved to be the best protocol for this transformation which gave a much higher yield of the naphthol (Scheme 2.40). An unexpected benefit emanating from this was the fact that the product obtained was at a much higher quality level, which made it much easier for downstream manipulations. Furthermore, this methodology was highly concise and extraordinarily compatible with functional groups. Putting all these

considerations together, exposure of various modified phenylacetyl chlorides to the same conditions gave a clean conversion of both reactants to the monomeric derivatives in high yields (For experimental details, see Sections 7.2.5.3 of Chapter Seven).

Scheme 2.40 Synthesis of **16a** and its derivatives in isobutyric anhydride



2.7.5 Summary

The overall efficiency of the CAEC route to manufacture **16a** profits from the incorporation of the thermal ketene formation with cycloaddition and rearrangement in a single step, and thus provides a convenient entry-point to VANOL and related ligands. The various phenylacetic acids that can be used for this reaction are often readily available, stable and easy to handle. In an effort to improve the reaction conditions, it was found that there was evidence that phenylketene was produced by either pyrolysis or basic dehalogenation of phenylacetyl chloride; yet the presence of either solvent or ammonium salts significantly suppressed the reaction with phenylacetylene by inducing the formation of byproducts,¹¹⁴ the exact identities of which were not fully elucidated. Together with the low efficiency of the originally reported procedures, these data have left the impression that isobutyric anhydride intrinsically promotes the CAEC reaction. Unlike any other medium tested, high activity does not have to be sacrificed for high quality in this solvent. Therefore, both high yields and

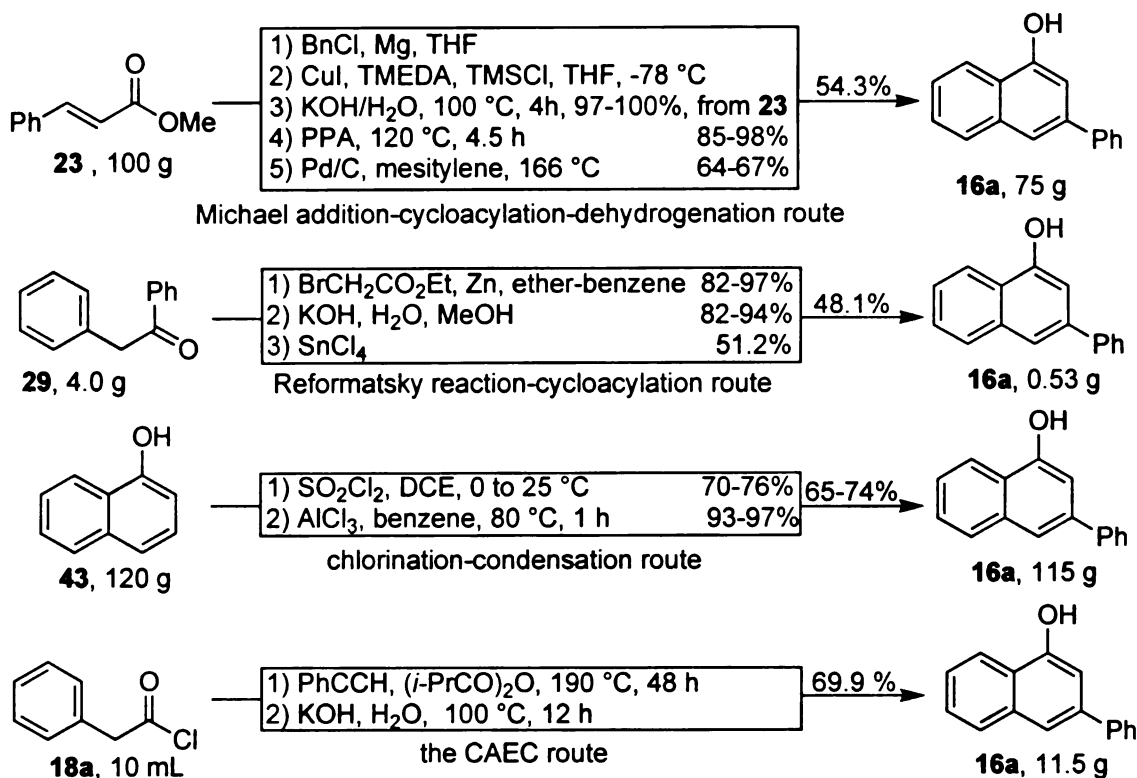
excellent quality were obtained. Furthermore, these advantageous influences observed for isobutyric anhydride were found to be valid for VANOL derivatives as well and its utility in the synthesis of these ligands will be presented in Chapter Six.

2.8 Route comparisons

The evolution of the various synthetic routes towards **16a** was guided by the inspection of the mechanisms for all six synthetic approaches. Strategically, four routes produced pure VANOL ligand. A comparison of the syntheses of the key intermediate, monomer **16a**, from commercially available materials is shown in Scheme 2.41.

In summary, the synthesis of **16a** was accomplished in 5 steps in 54.3% overall yield from commercially available methyl cinnamate (**23**, 100g scale). While the Reformatsky methodology was 2 steps shorter than that of the Michael addition route, the synthesis of **16a** from deoxybenzoin **29** proceeds in lower overall yield (48.1%). In addition to requiring fewer steps, the conversion of **43** to monomer **16a** was operationally much simpler and more reliable than the cycloacylation approaches listed above. Notably the yields and the quality of **16a** were much better than with other methods. The chlorination of **43** and the subsequent condensation step could be telescoped into one without isolation of the intermediate 4-chloro-1-naphthol **42**, and the overall yields were even higher in the sacrifice in the quality. These factors all pointed to the condensation route from **42** as the most viable long-term route of choice.

Scheme 2.41 Route comparison of the syntheses of VANOL monomer **16a**



The first three approaches outlined in Scheme 2.41 involve carbocation intermediates and thus were considered with some circumspect as approaches to a diverse array of functionalized VANOL ligands. This led us to focus on the ketene-based involving rearrangement of a cyclobutenone. After extensive optimization, this one-pot synthesis allowed for the conversion of commercially available **18a** to **16a** in 69.9% yield. Besides being a very efficient transformation, an important advantage of this new procedure was the high functional group tolerance, and therefore various VANOL derivatives should be readily accessible by this method.

2.9 Concluding remarks

The initial objective was to devise a new ways to synthesis the VANOL monomer **16a**. In the end it was not only possible to realize this goal, but also to

expand upon and improve many various methodologies to access this compound. The yield of one route was tripled from <30 to >90% based on commercially available starting materials. The success of the evolution of these methodologies could be attributed to a better understanding of the process as a consequence of the inspection of the mechanism. These mechanistic studies were constructive to move toward a working hypothesis, and the direct observation of improvement of the efficiency solidified this working hypothesis and enabled a new approach to the synthesis of VANOL and its derivatives.

The impact of the research on VANOL synthesis in organic chemistry can be highlighted by the way that it enabled various combinations of these methods to access different chemically modified ligands for elucidation of the mechanism of aziridination reaction (see Chapter Six for details).^{18f} It also shows that new methodology opens new horizons, which is best illustrated with the example of BINAP: although the original synthesis^{171c} was straightforward, it was not applicable on a large scale. As a result, the catalytic applications were sparse. With the arrival of new, asymmetric synthesis decades later,^{171a,b} its applications are growing rapidly. Therefore, it was expected that the ready accessibility of VANOL would foster a fast-moving and widely-impacted field of contemporary chemistry that plays a central role in the development of enantioselective catalysis.

CHAPTER THREE

SYNTHESIS OF 2-PHENYL-4-PHENANTHROL AS VAPOL MONOMER

Interest in the chemistry of VAPOL blossomed^{19,22,23,24} when it was established that the aziridination reaction^{12,13,18} could produce products rich of chirality in a very pure fashion using VAPOL-based catalyst. However, its rather difficult preparation was believed to be a major drawback in the wide application of this ligand. These considerations constitute the focal point of this chapter: the development of reliable methods allowing facile access to this ligand on large scale in an economically viable fashion.

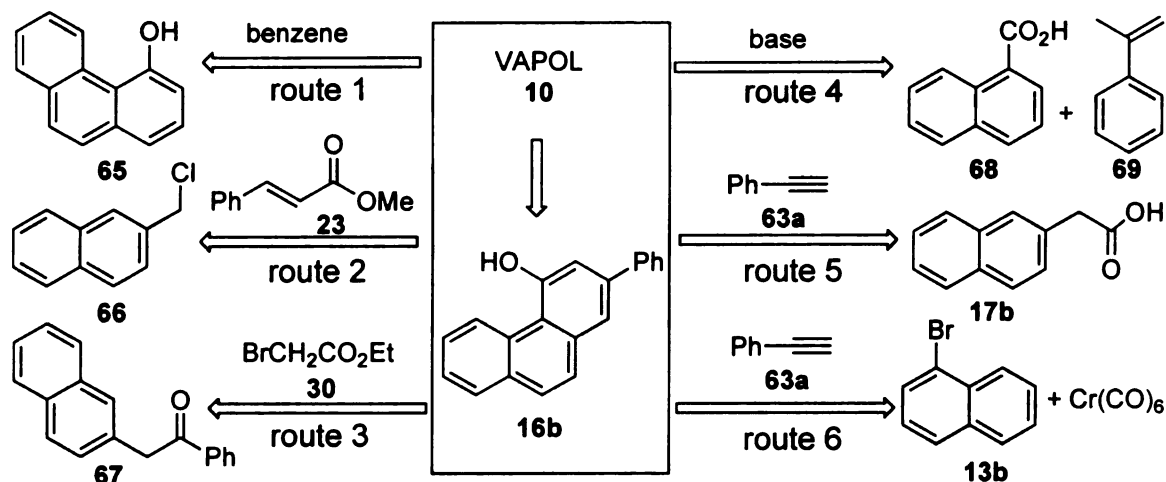
3.1 Introduction

Classical syntheses of phenanthrene systems normally are lengthy and laborious, sometimes inherently limited by a lack of well-defined regiocontrol element.¹¹⁷ Regioselectivity was deemed crucial for VAPOL due to its unique substitution pattern. VAPOL shares similar structural features with VANOL, the most prominent of which is that the phenyl group resides *meta*- to the hydroxyl functionality. Thus, with the vast experiences and knowledge gained in VANOL synthesis (Chapter two), efforts were then turned to VAPOL with an eye on the possibility of extending the successful synthetic strategies for VANOL to the preparation of VAPOL. Different approaches to VAPOL are depicted in Scheme 3.1, and the monomer **16b** was quickly identified as the key building block.

From a practical standpoint, it became immediately obvious that the modular synthesis *via* condensation of 1-chloro-4-phenanthrol with benzene (route 1, Scheme 3.1) was unattainable, since 4-phenanthrol **65** is not readily accessible.

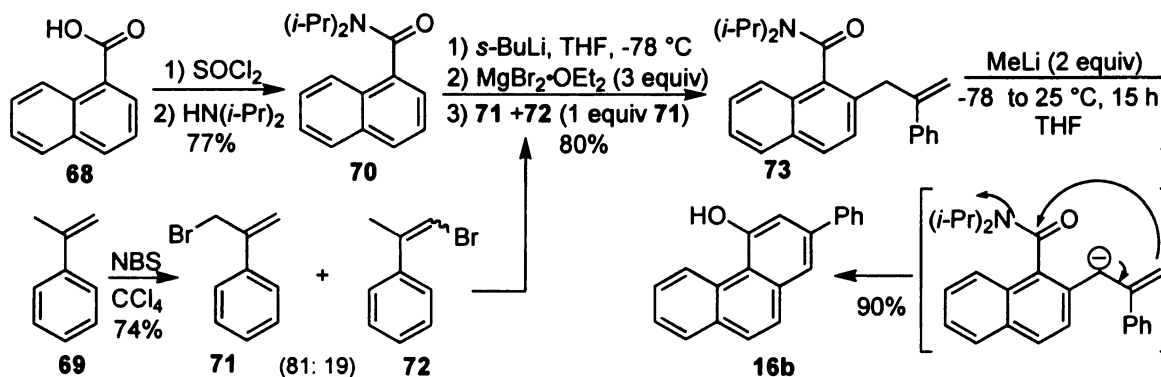
Similarly, other methods starting from linear materials (route 2 and 3) could only be integrated into a synthesis of VAPOL difficulty due to limited availability of the starting materials.

Scheme 3.1 Proposed pathways to synthesize **16b**



Over the last few years, a novel base-induced anionic cyclization reaction for the synthesis of substituted naphthols has been developed.¹¹⁸ The same methodology has been used to assemble the framework of VAPOL (route 4, Scheme 3.1) by Zhang, Mitchell and Rapalakos in our group (Scheme 3.2).^{118b}

Scheme 3.2 Preparation of monomer **16b** via the Snieckus phenol synthesis^{118b}



Thus, the precursor **73** (Scheme 3.2) for this transformation was synthesized using the directed *ortho* metallation of aryl amides developed by Snieckus^{118a} as

shown in Scheme 3.2. Thus, lithiation of the aromatic benzamide **70** was directed *ortho* to the amide group, and then subsequent transmetallation and alkylation with allyl bromide **71** afforded the desired *o*-allylbenzamide **73**. Treatment of this amide with a strong base such as MeLi resulted in the formation of **16b** in good yield.^{118b}

During the validation of this approach, it was readily recognized that this process for making **16b** was far from ideal in terms of supplying large quantities. The major weakness was the requirement of excess amounts of strong bases and the need for cryogenic conditions. Also, the reaction requires freshly prepared MgBr₂ (up to 6 equiv) to induce the alkylation and cyclization on the aromatic ring.^{118b} Upon scaling up from 1 g to 10 g, the yields of **73** dropped significantly (from 80% to 60%), and the final product **16b** was contaminated by several impurities that produced impossible to remove without chromatographic purification.

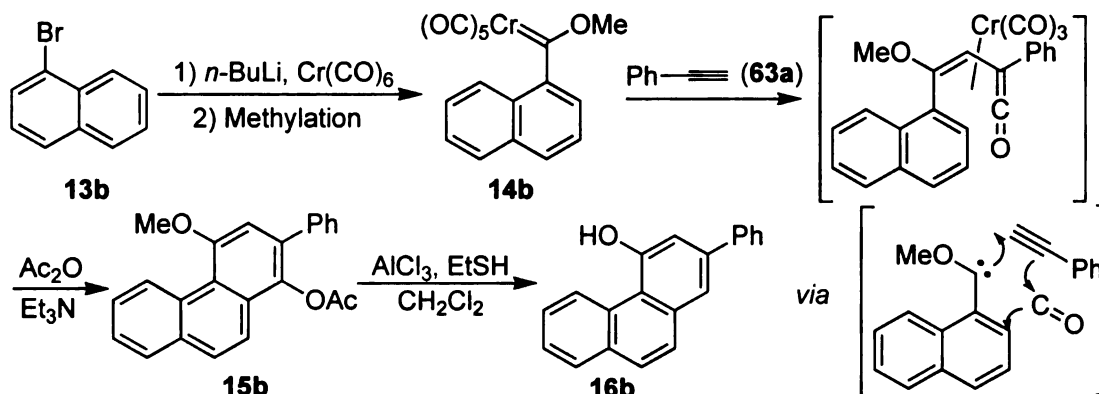
Conversely, at the beginning of this project, the aforementioned CAEC cascade reaction (i.e. [2+2] cycloaddition/ electrocyclization cascade reaction, route 5, Scheme 3.1; See also Scheme 2.38 of Chapter Two) was found to be impracticable for the synthesis of VAPOL for a number of reasons.^{17b} Apart from low yields, it was not possible to purify **16b** from the black tarry material obtained from this reaction without careful column chromatography, a situation generally not favored for large-scale synthesis.

Thus, at the time that the present work was begun, the route to VAPOL that was most easily adoptable was the approach involving the benzannulation of a

Fischer carbene complex prepared from **13b** and $\text{Cr}(\text{CO})_6$ (route 6, Scheme 3.1). This synthesis is shown in detail in Scheme 1.7 of Chapter one. The goal of the work presented on existing synthesis of VAPOL using the benzannulation. One of the drawbacks is the cost of $\text{Cr}(\text{CO})_6$ (\$561 /100 g).²⁵ Although the cost of $\text{Cr}(\text{CO})_6$ is beyond the control of the synthetic chemist, there are many other aspects of the synthesis involving the benzannulation with a Fischer carbene complex that were deemed possible to improve.

Part of the inducement to pursue improvements in the benzannulation approach outlined in Scheme 3.3 is that it had already been shown that it could be scaled up to 250 g of carbene complex **14b**.¹¹⁹

Scheme 3.3 Synthesis of VAPOL monomer **16b** via the benzannulation reaction



Laboratory-scale procedures are available for conducting benzannulation reaction of carbene complexes.^{119,122} However, reports in the literature pertaining to the optimization of the whole process in order to meet the requirements of large-scale synthesis are rare. Thus, in pursuing improvements on the synthesis of **16b** to enhance scale access to VAPOL, the following interdependent parameters were considered:

Reagents—As noted above, *n*-BuLi and Cr(CO)₆ are required for the large-scale preparation of **16b**, and represent as the most important reasons for the cost problem with this synthesis. However, no viable alternative to chromium Fischer carbene complex exists for the benzannulation.¹²²

Procedures—Another scale-up challenge is to simplify the procedures to facilitate throughput. For instance, variation in the order of addition of substrate, alkyllithium, and electrophile are possible in the bromine-lithium exchange step. This will ensure minimal material transfer steps and the isolation of intermediates, since it is commonly the case that isolation is usually costly and invariably leads to some loss of material.

Medium—The use of solvents other than THF, or of a mixture of solvents with THF as a component of a predominantly hydrocarbon medium, offers advantages. When trying to improve economic efficiency, hydrocarbon solvents are preferable since etherate solvents especially THF have to be dried and deoxygenated when dealing with strong bases and carbene complexes.

Temperature—It is not always necessary to prepare carbene complexes at the temperatures typically used in a laboratory setting (-78 °C). Halogen-lithium exchange reactions have been conducted at temperatures as high as 0 °C.¹²⁰ It is obvious that reactions conducted at higher temperatures will save money by the elimination of the burdensome cooling equipment.

3.2 Synthesis of 16b via the benzannulation of a carbene complex

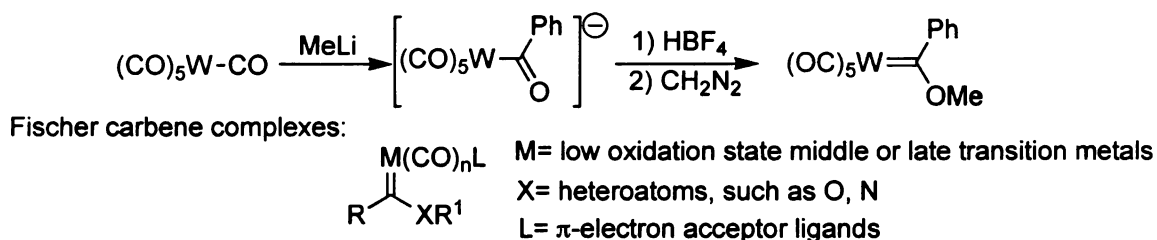
A rapidly growing class of methods for the synthesis of various phenols involves the use of transition metals in cyclization reactions.¹²¹ Currently, the

most widely used transition metal-mediated method for the synthesis of naphthalene and other aromatic compounds is the Wulff-Dötz benzannulation.¹²² An example is the reaction of an alkoxyated aryl carbene complex such as **14b** with an alkyne to afford **15b**.

3.2.1 Carbene complexes and their benzannulation reaction with alkynes

Since the discovery of the pentacarbonyl[methoxybenzylidene]tungsten(0) complex by Fischer and Maasbol in 1964 (Figure 3.1),¹²³ a rich chemistry of transition metal carbene complexes has evolved. Most of this work has dealt with heteroatom-stabilized carbene complexes, namely Fischer-type complexes particularly with group 6 transition metals. This has been the subject of much discussion and investigation both synthetically and mechanistically in the past three decades.^{122,123,124a}

Figure 3.1 Fischer carbene complexes: discovery and structural features



Applications of Fischer carbene complexes have been extensively examined in organic synthesis.^{124a} Undoubtedly the benzannulation reaction with alkynes has been one of the most widely used in organic synthesis. Dötz^{124b} and Wulff^{124c} are the pioneers in developing this interesting and practical protocol, which paves a way for facile access to a variety of aromatic compounds. Mechanistically, the newly formed benzene ring results from assembly of three carbons of the α,β -unsaturated carbene complex, two carbons of the alkyne and one carbon of a

carbon monoxide ligand (Scheme 3.3 and Scheme 3.9).¹²⁵ The synthetic value of this reaction stems from generally high yields and mild reaction conditions, occurring just above ambient temperature. It tolerates a widely variety of substitution patterns. With its broad scope and simplicity of operation, the benzannulation reaction is one of the most powerful and versatile synthetic tools for the synthesis of poly-substituted phenols. It is these features that make for an attractive synthesis of VAPOL starting from 1-bromonaphthalene (Scheme 3.3).

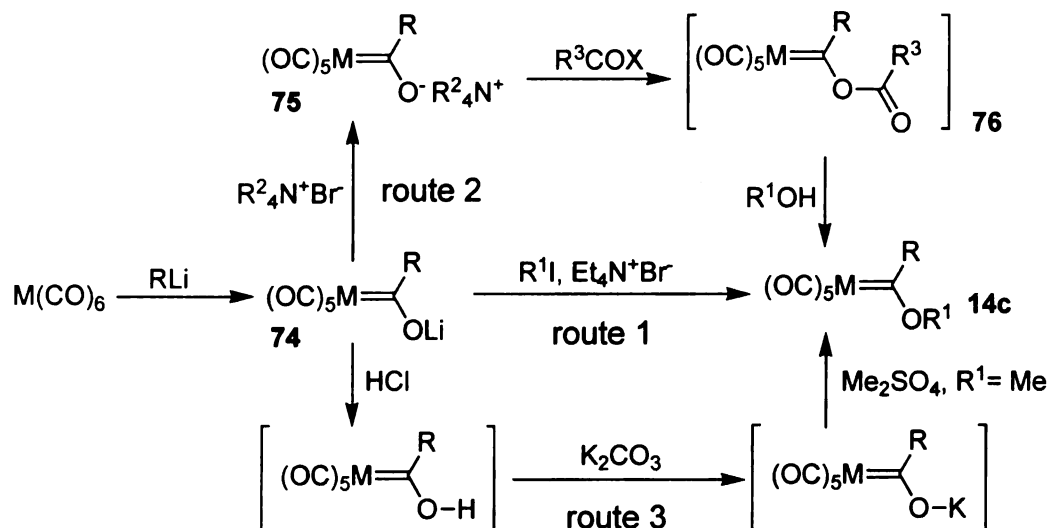
3.2.2 Preparation of chromium-based carbene complexes: an overview

The most widely used method for the preparation of Fischer carbene complexes involves the addition of an organolithium species to a metal carbonyl as originally reported by Fischer.¹²³ The alkoxy complexes can be formed directly from the metal acylate by *in situ* alkylation with alkylating reagents, such as alkyl fluorosulfonates, trialkyloxonium salts or alkyl trifluoromethane sulfonates.¹²²

In order to make the procedures more economically efficient, cheaper alkylating reagents have been applied to the preparation of carbene complexes. For instance, alkyl iodides (route 1, Scheme 3.4) have been reported as alkylation reagents of Fischer carbene complexes in the presence of phase-transfer agents.^{126a} However, it is not generally useful because they alone are not electrophilic enough to react with the lithium acylates **74** to give high yields of carbene complexes. The reactivity of **74** can be increased by converting it to the tetraalkylammonium salt **75** (route 2), followed by transforming it into "mixed anhydride" **76**. The intermediate **76** was then attacked by nucleophiles such as

alcohols at the electrophilic carbene center to give the alkoxyl carbene complex **14c**.^{126b}

Scheme 3.4 Methods for the alkylation of the lithium acylmetalate **74**

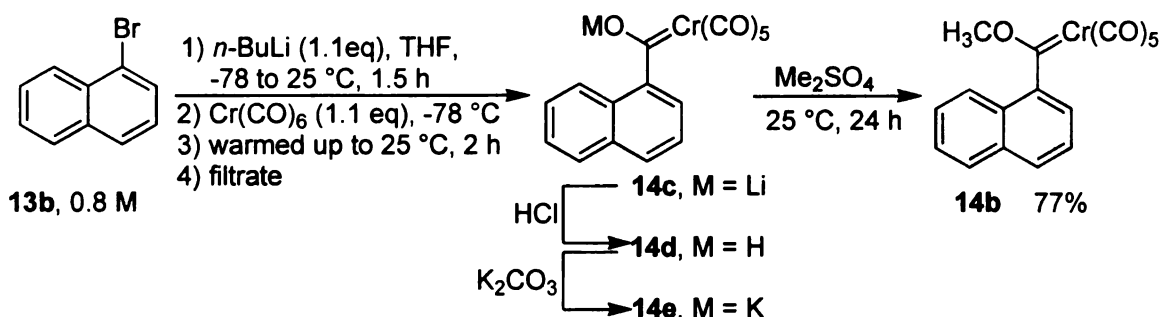


While successful, these methods rely on the use of extra reagents and steps. This posed a serious limitation on the applicability and scalability of these alkylation methods. Attention was therefore turned to the possibility of using dimethyl sulfate as methylating agent (route 3, Scheme 3.4). Although Me_2SO_4 is toxic and slow to react with lithium acylmetalates **74**,^{17b,119} it is cheap compared to oxonium salts and methyl triflate which are the most effective alkylating agents. Bearing in mind that the sluggish reaction of Me_2SO_4 with **74** probably results from the strong bonding between lithium and oxygen, a solution was considered which involved conversion of **74** to the corresponding potassium acylate prior to methylation.

The reported procedure^{17b} starts with the preparation of 1-naphtyllithium in dry THF at -78°C , which was transferred to Cr(CO)_6 via a cannula (Scheme 3.5). The resultant lithium acylate **14c** was suction filtered through Celite to

remove any remaining $\text{Cr}(\text{CO})_6$. The filtrate was diluted with diethyl ether and washed with 5 % aqueous HCl, to which was quickly added potassium carbonate and was allowed to stir until bubbling ceased. Dimethyl sulfate was then added and allowed to stir for 12 h at ambient temperature. Purification by crystallization from hexanes (two crops) afforded carbene complex **14b** in 77% yield (34.0 g) from 121 mmol of **13b**. This is the starting point for the optimization of this approach to the VAPOL monomer **16b**.

Scheme 3.5 The reported protocols to prepare **14b**^{17b}



3.2.3 Preparation of chromium-based alkoxy carbene complexes: optimization

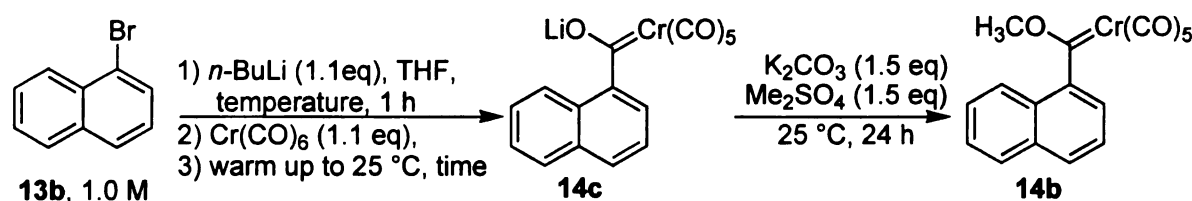
In the preparation of carbene complex **16b**, the lithium-halogen exchange¹²⁷ reaction of 1-bromonaphthalene **13b** with $n\text{-BuLi}$ is the first step. The resulting 1-naphthyllithium was subsequently trapped with $\text{Cr}(\text{CO})_6$. Operationally, it was necessary to address two major drawbacks of the reported procedure^{17b} before proceeding further. First, the original procedure^{17b} calls for the transfer of the aryllithium to $\text{Cr}(\text{CO})_6$, which adds to the technical difficulty on large scale. Second, the lithium-halogen exchange reaction was performed at low temperature due to the thermally instability of aryllithium.

Accordingly, two major changes were implemented in the original route.

Firstly, the order of addition of the reagents was reversed, in a way that solid $\text{Cr}(\text{CO})_6$ was added to a THF solution of the aryllithium under positive N_2 pressure.¹¹⁹ Secondly, the reaction was performed at $-50\text{ }^\circ\text{C}$ in a dry ice/ethanol bath, since ethanol was easy to handle in large quantities.

These improvements in the procedure simplified the reaction on large scale and provided necessary quantities of **14b** for the next step (Table 3.1, entry 1). Unfortunately, it suffered from lower yield (Scheme 3.5). No improvement in yield was observed even when the temperature was lowered to $-78\text{ }^\circ\text{C}$ (entry 2).

Table 3.1 Preparation of carbene complex **14b**



Entry	Scale of 13b (mL)	Temperature ($^\circ\text{C}$)	Time (h) ^a	14b (%)
1 ^b	60	-50	2	68.5
2 ^b	60	-78	2	66.5
3	60	-78	6	65.8
4	3	-78	12	75.8
5	60	-78	12	86.0
6				83.0
7 ^c	3	-78	12	84.0
8 ^c	3	0	12	48.2

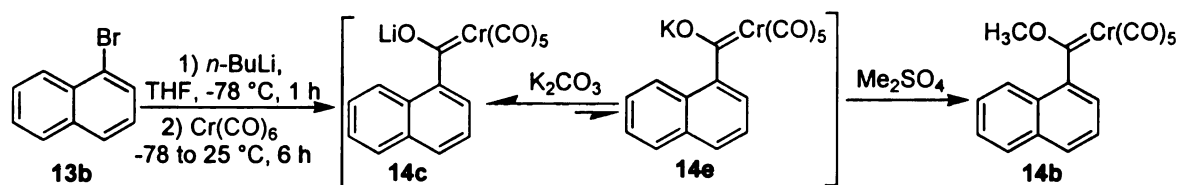
^a Time to prepare **14c**. For details, see: Section 7.3.1.1 of Chapter Seven. ^b **14c** was treated with 2 M HCl before addition of K_2CO_3 . ^c BuLi was added to a mixture of **13b** and $\text{Cr}(\text{CO})_6$.

It was noticed that a lot of $\text{Cr}(\text{CO})_6$ (about 10 g) was recovered during filtration in the reaction in entry 2 of Table 3.1. In addition, naphthalene (2.3 g) was also obtained from this reaction as a byproduct. These observations clearly indicated that the reaction between 1-naphthyl lithium and $\text{Cr}(\text{CO})_6$ did not go completion. Another concern was the requirement of a HCl workup to effect the conversion of

14c to **14e** prior to methylation (Scheme 3.5). It is well known that the carbene complexes especially hydroxyl carbene complexes are vulnerable to oxygen and acid.¹²² Therefore, in addition to material loss during unit operations, decomposition of **14d** and **14b** might also be responsible for lower than desired yields.

The reaction was then repeated at $-78\text{ }^{\circ}\text{C}$ with an extended time period (Table 3.1, entry 3). After the mixture of the aryllithium and $\text{Cr}(\text{CO})_6$ was stirred in THF while warming up to ambient temperature, K_2CO_3 and Me_2SO_4 were added without the HCl workup. The resulting red suspension was allowed to react for 24 h. The idea was that **14e** could form *in situ* by cation exchange in equilibrium between **14c** and **14e**, and that subsequent methylation would drive the reaction to completion (Scheme 3.6). Therefore, the direct inclusion of K_2CO_3 and Me_2SO_4 in the system remarkably simplified the procedure, and a comparable yield was obtained (entry 3). It was also pleasant to find the yields of **14b** could be improved with a longer reaction time (entry 4), and that the outcome of the reaction could be reproduced on large scale (entry 5 and 6).

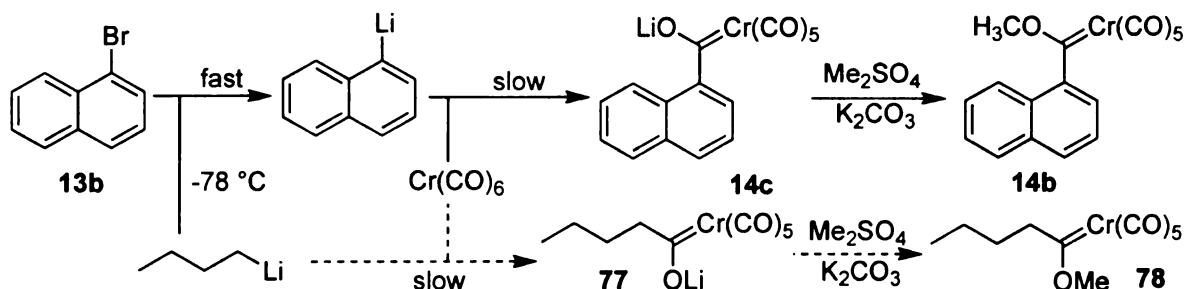
Scheme 3.6 *In situ* formation of **14e** and its conversion to **14b** via methylation



Still not satisfied with these results, the procedure could be further simplified if *n*-BuLi could be added to a mixture of **13b** and $\text{Cr}(\text{CO})_6$. However, the realization of the synthesis of the naphthyl complex **14b** might be seriously compromised by the formation of *n*-butyl complex **78** if the halogen-lithium

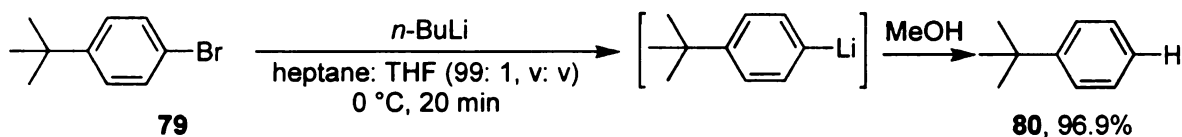
exchange reaction is not fast enough (Scheme 3.7).

Scheme 3.7 Possible competing reactions of *n*-BuLi with Cr(CO)₆ and **13b**



The new proposed conditions were tested by the addition of *n*-BuLi to a mixture of Cr(CO)₆ and **13b** in THF (Table 3.1, entry 7). Extra care was taken to maintain an internal temperature less than -70 °C in order to obtain the best yields and consistent results. Surprisingly, this reaction produced **14b** in yields comparable to that in which *n*BuLi is added to **13b** first (Table 3.1, entries 5 and 6). The yield dropped appreciably when the reaction was carried out at 0 °C with this new protocol (Table 3.1, entry 8).

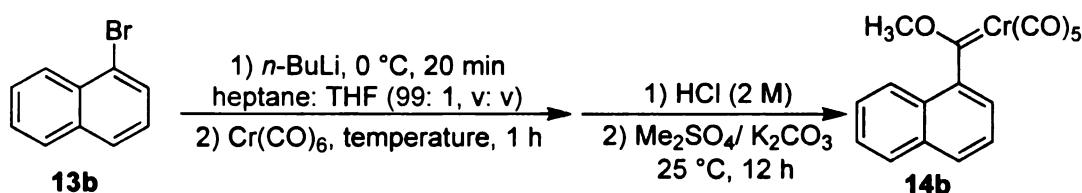
Scheme 3.8 Lithium-halogen exchange reaction of **79** in heptane at 0 °C



In an effort to avoid sub-zero temperatures, a probe of the effects of solvent on this process was undertaken. Bailey and coworkers¹²⁰ have recently reported that the halogen-metal exchange of **79** with *n*-BuLi is rapid at 0 °C in heptane containing 1% of THF (Scheme 3.8). When 1-naphthyllithium was generated according to Bailey's protocol and then utilized in the above procedure for the preparation of carbene complex **14b**, no detectable amount of **14b** was observed. Employment of an inverse addition sequence was also attempted.

Therefore, **13b** was added to a solution of *n*-BuLi under the same conditions (Table 3.2, entry 2). This ensured that *n*-BuLi would be present in excess during the addition, thus preventing competitive quenching of the initially formed 1-naphthyllithium by any possible acidic proton sources. Nevertheless, **14b** was not detected and the only isolated compound was recovered Cr(CO)₆. A low yield of **14b** (entry 3) was furnished when Cr(CO)₆ was added to the mixture of *n*-BuLi and **13b** after the mixture was cooled down to –50 °C.

Table 3.2 Preparation of carbene complex **14b** in heptane-THF at 0 °C



Entry	Scale of 13b (mL)	Temperature (°C) ^a	14b (%)
1 ^b	3	0 to 25	nd ^c
2 ^d	3	0 to 25	nd ^c
3 ^d	3	-50 to 0 ^e	18.0

^a The reaction was stirred for 30 min at 0 °C after Cr(CO)₆ was added, and then warmed up to 25 °C over 1 h. ^b *n*-BuLi was added to **13b** over 10 min. ^c nd= not detected. ^d **13b** was added to BuLi over 10 min. ^e The reaction was cooled down from 0 °C to –50 °C before Cr(CO)₆ was added.

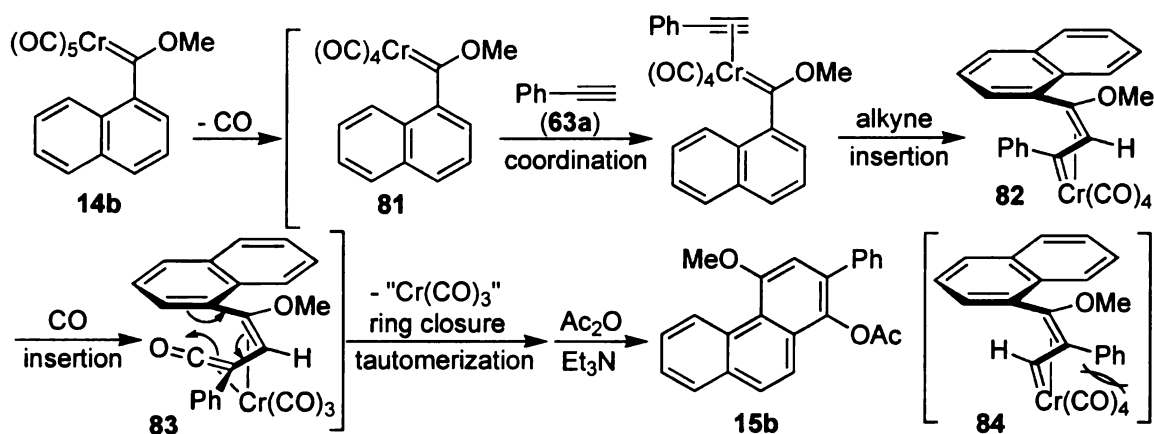
Although further optimization of the synthesis of **14b** at 0 °C was not further pursued due to time constraints, one should be aware that the poor results in Table 3.2 do not necessarily mean that ultimately a solution can not be found. One of the important features of alkyl lithium reagents is that the aggregation states are strongly effected by the solvent,¹²⁸ which can significantly alter their reactivity. Thus, the reaction of aryllithium with Cr(CO)₆ might require a longer time to go to completion in heptane. Even so, these experiments shed some light on the nature of the reaction.

In summary, an improved process has been developed that offers a number of advantages for the preparation of alkoxy-bearing Fischer carbene complexes. By *in situ* exchange of lithium to potassium counterion, methylation of metal acylate complexes using Me_2SO_4 proved to be not only equally powerful, but also economically more efficient and convenient over the classic methylating agents such as Meerwein salts. In addition, in a preliminary study of a “one-pot” preparation of carbene complexes by addition of butyllithium to a mixture of $\text{Cr}(\text{CO})_6$ and **13b** it was revealed that further simplification of the procedure is possible. This protocol should be preparatively useful for accessing other Fischer carbene complexes as well.

3.2.4 Benzannulation reaction of carbene complexes 14b with phenylacetylene 63a

The next focus of the synthetic reassessment was to convert the carbene complex **14b** into phenanthrene **15b**. Improvement in the efficiency in benzannulation protocol has been a product of a continuous effort to elucidate the mechanism of Wulff-Dötz reaction. The current understanding of the mechanism of the reaction of alkyne **63a** with α,β -unsaturated Fischer carbene complexes such as **14b** is presented in Scheme 3.9.¹²⁵ The first step involves dissociation of carbon monoxide from the starting carbene complex to give the 16-electron species **81**. The subsequent coordination and insertion of alkyne **63a** to **81** gives rise to the vinyl carbene complexed intermediate **82**. Upon insertion of CO, the η^4 -vinyl ketene complex **83** is generated. This intermediate **83** undergoes electrocyclic ring-closure, tautomerization and acetylation gives **15b**.

Scheme 3.9 Mechanism of the benzannulation reaction of **14b** with **63a**



One important aspect of the reaction is the nature of the workup procedure. Great care has to be taken since the phenol product is generally sensitive to oxidants, but at the same time oxidation is usually required in the workup to remove the chromium complexed to the products.¹²² The reaction was first examined (Table 3.3, entry 1), and **14b** was consumed within 1 h as indicated by TLC analysis. The crude mixture was then refluxed with acetic anhydride using triethylamine as base to give **15b** in 76.7% isolated yield.

Table 3.3 Benzannulation reaction of **14b** with **63a** in THF

Entry	14b (g)	Conditions ^a	15b (%) ^b
1	12	65 °C, 4 h; under N ₂ atmosphere (by using a N ₂ balloon)	76.7
2	24		66.9
3	104		64.7
4	101		52.6
5	100		58.4
6	110	55 °C, 12 h; under positive N ₂ pressure (by using a N ₂ flow)	76.7
7	110		76.7

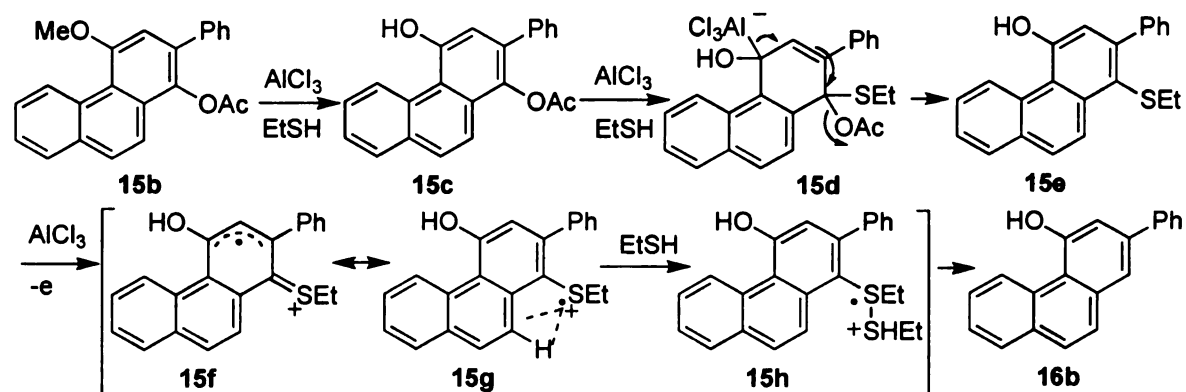
^a Phenylacetylene **63a** was added over 3 h. For experimental details, see: Section 7.3.1.2 of Chapter Seven. ^b Isolated by crystallization using hexanes.

With these conditions identified, the one-pot reaction was then carried out on large scale. Surprisingly, the yields were always lower than anticipated when the reactions were performed under a blanket of N₂ in a balloon (Table 3.3, entries 2-5). It was presumed that the inconsistency in the yields resulted from the presence of O₂ in the system. This lingering O₂ could have facilitated oxidative decomposition of the carbene complex, especially at higher temperatures. Accordingly, a conscious attempt was made to purge the air out of the reaction vessel by maintaining a very low nitrogen sweep. Meanwhile, the reaction temperature was lowered from 65 °C to 55 °C with an elongated reaction time (entry 6). As expected, under these modified conditions, significantly higher yields were consistently obtained on 110 g scale of **14b** (entry 7).

3.2.5 Reductive deprotection of 4-acetoxy group of **15b**

Monomer **16b** can be generated by reductive removal of the 4-acetoxy protecting group from **15b**.^{17b} The conditions should be mild to avoid side-reactions. In an effort to cleave the 4-methoxyl group in **15b** using AlCl₃-EtSH, Dr Bao in this research group made an interesting discovery that reduction of acetoxy group also took place *in situ* to give desired compound **16b**.^{17b}

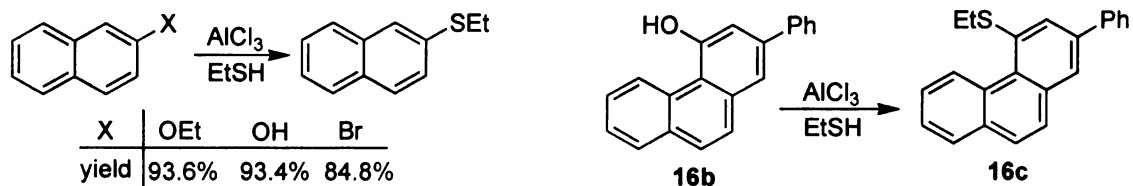
Scheme 3.10 Mechanism of reductive deprotection of **15b** to produce **16b**



The mechanism shown in Scheme 3.10 to account for the formation of the phenanthrol **16b** from **15b** is based on a mechanism proposed for reduction of related naphthalene compounds by Fujita.^{74a} Dr. Bao's observed that varying amounts of the *p*-acetoxy phenol **15c** could be isolated from the reaction if the reaction time was insufficient. Thus, it is believed that the cleavage of the methyl ether proceeds prior to the reduction of the acetoxy group. Subsequent steps in the overall process involve conversion of the acetoxy compound **15c** into the sulfide **15e** followed by a thiol mediate reduction of **15e** to **16b**. However, α -substituted but not β -substituted naphthalenes can undergo this type of reduction (Scheme 3.11).^{74a} In the latter case, no reduction was observed under identical conditions, and the only compound isolated was ethyl 2-naphthyl sulfide.

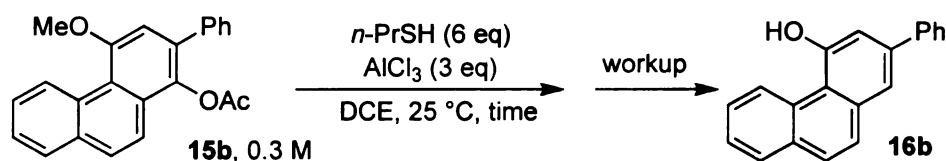
This mechanism raised several operational concerns. First, time and temperature control appeared essential to drive the reaction to completion. Second, over reaction of the product **16b** with EtSH could lead to the formation of sulfide **16c** since this transformation has been observed for 2-naphthol (Scheme 3.11).^{74a} In addition, the use and disposal of EtSH raises environmental concerns due to its strong pungent odor and high volatility. Hence, 1-propanethiol was used to for the VAPOL synthesis in favor of its higher boiling point and lower vapor pressure.

Scheme 3.11 Possible side reaction of **16b** under the given conditions



Experiments were performed in order to explore the limits of time and temperature that could be tolerated on large scale. The results from these experiments are summarized in Table 3.4. Following the small-scale procedure¹¹⁹ where the temperature was controlled at 25 °C, compound **16b** was obtained in 56.4% yield (Table 3.4, entry 1), which was similar to that of our small-scale results.¹¹⁹

Table 3.4 Generation of **16b** by reacting **15b** with *n*-PrSH and AlCl₃



Entry	15b (g)	Time (h)	Workup conditions ^b	16b (%) ^c
1	20.0	12	Aq. NaHCO ₃ ; then filtered through Celite	56.4
2	45.3			59.5
3	63.6 ^a	12	Quenched by HCl; then extracted by CH ₂ Cl ₂	83.2
4	105 ^a			73.7
5	79.8 ^a	14		83.2
6	80.1 ^a	36		63.5 ^d

^a Addition of **15b** in 4 portions every 5 min. For experimental details, see: Section 7.3.1.3 of Chapter Seven. ^b Most of *n*-PrSH was removed and recovered by vacuum distillation. ^c Isolated by crystallization. ^d After columns; at least two unknown byproducts were also detected.

The reaction shown in entry 1 of Table 3.4 was deemed unacceptable to proceed to scale up. For one thing, the yield was low and needed further improvement. As noted before, mild conditions are important to avoid side reactions. However, it was found that the reaction was quite exothermic. Therefore, the reaction was repeated by addition of **15b** in portions. Moreover, a revision of the workup procedure proved important for scale-up. The original procedure involved careful treatment of the crude reaction mixture with aqueous NaHCO₃.¹¹⁹ This led to vigorous release of gases and heat. Additionally, massive

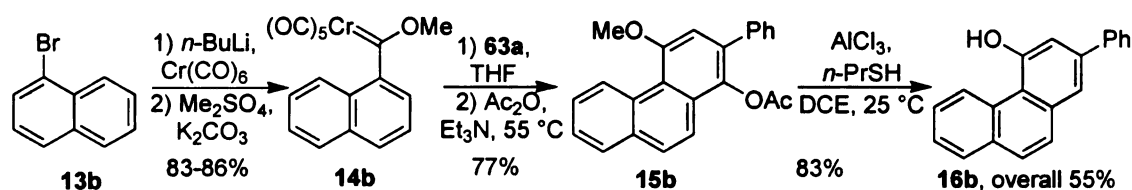
amounts of insoluble aluminum oxides formed from AlCl_3 , which resulted in loss of the product.

To aid material throughput, the crude reaction mixture was chilled in an ice bath and pre-cooled HCl (6 N) was used to quench the reaction. As a result, the reaction generated the required **16b** more reliably and in a more efficient manner (Table 3.4, entries 3 to 6).

3.2.6 Summary

A simple and site-specific preparation of the VAPOL monomer **16b** from 1-bromonaphthalene **13b** has been developed. The work described above resulted in two significant improvements in the original procedure. One is the discovery of an easier and less hazardous way to prepare the carbene complex **14b**. Another is the introduction of an acidic workup for the reductive deprotection of **15b** that greatly enhances material throughput. Accordingly, this synthesis generated 52 grams of **16b** (Scheme 3.12) from 105 grams $\text{Cr}(\text{CO})_6$.

Scheme 3.12 Overview of the synthesis of VAPOL monomer **16b** from **13b**



3.3 Synthesis of VAPOL monomer **16b** via a thermal CAEC cascade reaction

Although the synthesis of VAPOL using a carbene complex was feasible on large scale, it was found to have several intrinsic flaws. The major problem was the cost of $\text{Cr}(\text{CO})_6$ (\$5/g).⁵⁹ A second but less prohibitive issue is that BuLi is corrosive, highly flammable and sensitive to air and moisture and therefore hard

to handle particularly in large quantities. These factors necessitate dry solvent and the careful control of the reaction conditions, and make it less attractive for large-scale commercial exploitation.

3.3.1 Background

To reach the target molecule **16b**, the route involving [2+2] cycloaddition/electrocyclization cascade reaction (i.e. the CAEC cascade reaction) of a ketene cyclization looks particularly attractive since this approach is the shortest possible pathway (Scheme 3.1, route 5). The starting material for this approach is 2-naphtylacetic acid which costs \$0.5/g (Ochem incorporation. In fact, it has been prepared on large scale; for details, see reference 68).⁶⁸ In the original investigation of this approach^{17b} it was found that isolation of good quality **16b** from the crude mixture of this reaction was troublesome and challenging because it was rich in unidentifiable byproducts. This unwanted residue was thought to interface with subsequent steps in the synthesis of VAPOL, thereby rendering this material unsuitable for downstream processing.^{18e}

Fortunately, by the time this work was initiated, it was found that the synthesis of VAPOL was much less sensitive to the purity of **16b**, much thanks to the new conditions for the oxidative coupling reaction (Chapter Four). Consequently, the concentration was turned to the pathway from **17b** to obviate the problems presented by the benzannulation reaction.

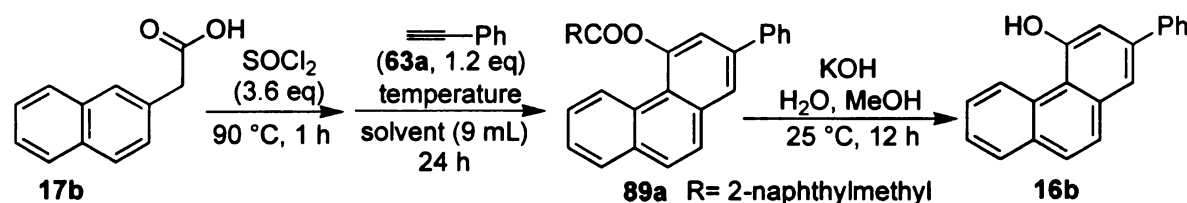
3.3.2 Solvent effects on the thermal CAEC cascade reaction

The synthesis of the VAPOL monomer **16b** via the CAEC cascade reaction was conducted under the reported^{17b} solvent-free conditions (Table 3.5, entry 1).

This involves the conversion of the carboxylic acid **17b** to the corresponding acid chloride **18b** and then, without purification, the acid chloride is heated neat with phenylacetylene **63a**. The primary product of the reaction is the ester **89a** that results from the trapping of the ketene intermediate with the phenol **16b**. A black tar was produced from this reaction. In an effort to reduce the concentration of the ketene, the acid chloride **18b** was added in two portions (entry 2). However, a similar black tarry crude product was obtained, from which no consequential amount of the product was isolated.

It was reasoned that these poor results could be attributed to a number of factors, and among them, the drastic conditions stood out as the major concern. One of the consequences of such harsh conditions was the partial destruction of the substrates through their prolonged contact with the walls of the reaction vessel. This necessitated an efficient stir technique to help conduct energy.

Table 3.5 Preparation of **16b** from **17b** and **63a** with or without solvent



Entry	17b (mmol)	Solvent	Temperature (°C) ^a	Time (h)	16b (%) ^b
1	153	N. A.	185	26	not determined
2 ^c	76.6	N. A.	185	32	not determined
3	49.4	Decalin	190	16	32.2 ^d

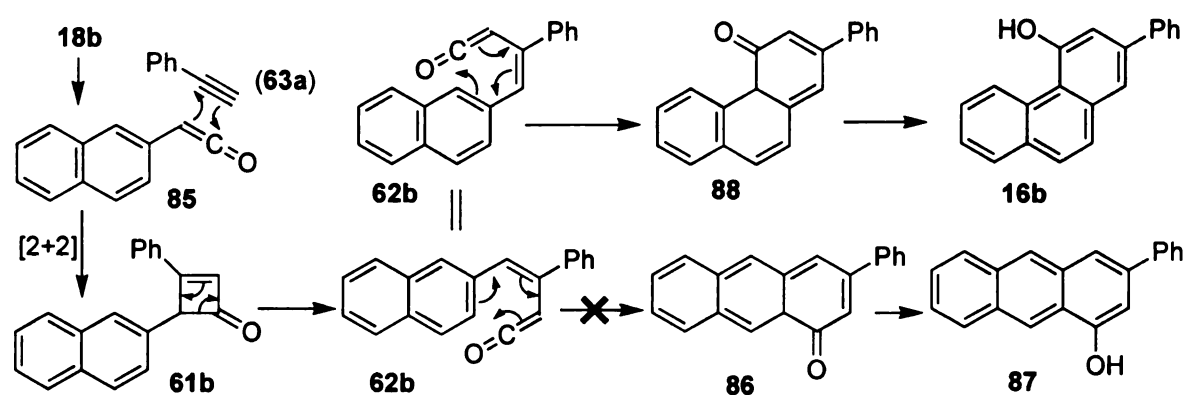
^a Oil bath temperature. ^b Yield was based on **17b**. ^c **18b** was added in two portions. ^d LiAlH₄ (1.1 eq) in 100 mL ether was used for workup at 25 °C for 12 h; isolated by column chromatography.

Although solvents are generally not used for this kind of transformation,^{110b} it was thought that the presence of a small amount of solvent with a high boiling point might improve the reaction. Thus, decalin was used for the reaction due to

its non-volatility, low toxicity, and its inertness to harsh reaction conditions (Table 3.5, entry 3). Independently, Redic and Schuster have employed decalin in a related reaction.¹¹² After LiAlH_4 workup, a brown solid was isolated. Both TLC and the ^1H -NMR spectrum were in agreement with those reported^{17b} for **16b**. Decalin could be easily removed by column chromatography as a consequence of its low polarity. The yield of **16b** (32%, Based on **17b**) is low partly because one equivalent of **17b** was used to trap the phenol **16b** to form ester **89a**.

An unknown product was obtained after silica gel column separation. It was reasoned that the structure of this byproduct was unlikely to be the regioisomer **87** in Scheme 3.13. This is because in order to form the anthrol **87**, the aromaticity has to be broken for both benzenoid rings in the intermediate **86**.¹²⁹ Thus, it was conceivable that this byproduct was 2-(2-naphthyl)-1-ethanol, which resulted from the reduction of intermediary **89a** by LiAlH_4 . The structural elucidation of this compound will be discussed in Section 3.4.2 (Scheme 3.15).

Scheme 3.13 Mechanism of the CAEC cascade reaction of ketene **85** with **63a**



3.3.3 Optimization of the thermal CAEC cascade reaction in mineral oil

Although the above-described CAEC cascade strategy has the potential to provide rapid access to **16b**, the pitfalls of this approach from a large-scale

perspective are not insignificant. First of all, it is well known that decalin readily forms explosive organic peroxides at elevated temperatures.¹³⁰ Therefore, the use of decalin posed a significant safety concern. The buildup of peroxide could be avoided by using a different solvent. Hence, in view that no tertiary proton exists in mineral oil, formation of peroxides of this material is considered unlikely, and it was examined as a solvent for the reaction. The two side-by-side reactions produced **16b** in comparable yields (Table 3.6, entry 1 & 2).

To further improve the yield, the effects of changes of the reaction parameters in mineral oil were investigated. The yield dropped significantly when the reaction was conducted at a lower temperature (Table 3.6, entry 3). However, no improvement was observed in the yield at a higher temperature (entry 4). The reaction was also examined with increased amounts of alkyne **63a**. The yield increased slightly with 1.3 equiv of **63a** (entry 5), but dropped when further increased to 2.6 equiv of **63a** (entry 6).

Table 3.6 Preparation of **16b** from **17b** and **63a** with or with different solvents

Entry	Solvent	Temperature ^a (°C)	63a (eq)	16b ^b (%)	Mp of 16b ^f (°C)	Color of 16b
1	Decalin	190	0.67	36.8	144-5	Brown
2	Mineral oil	170		38.4	140-1	
3		210		21.7	150-1	
4		190		37.2	147-8	
5 ^{c,d}	Mineral oil	190	1.31	41.4	140-1	Iron grey
6 ^{d,e}		190	2.62	34.5	149-0	Iron grey

^a Oil bath temperature. For experimental details, see: Section 7.3.2.1 of Chapter Seven. ^b Isolated by column chromatography, and the yield was based on **17b**. ^c New bottle of SOCl₂ was used; ^d LiAlH₄ (1.72 eq) was used; ^e LiAlH₄ (2.59 eq) was used. ^f The mp of **16b**^{17b}: 154-5 °C

3.4 The CAEC cascade approach with *in situ* trapping of the phenol moiety

As presented in Table 3.6, only one out of two molecules of **17b** could be converted to the intended phenol **16b** since the ketene formed from one molecule of **17b** was trapped by phenol **16b** and thus in effect is wasted. This means that the theoretical yield of **16b** is 50%. Given that acid **17b** is relatively more costly than alkyne **63a**, suppression of the formation of the ester **89a** was desired. Based on the mechanism (Scheme 3.13), the idea was conceived that a trapping agent could be found that could compete with the *in situ* generated ketene in the reaction with the phenol function in **16b** but not otherwise affect the reaction.

3.4.1 Protecting phenols: an overview

In developing a synthesis of any phenol-containing product, protection is often mandatory to prevent side-reactions of the nucleophilic hydroxyl group. In general, it can be protected as ethers or esters. Formation of ethers usually requires the presence of base since in most case the hydroxyl group itself is not nucleophilic enough. Another problem associated with ether-forming agents is that they are usually too volatile to be amenable for requiring reaction conditions with high temperatures.

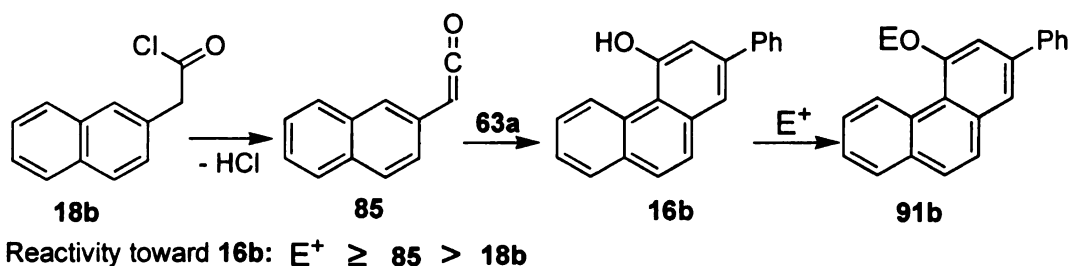
Protection of phenolic hydroxyl groups as esters, on the other hand, seems much more promising as exemplified by the isolation of the ester **89a** from the thermal reaction of the acid chloride of **17b** with phenylacetylene **63a** (Table 3.6).

The cleavage of the resulting esters is among the simplest and most often performed organic transformation. Moreover, the corresponding esterification reagents (acid halides and anhydrides) are generally reactive to a hydroxyl groups, are thermally stable, and are inexpensive and generally non-toxic. The CAEC cascade reaction was then tested in the presence of various esterification reagents, which, if operable, might be broadly useful.

3.4.2 Thermal CAEC cascade reaction utilizing acid chlorides as trapping agents

The realization of such an *in situ* protection protocol is crucially dependent on the ability of the trapping agent (i.e. E^+ in Scheme 3.14) competitively to react with **16b**. In other words, the reactivity of a given trapping agent E^+ toward **16b** should be no less than that of either the ketene **85** or the acyl chloride **18b**.

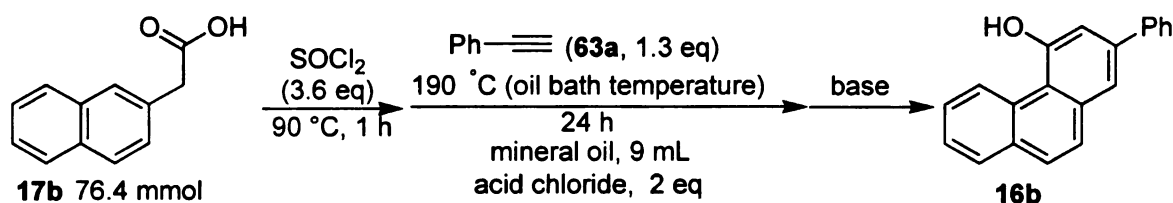
Scheme 3.14 *In situ* protection protocol for phenol **16b**



The electrophilicity of various acid chlorides could be profitably used as trapping agents to overcome the reactivity of ketene. Hence, various acid chlorides were tested and the results are summarized in Table 3.7. Noticeably, excess SOCl_2 was used to convert **17b** to acyl chloride **18b**. We performed the reaction in a one-pot fashion without removal of excess SOCl_2 , hoping that the phenol **16b** could be trapped as a sulfite. Contrary to our expectations, the desired product was not observed; instead a tarry black complex was obtained

(Table 3.7, entry 1). The reaction with POCl₃ fared a little better, giving a small amount of **16b** (entry 2).

Table 3.7 Preparation of **16b** using acid chlorides as trapping agents



Entry	Acid chloride ^a (mL)	Bp ^b (°C)	Base (eq)	16b (%) ^e	Mp of 16b (°C) ⁱ	Color of 16b
1 ^c	SOCl ₂	76	LAH (1.6) ^d	nd	nd	Black ^f
2	POCl ₃ (15)	105		16.1	128-0	Black
3 ^g	CH ₃ COCl (10)	51		23.3	148-9	Light yellow
4	PhCOCl (17)	198	KOH (4.7) ^h	44.3	152-4	Dark brown
5	PhSO ₂ Cl (20)	251		nd	nd	Black ^f
6 ^j	CH ₃ (CH ₂) ₆ COCl (25)	196		50.8 ^j	125-7	Chocolate

^a Crude without purification. ^b Boiling point of the acid chloride. ^c The excess SOCl₂ was not removed prior to thermolysis with **63a**. ^d Reduction performed in 100 mL ether at 25 °C overnight. ^e Isolated by column chromatography. nd= not determined. ^f Color of crude product; further purification was not performed. ^g The reaction time was 36 h. ^h Performed in 100 mL refluxing H₂O. ⁱ A new bottle of **63a** was used without purification. ^j The yield of 4-(2-phenyl)-phenanthryl octanoate. ^h The reported ^{17b} melting point of **16b** is 154-5 °C.

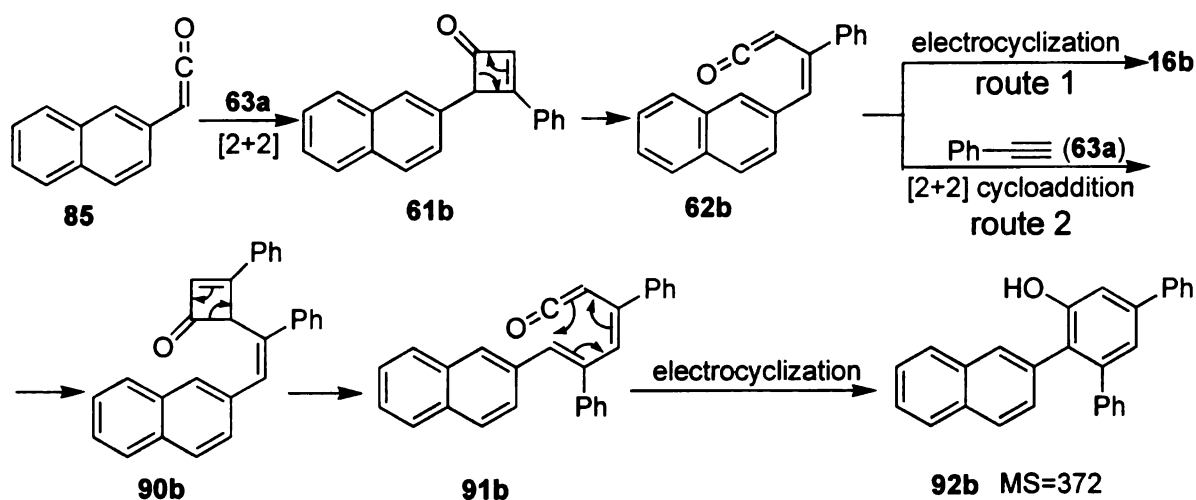
Attention was then switched to organic acid chlorides which have the advantage of presenting fewer hazards. A low yield of **16b** was obtained in acetyl chloride (Table 3.7, entry 3) although it produced material with much higher quality. This could probably be attributed to the low boiling point of CH₃COCl, which considerably reduced the internal temperature and thus decelerated ketene formation. This was supported by the observation of an increase in the yield by switching to PhCOCl as trapping agent (entry 4). Nevertheless,

considering that the yield was still < 50%, it seemed that this strategy did not work and the reason is unclear.

During the reductive cleavage of the crude esters with LiAlH₄, another problem arose as a result of the exothermic and violent nature of the reaction. This raised tremendous safety concerns associated with the presence of large amounts of trapping agents. This problem could be circumvented by switching the workup method to hydrolysis with aqueous KOH (Table 3.7).

The byproduct that was noted earlier (Section 3.3.2) was produced in these reactions, and could be isolated in pure form as a yellow solid. Since this compound could be isolated from both the reactions with a LiAlH₄ workup or with a KOH workup, the earlier tentative assignment of this material as 2-naphthyl-1-ethanol was severely challenged. Therefore, it was decided to elucidate its structure before proceeding. The structure was established to be 2-(2-naphthyl)-3,5-diphenylphenol (**92b**), which was supported by the observation of the molecular ion peak ($M^+=372$) in mass spectrum. Additional evidence for this structure was obtained by related spectroscopic studies (For experimental details, see: Section 7.3.2.2 of Chapter Seven). Thus, while it is still believed that, the desired product **16b** was generated *via* the mechanism outlined as route 1 in Scheme 3.15, the byproduct **92b** likely arose from insertion of two equivalent of phenylacetylene **63a**, with the second one being cycloadded to ketene **62b** that was derived from **61b** (Route 2, Scheme 3.15). Following the same reaction sequence to form **16b** in Scheme 3.13, the resulting cyclobutenone **90** underwent ring-opening and subsequent electrocyclization reaction to give **92b**.

Scheme 3.15 Formation of **92b** via double insertion of phenylacetylene **63a** to **85**

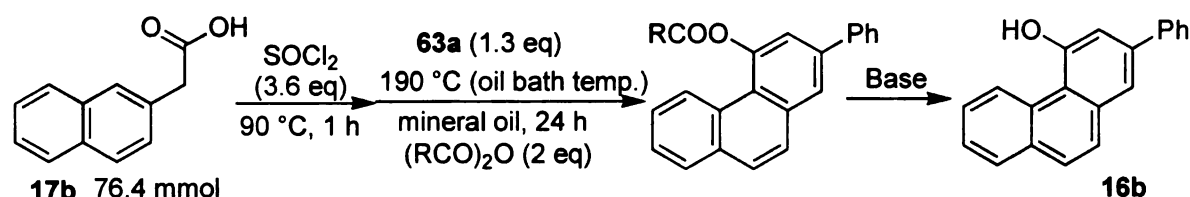


3.4.3 Thermal CAEC cascade reaction using anhydrides to trap 16b *in situ*

Anhydrides are also commonly used acylating reagents. These reagents tend to be less reactive than acyl chlorides and the common ones have higher boiling points. This made them particularly desirable for this high temperature. Hence, a protocol with these reagents would be preferred over that with acyl chlorides provided an anhydride with proper reactivity could be identified.

The reaction of acid chloride **18b** (prepared from **17b**) with alkyne **63a** in mineral oil was examined in the presence of 2 equiv of acetic anhydride (Table 3.8, entry 1). Under these conditions, a low yield of **16b** was obtained, which presumably resulted from relatively low boiling point of this anhydride. Consequently, performance of this reaction at an extended time improved the yield (entry 2). The use of propanoic anhydride did not affect the outcome of the reaction and the yield was still less than 50% (entry 3). The quality of the product from these reactions was much better than those with acyl halides in terms of melting point and color.

Table 3.8 Preparation of **16b** using anhydrides as trapping agents



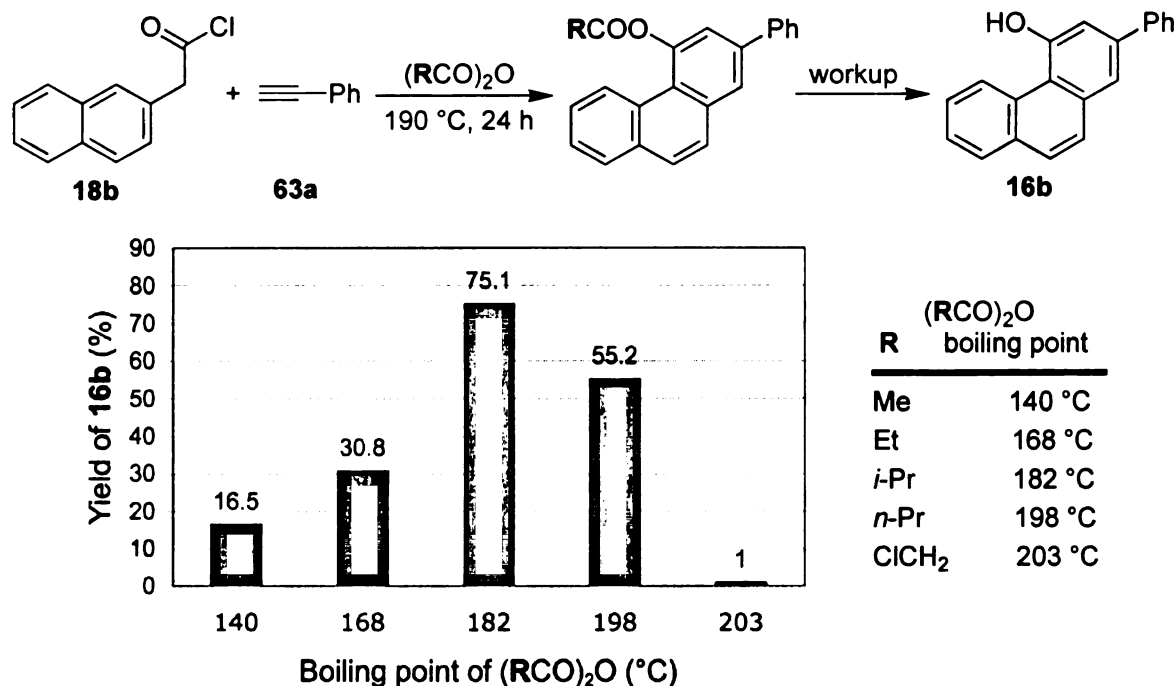
Entry	R	Bp of anhydride ($^\circ\text{C}$)	Base (eq)	16b (%) ^a	Mp of 16b ($^\circ\text{C}$) ^h	Color of 16b
1	Me	140	LAH (1.6) ^c	16.5	152-3	Light yellow
2 ^b	Me	140		47.9	153-5	
3	Et	168		30.8	153-4	
4	<i>i</i> -Pr (93)	182	KOH (5.8) ^d	75.1	151-2	Orange
5 ^e	<i>n</i> -Pr	198		55.2 ^f	149-0	Orange
6	ClCH_2	203		Trace	nd	Black ^g

^a Isolated by column chromatography. For experimental details, see: Section 7.3.2.2 of Chapter Seven. ^b The reaction time was 64 h; ^c Reduction performed in ether (100 mL) at room temperature overnight. ^d Performed at $100\text{ }^\circ\text{C}$ in 100 mL H_2O overnight; ^e **63a** from a new bottle was used. ^f Hydrolysis was performed twice at $120\text{ }^\circ\text{C}$ using 11.7 eq KOH. ^g Color of crude product, nd = not determined. ^h The reported^{17b} melting point of **16b** is $154\text{--}5\text{ }^\circ\text{C}$.

It was postulated that low yields of **16b** with acetic and propanic anhydrides were a result of the inadequate rate of formation of **16b**. This in turn was because the requisite temperature was unattainable as a side-effect of the presence of the anhydrides. Indeed, support for such a hypothesis was when isobutyric anhydride **93** was used, and a 75% yield of monomer **16b** was obtained (Table 3.8, entry 4) after hydrolysis in aqueous KOH. Surprisingly, the yield dropped when butyric anhydride was used (entry 5), and only a trace amount of product was detected in the presence of chloroacetic anhydride (entry 6). The efficiency of these trapping agents is diagramed in Figure 3.2. This, along with the results previously recorded (Table 3.7), clearly showed that anhydride **93**

suffers the least competitive stress from acid chloride **18b**, and thus minimized the accompanying yield loss due to formation of ester **89a** (Table 3.6).

Figure 3.2 Effects of anhydrides for CAEC cascade reaction to prepare **16b**

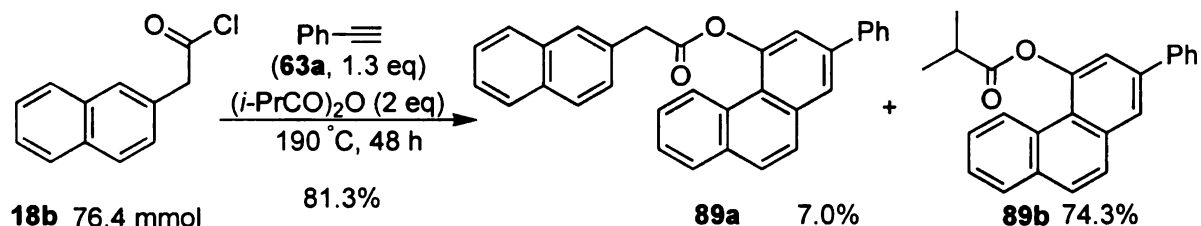


The crude ester intermediates generated from $(n\text{-PrCO})_2O$ (Table 3.8, entry 5) proved highly recalcitrant toward hydrolysis. Several attempts to effect complete cleavage failed, leading to incomplete conversion even after heating at 120 °C in aqueous KOH. However, it was found higher temperature had an adverse effect on this hydrolysis reaction. For instance, in the reaction with anhydride **93** it was noticed that the yield dropped slightly (from 75% to 68.3%) if hydrolysis was performed at 120 °C. Therefore, caution should be taken when generalizing the data.

In view of the striking difference of $(i\text{-PrCO})_2O$ (**93**) with other trapping agents, an analysis of the distribution of the primary products would be instructive to probe the reaction mechanism. Hence, the crude mixture with isobutyric

anhydride as trapping agent was scrutinized prior to hydrolysis (Scheme 3.16). These data clearly demonstrated that the *in situ* protection protocol was successful. The byproduct **92b** was not detected. Up now, it was not clear whether **92b** was lost during workup or it was not produced from the reaction.

Scheme 3.16 Product distribution using isobutyric anhydride as trapping agent



3.4.4 Summary of the role of trapping agents in the CAEC cascade reaction

Although the original synthesis of VAPOL by the benzannulation of a carbene complex was straightforward, it was impracticable on large scale owing to the cost of some of the crucial components. The thermally induced CAEC cascade approach, on the other hand, is shorter and more affordable. The ketene formation-cycloaddition and *in situ* esterification of **16b** incorporates a saponification step into a single process; this in turn leads to the generation of the VAPOL monomer in the most efficient manner.

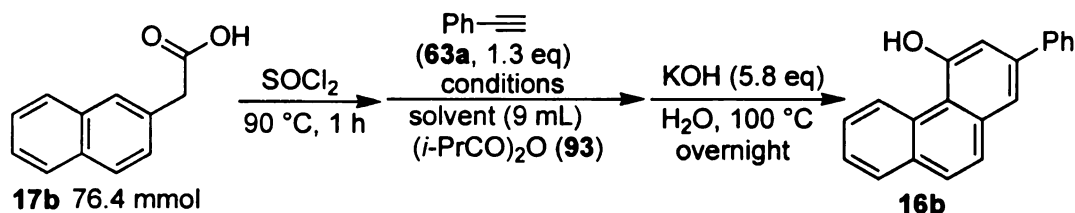
The choice of solvent was crucial to get acceptable yields. *In situ* protection strategy of phenolic moiety of the product was investigated and established and which benefited from insight into the mechanism. The inclusion of isobutyric anhydride had a miraculous impact on the outcome of the reaction; the resulting phenanthrol **16b** was isolated in remarkably excellent yields and with good quality. Direct analysis of the reaction mixture prior to workup showed the

presence of predominantly the ester from trapping by isobutyric anhydride, suggesting that the *in situ* trapping strategy proceeds expected.

3.5 Optimization of the CAEC reaction using **93** as trapping agent

Using (*i*-PrCO)₂O (**93**) as acylating reagent, typical reaction variables were then examined, and the results are summarized in Table 3.9 with entry 1 as the standard condition. The results in entry 2 indicate that mineral oil is not required for reaction, thereby simplifying the purification. Not surprisingly, the yields were dependent on the amount of anhydride employed (entry 3 & 4). After a few attempts, it was found that the optimal loading of **93** was 2 equivalents with respect to carboxylic acid **17b**.

Table 3.9 Optimization of the reaction with isobutyric anhydride as trapping agents



Entry	Solvent	SOCl ₂ (eq)	Time (h)	Temperature (°C) ^b	93 (eq)	16b (%) ^c	Mp of 16b (°C) ^d
1 ^a	Mineral oil	3.6	24	190	2	68.3 ^e	151-2
2 ^a	None	3.6	24	190	2	70.8	147-8
3					1	42.5	149-51
4					4	54.7	152-3
5				210	2	51.1	152-3
6		1.8	24	190		65.2	152-3
7			48	190		80.7	154-5

^a A fresh bottle of **63a** was used without purification. For experimental details, see: Section 7.3.2.2 of Chapter Seven. ^b Oil bath temperature. ^c Isolated by column chromatography. ^d The reported ^{17b} melting point of **16b** is 154-5 °C. ^e Hydrolyzed at 120 °C (oil bath temperature).

The reaction was very sensitive to the temperature. A notable decrease in the yield was observed when the temperature was raised to 210 °C (Table 3.9, entry 5). At this temperature, isobutyric anhydride (bp: 182 °C) started to boil, which significantly retarded the condensation of alkyne **63a** (bp: 144 °C) and thus its return to the reaction mixture. A decrease in the amount of SOCl₂, on the other hand, did not affect the yield (entry 6). To our delight, a significant improvement in the yield of **16b** could be obtained with an elongated reaction time (entry 7).

3.5.1 Efforts to minimize the formation of the byproduct **92b**

Another challenging aspect of this process was the separation of the major byproduct formed in the reaction (i.e. **92b**, Scheme 3.15). This highly substituted phenol displayed polarity profiles very similar to the VAPOL monomer **16b** upon silica gel chromatography. With the structure of **92b** in hand, ways to stifle the formation of **92b** were attempted.

The reaction was carried out at a lower temperature with an extended time but this failed to improve the yield of **16b** (Table 3.10, entry 2). Increased amounts of **17b** was recovered from the reaction. This indicated that maintaining the temperature at 190 °C was vital for the reaction.

It was then rationalized that the side-reaction should be disfavored by lower concentrations of alkyne **63a** in the system. This prompted the examination of the effect of the adding **63a** in portions. However, this failed to ameliorate the problem (Table 3.10, entry 3), and about the same amount of byproduct was isolated from this reaction. The concentration of **63a** was further lowered by continuously adding **63a** over a period of 30 h by syringe pump (entry 4). Indeed,

this time no byproduct **92b** was detected at all from the reaction. However, this was gained at an immense price of the loss of most of the desired product **16b**. Instead, an asphalt-like tar formed as a stringy undissolved mass, probably as a result of polymerization of the ketene species.¹⁰⁵

Table 3.10 Variation of the conditions to minimize the formation of **92b**

17b	76.4 mmol		16b	92b
Entry	Conditions ^a	16b ^b (%)	92b ^b (%)	17b ^b (%)
1	190 °C, 48 h	79.3 (91 ^c)	7.93	13.0
2	170 °C, 48 h	66.5 (88 ^c)	11.1	24.6
3	190 °C, 48 h, 63a was added in portions ^d	76.7	8.33	nd ^e
4	190 °C, 48 h, 63a was added over 30 h ^f	13.6	nd ^g	nd ^g

^a Crude **18b** was used without purification, and the temperature was oil bath temperature. For experimental details, see: Section 7.3.2.2 of Chapter Seven. ^b Isolated by column chromatography. ^c Based on recovered **17b**; ^d The procedure: 0 h, 3 mL; 6 h, 3 mL; 12 h, 3 mL; 24 h, 3 mL; continued to reflux for 24 h. ^e nd = not determined. ^f The scale was 306.1 mmol of **17b**, and phenylacetylene was added *via* syringe pump. ^g nd = not detected.

3.5.2 Investigation of the effects of the chlorinating agent

Another concern was the environmental impact imposed by SOCl₂. It was deemed superior to PCl₅ because the byproducts of the SOCl₂ are all gaseous (HCl and SO₂), and this greatly simplifies the purification procedure. However, SOCl₂ is toxic, corrosive and a lachrymatory with a pungent odor. Clearly an alternative to SOCl₂ would be desirable.

Oxalyl chloride is generally considered to be a mild more selective reagent for the conversion of acids to acid chlorides, and was subsequently examined in

these reactions. A comparable yield of **16a** was obtained using (COCl)₂ only in the case where (COCl)₂ was added all at once (Table 3.11, entry 2). However, this procedure could be problematic on large scale because the reaction vigorous liberation of a large amount of gases, while slow addition of (COCl)₂ considerably lowered the yield of **16b** (entry 3).

Table 3.11 Preparation of **16b** using oxalyl chloride to generate **18b**

Entry	Method to make 18b	Time (h)	16b (%) ^d	Mp of 16b ^h (°C)
1	I ^a	24	68.6	153-5
2	II ^b	24	66.5	151-2
3	III ^c	24	47.0	151-3
4	III	12	12.7 ^e	142-3
5	III	slow addition of 18b ^g	14.4 ^f 49.1	151-2 153-4

^a SOCl₂ (3.6 eq) was used. For experimental details, see: Section 7.3.2.1 of Chapter Seven. ^b

Oxalyl chloride was added all at once. ^c Oxalyl chloride was added slowly over a period of 1 h. ^d

Isolated yield by silica gel chromatography. ^e Yield of first crop. ^f Yield of second crop. ^g **18b** was

added slowly over 12 h, and then continued heating at 190 °C for another 12 h. ^h The

referenced^{17b} mp of **16b** is 154-5 °C.

As discussed earlier, ester **89a** could be isolated as the minor component in the primary product mixture (Scheme 3.16). The presence of this ester suggested that, by lowering the concentration **18b**, the selectivity for the desired ester **89b** might be able to be boosted. Therefore, motivated to achieve the complete conversion of **18b** to **16b**, the standard conditions were repeated but with acid chloride **18b** added slowly to a mixture of alkyne **63a** and anhydride **93**

(Table 3.11, entry 5). However, no improvement in the yield of **16b** was observed in this case. To summarize, the use of (COCl)₂ in this reaction was not as satisfactory as SOCl₂; thus, we proceeded to scale up the synthesis with SOCl₂.

3.5.3 Summary of optimizations of the CAEC cascade reaction

In brief, optimal conditions were found to involve the generation of the acid chloride **18b** using 3.6 equiv of SOCl₂. The cycloaddition of the *in situ* generated ketene and phenylacetylene **63a** was observed to take place at 190 °C, and it requires 48 h to gain the best yield in isobutyric anhydride **93**. The only detectable byproduct was **92b** which resulted from double insertion of the alkyne **63a**, and its removal on large scale could be tricky owing to the similarity of its properties to phenol **16b**. Much to our disappointment, efforts to minimize its formation led to failure or to an unacceptable loss in the yield of **16b**. With the key parameters established, the transition to large-scale synthesis was anticipated to be smooth.

3.6 Preparation of phenol **16b** on large scale *via* the CAEC cascade strategy

Guided by the outcome of the above-described studies and encouraged by its success, the *in situ* ketene formation and CAEC cascade reaction with alkyne **63a** was then conducted on large scale (Table 3.12).

3.6.1 Exploration of workup methods on large scale

In the first experiment, the standard conditions of the reaction were followed (Table 3.12, entry 1), and the synthesis proceeded uneventfully. It was found that the phenol **16b** could be crystallized from CH₂Cl₂. Thus, the first crop afforded fine crystals, and was found to be pure **16b**. The residue from the mother liquor

was collected, from which a 2nd portion of product was isolated *via* silica gel columns. In this way, the combined yield was found to be comparable to the small-scale reaction.

In order to avoid using chromatography column, alternative procedures were examined that involved only crystallization. Thus, after the 1st crop of product was collected by crystallization from CH₂Cl₂ (entry 2), the residue from the mother liquor was further crystallized from a mixture of hexanes (150 mL) and CH₂Cl₂ (100 mL). However, this maneuver led to a powdery solid (4.6 g) that was later shown to be the phenol **92b** based on melting point and ¹H-NMR analysis.

Table 3.12 Large-scale preparation of phenol **16b** from acid **17b**

Entry	1 st crop of 16b (g) ^a	2 nd crop of 16b (g)	Method to isolate 2 nd crop of 16b ^b	16b (%) ^c	92b (%) ^c	17b (%) ^g
1	40.8	17.5	Columns	70.5	10.5	13.1
2	34.4	17.3	Columns	62.5	10.1	21.7 ^d
3	44.6	9.1	Crystallization	64.9	12.1	13.1
4	Mixture ^e	24.0	Filtration ^f / Crystallization	68.0	8.3	9.30

^a Oil bath temperature; Isolated by crystallization using CH₂Cl₂. ^b For experimental details, see:

Section 7.3.2.6 of Chapter Seven. ^c The combined yields. ^d Crude yield without crystallization. ^e

Crystallized using 2-propanol. ^f Filtered through silica gel. ^g Crystallized from EtOH/ H₂O.

A screening exercise was undertaken in an effort to identify a solvent system for the separation of the two phenols **16b** and **92b** by crystallization. As a result, 2-propanol was quickly recognized to work best while ethyl acetate, toluene, methanol and ethanol failed to give either of the two compounds in pure form. In fact, a solubility test illustrated the stark solubility difference: in 100 mL boiling 2-

propanol, 157.4 g **16b** could be dissolved, but only 1.75 g of **92b** was soluble.

These solubility data suggests a potential method for the isolation of the byproduct from the crude reaction mixture. After crystallization from CH₂Cl₂ to isolate the 1st crop of **16b**, most of the byproduct **92b** could be removed by repeatedly crystallization (Table 3.12, entry 3).

In light of the advances in crystallization with 2-propanol, it was envisioned that **92b** should be removed from the crude reaction mixture using this solvent. However, all attempts to cleanly remove the byproduct from the crude reaction mixture by crystallization from *i*-PrOH failed. The solid that was obtained contained substantial amount of phenol **16b** (Table 3.12, entry 4). Thus, it appeared the best course is to do the first crystallization from CH₂Cl₂.

It was also noticed that there was a black component with low polarity in the crude reaction mixture and it could not be completely removed by crystallization. To remove these impurities, the residue from the mother liquor was carefully concentrated in vacuo with 150 mL of silica gel, and then put on top of another layer of 400 mL of silica gel. This material was then flushed under vacuum (water aspirator) with a mixture of CH₂Cl₂: hexanes= 1:1. The first 1 L of eluent was discarded.

Elution was continued and 3 L collected; the concentrate of this fraction yielded 18.7 g of orange solid. Subsequently, this material was crystallized from a mixture of dichlorethane: hexanes = 2:1, and phenol **16b** could be obtained in 12.3% yield. The combined yield of **16b** (68.0%, entry 4) matched other methods employed.

3.6.2 Isolation of 16b by filtration and crystallization on large scale

We were happy to find that the method could reliably provide overall yields of >60% for the pure VAPOL monomer **16b** of good quality and in high efficiency, when employing this filtration technique in conjunction with crystallization. The results are listed in Table 3.13.

Table 3.13 Large-scale preparation of **16b** using a combination of filtration and filtration to isolate the product

Entry	1 st crop 16b (%) ^a	2 nd crop 92b (%)	3 rd crop 16b (%) ^b	Combined yield of 16b (%)	Recovered 17b (%) ^c
1	41.6	9.0 ^d	14.2	55.8	10.1 ^e
2	52.2	5.0	11.9	64.1	9.0
3	35.2	10.3 ^d	15.0	64.5 ^d	6.5 ^e
4	40.0	11.4 ^d	13.4	71.7 ^d	10.3

^a Oil bath temperature; isolated by crystallization using CH₂Cl₂. For experimental details, see: Section 7.3.2.6 of Chapter Seven. ^b After filtration through silica gel and crystallization from 2-propanol, by using a mixture of dichloroethane: hexanes= 3:1. ^c After crystallization from EtOH/H₂O. ^d ¹H-NMR yield. ^e Without crystallization from EtOH/H₂O.

3.6.3 Summary of large-scale synthesis

To summarize, this procedure produced a one-pot synthesis of **16b** that has many advantages: (i) the starting materials are cheap and readily available; (ii) the key reaction is high yielding; (iii) the product is easily isolated in a purified form. This synthesis was successfully scaled up in to about 50 g of **16b**, using 57 g of **17b** as batch input. The resultant monomer **16b** was subsequently transformed into VAPOL *via* oxidative coupling (see Chapter four for details).

3.7 Summary: the CAEC cascade reaction for the preparation of **16b**

Having a readily accessible source of phenol **16b** is a crucial issue for the development of the chemistry of VAPOL. Given that the only viable method to prepare **16b** prior this work was through metal carbene complexes, chemists were forced to come to grips with major economic concerns of this route. In an effort to validate the CAEC cascade pathway, on the other hand, two major obstacles stood in the way of its widespread applications: the disappointingly low yields and the poor quality of the product. While the second issue could be easily addressed by introducing mineral oil as solvent, no groundbreaking improvement in the yield of **16b** was observed.

These considerations greatly highlighted the unique ability of $(i\text{-PrCO})_2\text{O}$ (**93**) to assisted in the efficiency of transformation. In addition to providing ambient condition for the reactions, the method held promise as an efficient trapping agent to protect the phenolic hydroxyl moiety *in situ*. The distribution of the products in Scheme 3.16 provides the most compelling evidence for the success of the proposed *in situ* protection strategy. Putting all these parameters in place gave a clean conversion of **18b** to **16b**.

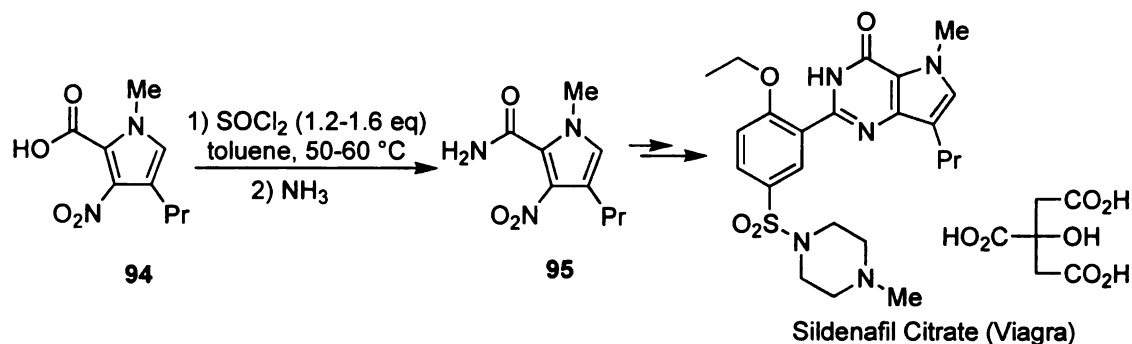
In an extension of this work, it was found this procedure was also suitable for the synthesis of VANOL and its derivatives with a wide range of functional diversity (see Chapter six). Conceivably, this method could be generalized for the synthesis of a variety of multifunctional phenols, particularly when the acid partners are more valuable.

3.8 Future work

Although the synthesis of VAPOL described in this chapter was amply demonstrated to be safe and efficient, the use of excess SOCl_2 is considerably problematic on large scale. The production of the requisite ketene **85** via thermal cracking of **18b** is overly harsh. To address these concerns, it is deemed that there is still margin for further optimization of the conditions.

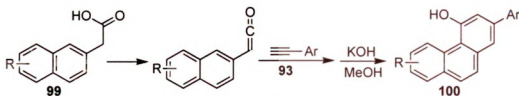
For instance, Dunn prepared **95** by using SOCl_2 in toluene as a solvent instead of performing the reaction in neat SOCl_2 .¹³² This successfully reduced the loading of SOCl_2 for the generation of **95** (Scheme 3.17), a key intermediate for the preparation of Viagra. This allowed the level of SOCl_2 to be reduced to 1.6-1.2 equivalents. Therefore, further reduction of the amount of SOCl_2 in VAPOL synthesis is the next factor to consider.

Scheme 3.17 Synthesis of **95** for preparation of Sildenafil citrate (Viagra)



The scope of the [2+2] protocol has been explored further with extensions to the formation of a variety of VANOL derivatives with different electronic and steric properties (See Chapter Six). Provided that a variety of substrate of the type **99** can be easily obtained,¹³⁴ this could be a versatile method for the formation of a family of VAPOL derivatives and polyfunctional phenanthrenes (Scheme 3.18).¹¹⁷

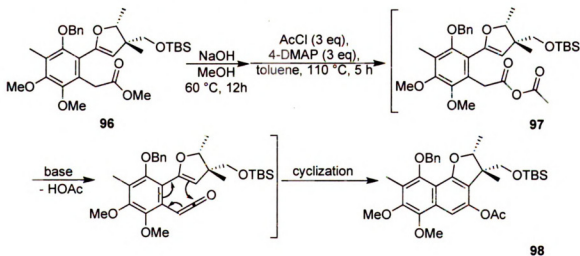
Scheme 3.18 Preparation of other phenanthrene derivatives using [2+2] protocol



Generation of ketene **85** (Scheme 3.14) at lower temperatures would also be important for future developments in the synthesis of VAPOL. This is possible as suggested by literature precedent. For example, in their total synthesis of the furaquinocins,¹³³ Suzuki and coworkers utilized an interesting route to deliver naphthol derivative **98** (Scheme 3.19). Treatment of a functionalized phenylacetic acid intermediate with acetyl chloride generated the mixed anhydride **97**, which upon heating under basic conditions produced the 2-naphthol ester **98** in excellent yield.

The production of ketene in this method completely eliminated acid chloride as precursor. If the same methodology can be applied to the synthesis of **16b**, the usage of noxious reagents SOCl_2 can be avoided.

Scheme 3.19 Synthesis of **98** as intermediate to prepare furaquinocins



3.9 Conclusions

Two strategies were developed for the formation of the 4-phenanthrol moiety of the VAPOL monomer **16b**. The first route utilized a Wulff-Dötz benzannulation reaction, and access to **16b** was achieved in 55% overall yield. However, the cost and toxicity of some of the crucial components made the method commercially restrictive.

The second and ultimately superior approach is based on the thermal CAEC cascade reaction of *in situ* formed ketene **85** with phenylacetylene **63a**. This method offers a facile access to **16b** in combination the subsequent cleavage of the ester functionality. Two findings have been critical for improving the method: solvent effects exhibited by mineral oil and the establishment of *in situ* trapping methodology, with the most dramatic effect presented by (*i*-PrCO)₂O (**93**). These ongoing developments have significantly broadened the capabilities of the reaction. While one-pot the [2+2] cycloaddition/electrocyclization of ketenes to alkynes, esterification and saponification reaction to make phenols are known,¹⁰⁵ no practical examples can be found in the literature to improve both yields and quality of the products at the same time. It seems likely, as investigation in this field intensifies, that their applications will extend to more transformations (Chapter Six).

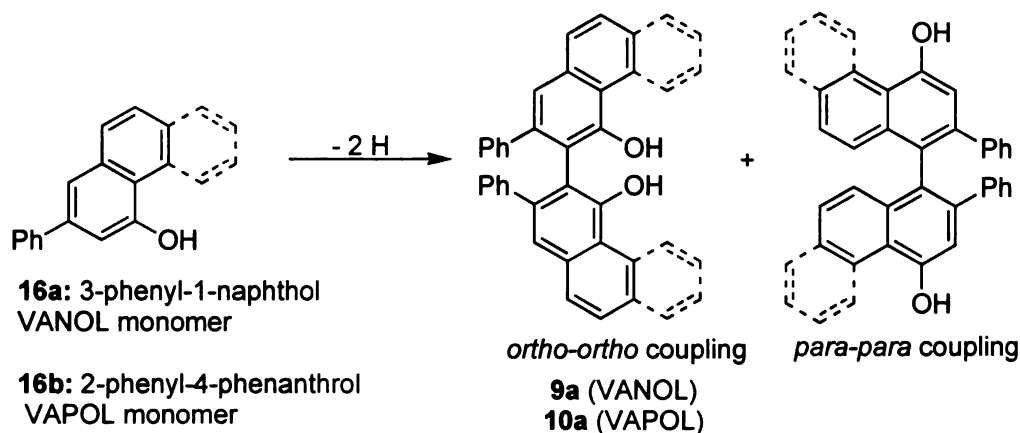
CHAPTER FOUR

SYNTHESIS OF VANOL AND VAPOL BY OXIDATIVE COUPLING

Wulff's descriptions of the enzyme-like behavior of the VANOL and VAPOL ligands in the stereospecific syntheses of aziridines have sparked rapidly growing requests for these ligands.^{19,22,23,24} The chemical efficiency of their preparation is at the heart of the supply problem for these ligands. This efficiency is essentially defined the efficiency of the synthesis of either the monomers **16a** or **16b** employed in the construction of the dimeric skeleton. With the development of efficient approaches for the construction of the monomers **16a** and **16b** in hand, the oxidative coupling to give VANOL and VAPOL can now be addressed.

The *ortho-ortho* phenolic linkage in VANOL/ VAPOL comprises two identical aromatic units (Scheme 4.1). Owing to the proximity of the phenyl moieties and the hydroxyl groups, these biphenols are remarkably congested, which constitutes a formidable synthetic challenge for chemists.

Scheme 4.1 Preparation of VANOL and VAPOL from their monomers



A key historical challenge in the preparation of VANOL and VAPOL has been the relief of the regioselective constraints posed by the preference of *para-para*

coupling (Scheme 4.1).^{17b} In this chapter, a look at some of the issues relating to the current art of the synthesis of VANOL will be provided, and its application in the preparation of other related ligands will be discussed.

4.1 Introduction

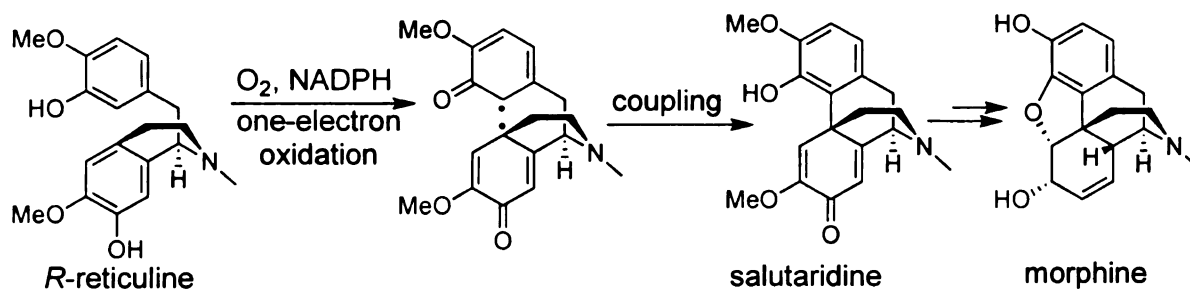
Axially chiral biaryls have become increasingly important as useful tools in asymmetric synthesis. A representative example is BINOL: as a chiral ligand, the use of this binaphthol is ubiquitous in organic chemistry.^{9b} This in turn has motivated extensive research efforts to identify even more novel applications.

Many methods have gained practical importance for the production of biaryls.¹³⁵ However, most of them require extra steps for functional group installation and elaboration. In contrast, in the oxidative self-coupling process, modifications on the monomeric precursors generally result in more convergent synthesis.¹³⁶ Oxidative coupling of 2-naphthols,¹³⁷ for example, has been widely used in preparation of synthetically useful compounds. Therefore, from a strategic sense, it seemed prudent to adopt the oxidative coupling approach for our purposes in the synthesis of VANOL and VAPOL and their derivatives.^{17b}

4.1.1 Oxidative phenolic coupling reaction

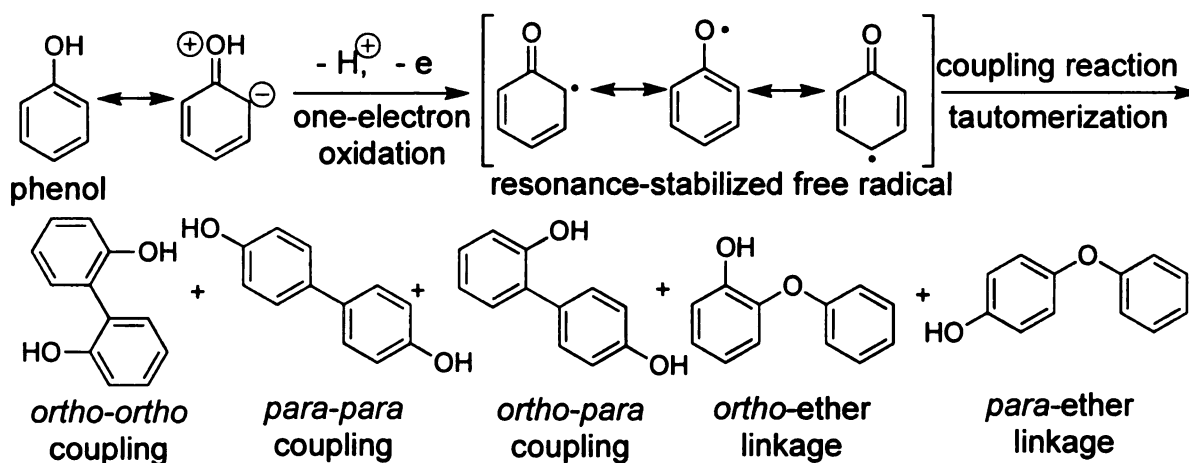
The oxidative phenolic coupling reaction is the oxidation of phenols and then the coupling of the resulting phenoxyl radicals (Scheme 4.2).¹³⁸ This can lead to diverse array of structures, and not surprisingly constitute a key step in the biosynthesis pathway for many natural products. For example, the sequence in Scheme 4.2 represents a portion of the biosynthesis of morphine, where the di-phenolic radicals derived from (*R*)-reticuline undergoes an *o,p*-coupling.¹³⁹

Scheme 4.2 Biosynthetic pathways for morphine alkaloid *via* oxidative coupling



Mechanistically, the joining of two phenol molecules by the oxidative coupling reaction can be rationalized *via* the one-electron oxidation of a phenol group (Scheme 4.3).^{138, 139} Single-electron oxidation of a simple phenol gives a free radical in which delocalization of the unpaired electron, gives resonance forms in which the free electron resides at positions *ortho* and *para* to the oxygen function. Coupling of two of these mesomeric structures gives a range of dimeric systems as exemplified in Scheme 4.3. Thus, carbon–carbon bonds at positions *ortho* or *para* to the original phenol, or ether linkages, may be formed.

Scheme 4.3 Mechanism of oxidative coupling reaction of phenol



4.1.2 Oxidative coupling reaction for naphthol-containing substrates

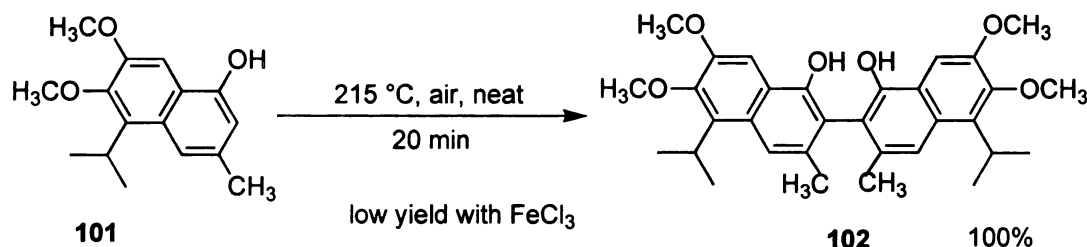
While this coupling process is one of the key features of many alkaloid biosynthetic pathways, it can also be mimicked in the lab.¹³⁸ In fact, the synthesis

of binaphthol compounds using the oxidative coupling reaction is widespread, and the reaction with 2-naphthol and its derivatives¹⁴⁰ as substrates has been well documented.^{9b}

Coupling of 1-naphthol and its derivatives, on the other hand, has received little attention and generally are less successful. Unlike the dimerization of 2-naphthol, the coupling of 1-naphthol is usually plagued by generation of different isomers, as both the *ortho* and the *para* positions are activated by the hydroxyl group. Accordingly, one-electron oxidation results in radicals at either position.^{17b} This opens reaction channels to other isomeric products, which in turn creates a selectivity issue.

A breakthrough dealing with this problem was provided by Edwards and Cashaw, who had embarked on the synthesis of gossypol (**102**, Scheme 4.4).¹⁴¹ They found that the 3-methyl-1-naphthol derivative **101** gave a low yield of the *ortho,ortho*-coupled product **102** when treated with FeCl₃. Surprisingly, a quantitative yield of binaphthol **102** was obtained if the melted **101** was exposed to air for 20 min in a test tube at 215 °C.

Scheme 4.4 Synthesis of **102** via oxidative coupling reaction of monomeric **101**

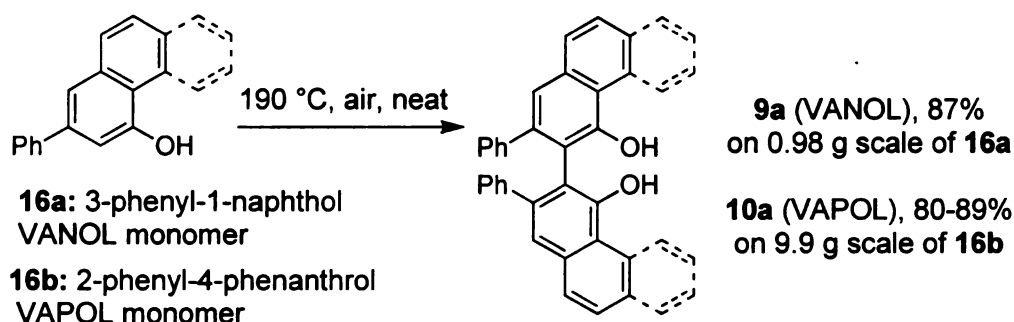


4.1.3 VANOL (VAPOL) synthesis via oxidative coupling reaction: early work

Although the significance of Edwards and Cashaw's work was recognized at the time, its immediate impact on synthetic organic chemistry remained

unexplored. Harnessing this unconventional reactivity provided important avenues for the synthesis of VANOL and VAPOL.^{17b} Thus, dimerization of **16a** and **16b** was successfully conducted in the same manner by fusing the corresponding monomers at 190 °C in air by Dr Bao (Scheme 4.5).^{17b,c} The reaction yielded both ligands in good yields on small scale.

Scheme 4.5 Preparation of VANOL and VAPOL *via* oxidative coupling reaction



The drawbacks to this approach are not readily evident until the reaction is carried out on large scale. It was found that the reaction mixture formed a hard solid layer encasing the starting material. This is because, unlike the monomers, the dimers have melting points much higher than 190 °C. This blocks the diffusion of air into the reaction mixture and causes the reaction to slow down. In the original work, the problem was addressed by using glass beads to enlarge the surface of the mixture,^{17b} and by interrupting the reaction and scraping the crude mixture loose from the walls of the container and gently grinding into fine powder followed by resubmitting to the reaction conditions.¹¹⁹

Another challenging aspect of this process is the manipulation of the crude product. After extended exposure to air at high temperature, the crude product is afforded in poor quality under these unusually drastic conditions. The isolation of the desired product from this mixture often requires chromatographic methods,

which we would want to avoid in a large-scale synthesis. In addition, it was found that **16a** was susceptible to oxidative decomposition promoted by impurities.^{18e} Hence, careful purity control was found necessary to achieve the maximum yields consistently. All these considerations contributed to a significant deterioration in material throughput.

4.1.4 Main purposes

The work at this point becomes a project to find a viable large-scale procedure to make the VANOL and VAPOL ligands from their monomers in a safe and effective manner. Another concern is the practicality of the process - overall yield, isolation, and purification. And we need to do all of this while minimizing costs.

Therefore, we sensed that some of the major considerations had to be addressed in defining a reliable process to deliver these two ligands:

Starting materials—a key observation of coupling reaction of monomeric **16a** (**16b**) is that the vigorous conditions can lead to decomposition of the substrate and product. The presence of trace amount of impurities appears to promote this occurrence. As a result, the first goal of this research is to establish manufacturing technologies that would ensure that the starting materials possessed the same purity profiles.

Oxidants—Air posed safety concerns. However, it is cheap and is effective in achieving the desired reaction. Therefore, at this stage it was decided to lay the foundations for any new method using air thus to avoid expensive metal-based oxidants.

Conditions—the requirement of fusing materials always poses a safety risk. In

addition, the potential for contamination by over-oxidized byproducts is a constant concern. Thus, a viable alternative to the oxidative dimerization procedure needs to be devised. The efficiency of formation of the biaryl axis in this process is also a key element to consider, since the corresponding monomers often requires many steps to prepare and thus are of considerable valuable. As an extension of this work, the functional group compatibility of any new procedure is also a central issue for the synthesis of various derivatives.

4.2 Dimerization of the VANOL monomer 16a using the first generation method (under neat conditions)

The work on searching for a viable large-scale procedure for the synthesis of VANOL was started by optimizing the existing synthetic method. The first problem to consider was the inefficiency in the contact of air with **16a**, since it was believed to be the vital issue in maintaining good conversion and keeping the reaction time at a minimum.^{17b,18e}

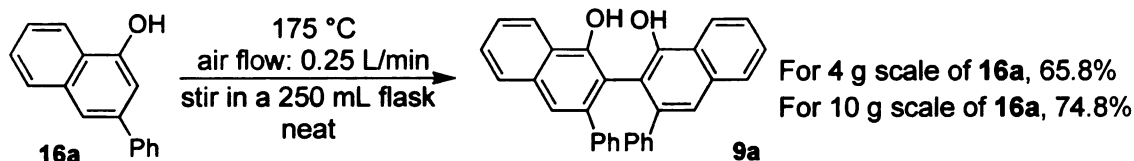
There are three ways to improve the efficiency of the contact of air with the reactants: (a) employ elevated pressures; (b) bubble air through the fused materials and (c) blow air to the surface. Option (a) is operationally inconvenient; option (b) is likely not feasible. So we opted for the third solution (option (c)).

4.2.1 Preliminary studies on small scale

Thus, a large reaction flask (250 mL) was used to carry on the reaction of 4.0 g of VANOL monomer **16a** in order to provide a large surface area (Scheme 4.6). To this flask was continuously infused with a slow stream of air. At the same time, the melted starting material **16a** in the flask was stirred with a large magnetic

stirrer bar to avoid local over-oxidation. Both starting material **16a** and the product **9a** show significant absorption in the ultraviolet region, and these absorptions can be used to monitor their presence in the system and used to track the reaction.

Scheme 4.6 Synthesis of VANOL using controlled airflow under neat conditions



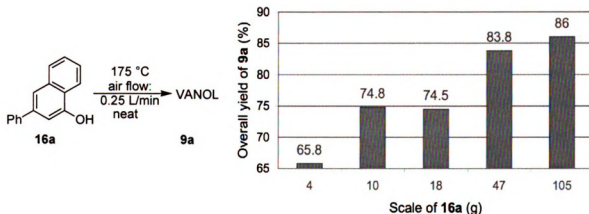
It turned out that these measures provided critical contributions to the improvement of the efficiency on small scale. Thus, the complete consumption of the starting material **16a** was observed on small scale (4.0 g). After column chromatography on silica gel, racemic VANOL could be isolated as a beige powder from the black crude mixture in decent yield (Scheme 4.6, see Section 7.4.1.1 of Chapter Seven for details). The reaction could be repeated on larger scale (10 g) with a slightly enhanced yield.

However, initial attempts to carry out reaction on larger scale (≥ 18.0 g of **16a** in a 2 L flask) resulted in an incomplete conversion. The produced VANOL (mp $231\text{ }^{\circ}\text{C}$)^{17b} solidified as it accumulated during the course of the reaction, which made stirring so difficult that the reaction was notably decelerated due to inadequate diffusion of air into the reaction mixture. To address this problem, the procedure was slightly revised. Based on the previous observation that racemic VANOL **9a** was much less soluble in CH_2Cl_2 than its monomer **16a**, the separation of VANOL was effected as described below by crystallization of the crude product before complete conversion was achieved.^{18e}

4.2.2 Condition optimizations on large scale

Therefore, the reaction flask was cooled down under N_2 flow once the stir bar stopped stirring the crude mixture. The resulting solid material was then carefully broken up in the presence of a small amount of CH_2Cl_2 , and the black suspension was chilled to $-20\text{ }^\circ\text{C}$. The solid was isolated and rinsed with pre-cooled CH_2Cl_2 . The beige powder was pure VANOL based on the $^1\text{H-NMR}$ spectrum and the melting point, and it was free of starting material based on TLC. The black filtrate, which was chiefly a mixture of unreacted **16a** and a small amount of VANOL, was put back into the reaction after removal of the solvent. This process was repeated until no starting material could be detected by TLC analysis of the filtrate. The reaction could be successfully scaled up to 100 g in this manner, and racemic VANOL could be delivered in good yields (Figure 4.1, see Section 7.4.1.2 of Chapter Seven for details).

Figure 4.1 The yield of **9a** on different scales of the coupling reaction

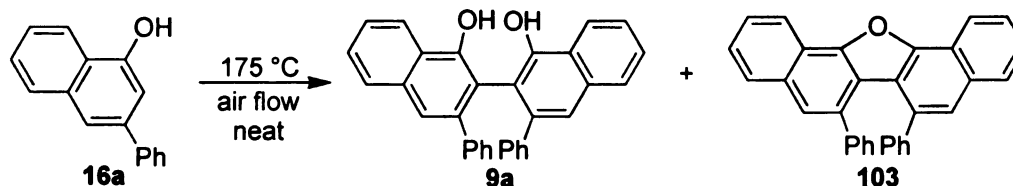


A distinctive feature of the reaction was the increase in of the yields as the reaction was performed on larger scale (Figure 4.1). This was postulated to be a result of material loss during unit operations.

Whereas it might be assumed that increasing the airflow would promote the conversion of the monomeric **16a** to VANOL **9a**, this also led to further oxidative destruction of both starting material and the product. Determination of the optimum airflow for this reaction should therefore be a major feature of the large-scale development. For this reason, the reaction was repeated on 100 g scale with various speed of the airflow, and the results are shown in Table 4.1.

Indeed, an increased airflow brought about an improvement in the yield of VANOL as predicted (Table 4.1, entry 2 vs. 1). However, it dropped again when a very strong airflow was employed (entry 3). Moreover, no increase in the reaction rate was observed. The reaction gave rise to a byproduct that was not detected on small scale, and whose structure was assigned as the furan **103** (for the reaction in entry 1, the yield of this compound was 7.1%). Interestingly, this contaminant is far from novel, as its discovery had been previously reported and the mechanism behind the formation of the ether linkage had already been thoroughly unraveled.^{17b,c}

Table 4.1 Oxidative coupling of monomer **16a** to prepare VANOL on 100 g scale



Entry	Conditions of the first run ^a			Numbers of total runs ^c	Total yield of 9a (%) ^e
	Airflow rate (L/min)	Time ^b (h)	9a (%)		
1	0.25	57	51.5	4	69.6
2	0.35	61	52.5	5	86.0
3	4.3	60	52.5	5	80.6
4 ^d	0.35	32	61.3	5	73.4
5 ^d	0.35	25	57.8	5	75.0

^a The amount of **103** in entries 2-5 was not determined. For experimental details, see: Section 7.4.1.2 of Chapter Seven. ^b Time indicated was that at which the stirrer bar stopped spinning. ^c Numbers of times the reaction was stopped and the product isolated by crystallization from CH₂Cl₂. ^d Stirrer was set to stir the reaction as fast as possible. ^e The product was isolated by crystallization from CH₂Cl₂.

The formation of the byproduct **103** was attributed for the prolonged heating time of the reaction,^{17b,c} which means that a longer residence time at the reaction temperature leads to an increased amount of the side reactions. To limit the degree of the dehydration and other side reactions that may promote breakdown of the product, methods to accelerate the reaction other than control of airflow had to be established.

In organic reactions difficulties are often encountered if the reagent was gaseous and the reactants are in solution. Without stirring, the two would react very slowly and the reaction would proceed only at the interface where these two phases were in contact. The rate of the reaction therefore would be depended upon the rate of stirring. Thus, the final improvement of the reaction was realized when the mixture was stirred as fast as possible. This maneuver gave rise to a remarkable rate enhancement of the oxidative coupling reaction of **16a** (Table 4.1, entries 4 and 5).

4.2.3 Summary

The synthesis of racemic VANOL **9a** was achieved with an oxidative coupling of **16a** as the key reaction. This reaction was conveniently accomplished with air serving as oxidant to generate radicals needed to trigger the regiospecific coupling process. On larger scale, a conversion problem was encountered

resulting from the insufficient air contact. This problem could be resolved by interruption of the reaction and isolation of the product from the reaction mixture and resubmitting the unreacted starting material to the reaction. After a screening effort, this protocol proceeded well without yield loss.

Using solvent-free conditions for this coupling reaction which was attractive in that it offered reduced pollution and lower cost. However, it was obvious from working on large scale that the throughput was hampered by the complication of the product existing as a solid under the reaction conditions. The necessity of repeatedly shutting down the reaction to isolate the product entailed unacceptably long processing time. The quality of the crude product was poor as it had a black color and tarry appearance. Hence, efforts were placed on eliminating the iterative aspects of the procedure and the development of new production conditions that are economically and environmentally sound.

4.3 Dimerization of 16a to prepare VANOL using mineral oil as solvent: small scale

The poor shape of the procedure in the previous section rendered it unsuitable for the final resolution in the synthesis of VANOL. Analysis of the impact of various factors on the results described above provided useful information from which it became blatantly clear that some solvent system would have to be devised such that the racemic VANOL produced in the oxidative coupling reaction can be efficiently dispersed to ensure the continuous exposure of monomer **16a** to air.¹⁴²

4.3.1 Introduction

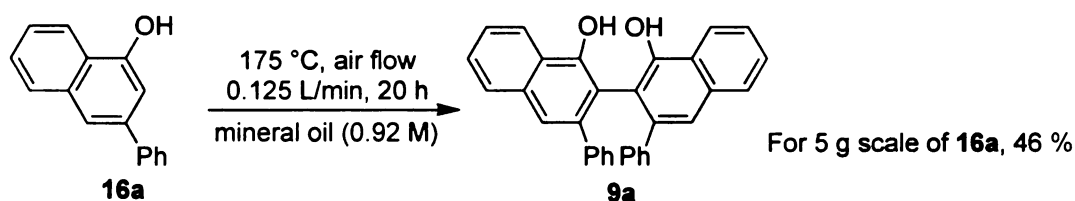
The provision of a more homogeneous milieu will assist in the more efficient transmission of heat and diffusion of air into the reaction mixture. This can be accomplished by conducting the reaction in solution. A major problem in exploiting the reaction medium in this way is the requirement for a solvent system that was thermally stable and non-reactive towards the substrate and product at the requisite temperature, and at the same time the removal of which was facile. Furthermore, the solvent must be non-volatile owing to the two-phase nature of the reaction. Otherwise, the vapor from the solvent could significantly dilute the air thus possibly decelerate the reaction. Moreover, since the ultimate goal is to conduct the reaction on large scale, any solvent that is used must be inexpensive and non-hazardous.

Taking the expense and safety into account, ordinary high boiling-point solvents such as diphenyl ether (bp 257 °C), 1,2-dichlorobenzene (bp 180 °C) are not applicable, and there have been little exploration in this regard.¹¹² Mineral oil was identified as the most promising solvent, as it is nonvolatile, nonflammable, nontoxic and stable in air at the elevated temperatures required. The removal of mineral oil post-reaction can be achieved by means of a wash with hexane, since racemic VANOL and VAPOL are essentially insoluble in hexanes. The cost that is brought by mineral oil to large scale is manageable, since it is fairly cheap and readily available in large quantities.

To demonstrate the viability of the reaction in the presence of mineral oil, the coupling reaction of **16a** was studied (Scheme 4.7; for experimental details, see:

Section 7.4.1.3 of Chapter Seven). Indeed, after stirring **16a** under a slow flow of air for 20 h at 175 °C, it was smoothly consumed and the formation of VANOL could be detected by TLC inspection of the crude reaction mixture. After cooling to ambient temperature, the mineral oil was removed by washing with hexanes to leave an orange solid which was identified as VANOL in 77.5% yield. After crystallization from CH₂Cl₂, purer VANOL was afforded as brown crystals.

Scheme 4.7 Synthesis of VANOL from **16a** in the presence of mineral oil



An extra benefit of employing a solvent is the appreciable improvement of the quality of the crude product. Once the reaction has reached completion, the crude product is an orange solid instead of a black tarry material. VANOL could be easily isolated and purified by simple filtration and subsequent crystallization.

Thus, the standard conditions could deliver VANOL with complete conversion in a short period even without optimization. However, new problems stood out as being targets for optimization of the new conditions. Firstly, the generation of radicals by oxidation with air required heating to high temperatures, which could accelerate both the coupling reaction and oxidative decomposition. This is perhaps reflected in the relatively low yield obtained from the preliminary experiment shown in Scheme 4.7. Consequently, the temperature effects of the reaction should be investigated.

Second, the concentration of the reactant in mineral oil is also an important factor since reactions involving radicals are generally diffusion controlled.¹⁴³

Therefore, insight into the effect of concentration on the oxidative coupling reaction would be constructive. Finally, while the detrimental effect of air on the coupling reaction has been noted previously (Table 4.1, Section 4.2.2), there had been little work done on the study of this important variable. With the finding that the reaction is successfully in mineral oil, these optimization can now be expediently addressed.

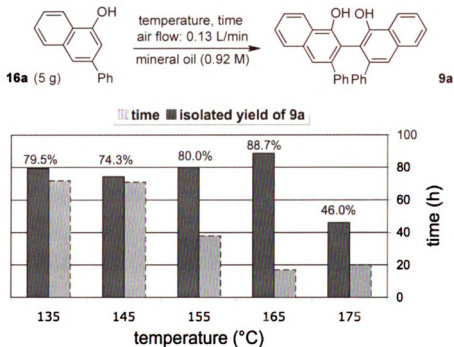
4.3.2 Temperature effects on the dimerization reaction of 16a

The yield of the reaction under previously described conditions was subsequently investigated as a function of the reaction temperature, and the results are summarized graphically in Figure 4.2 (for experimental details, see: Section 7.4.1.3 of Chapter Seven). The rectangles with solid line represents the yields at different temperatures and the rectangles with dashed line plots the reaction time for the same set of reactions. On the basis of the data in Figure 4.2, it becomes immediately clear that the yield of VANOL peaks at a temperature of 165 °C, and at the same time the reaction time reaches its lowest point. It should be noted, however, that the reaction time at 175 °C is not optimized. For the reactions at the temperatures of 145 °C and 135 °C, they were stopped at the indicated time before they reached full conversion. This decision was made because byproducts were observed to emerge by TLC analysis of the crude reaction mixture, and this is probably a result of the extended reaction time.

The decreased yield at 175 °C is most likely due to increased rate of oxidative decomposition of both the starting material and the product at this temperature. Performing the dimerization at 155 °C resulted in the need for a remarkably

extended reaction time to get a reasonable yield. A similar outcome was seen at even lower temperatures. The formations of **9a** at 135 °C is much more sluggish and occurs with an incomplete conversion even after extended reaction time.

Figure 4.2 The temperature effect on the coupling reaction of **16a** in mineral oil



It is well known that the great majority of carbon-centered radicals undergo very fast dimerization reactions.¹⁴³ However, the long reaction time required at lower temperatures clearly indicates that the rate-limiting step is the hydrogen abstraction to produce radicals. The observed dependence of the yield of VANOL on the temperature likely arises from the inadequate rate of radical formation.

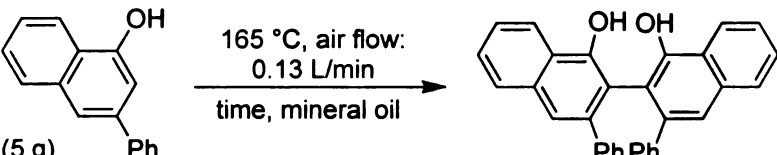
The conclusion was then drawn that there is a maximum temperature that clearly should not be superseded. On the other hand, temperatures that are too low lead to increased reaction time, which would constitute a drawback from a processing point of view. Therefore, it was judged that a temperature of 165 °C represents an ideal compromise between these counteracting effects, and this

temperature was used for the following optimizations and scaleup investigations.

4.3.3 Concentration effects on the phenol coupling reaction

Generally speaking, it is best to operate these reactions at the maximum convenient concentration in order to maximize rate. However, concentration can sometimes influence the reaction in terms of selectivity.¹⁴³ Therefore, substrate concentration is another parameter that should be thoroughly investigated during reaction optimization. The reaction under the more dilute conditions (entry 1, Table 4.2) produced VANOL in lower yield (Table 4.2, entry 2) and in addition, with a longer reaction time.

Table 4.2 Concentration effects of oxidative coupling of **16a** in mineral oil

				
Entry	Time (h)	Mineral oil (mL)	Crude yield of 9a (%)	9a (%)
1	40 ^a	50	88.7	82.8
2	17 ^a	25	91.3	88.7

^a Reactions were tracked by TLC. See: Section 7.4.1.3 of Chapter Seven for details.

4.3.4 Summary of small scale reaction

Looking for an improved and more general access to VANOL, the possibility that the presence of solvent might ameliorate the destructive effects of the harsh conditions thus motivated us to carry out the reaction with mineral oil as the reaction media. As a result, the incomplete conversions and associating extended processing time that plagued the earlier studies (Section 4.2) gave way to this synthetically more useful methodology.

Typical variations in the reaction conditions were carefully explored and some

clear trends emerged with regard to yield and reaction time. With a much increased understanding of the reaction and its controlling factors, the final synthesis procedure was settled upon (165 °C, 0.92 M for **16a** in mineral oil, air flow rate 0.15 L/min) and was ready for scale up.

4.4 Preparation of VANOL: large scale

Having determined the optimal reaction conditions on small scale, the procedure was now ready for the final scale-up. The results of the reactions in batches ranging from 20 to 50 g are summarized in Table 4.3.

Table 4.3 Preparation of VANOL **9a** *via* oxidative coupling reaction in mineral oil

c1ccc2c(c1)c(O)ccc2c3ccccc3
 $\xrightarrow[\text{time, mineral oil}]{165\text{ }^{\circ}\text{C, air flow: 0.15 L/min}}$
c1ccc2c(c1)c(O)c3c(O)ccc4c3ccc5c4c(O)ccc5c6ccccc62

16a (0.92 M) **9a**

Entry	16a (g)	Time (h)	Crude 9a (%)	Mp of crude 9a (°C) ^a	9a (%) ^b	Mp of 9a (°C) ^a
1	20	32	92.8	224-9	86.1	231-2
2	50	32 ^c	88.1	215-7	71.9	230-1
3	50	32	92.5	224-7	85.5	231-2
4	50	24	94.3	nd	85.2	231-2

^a The reported melting point of **9a**^{17b,c} is 231-3 °C; nd = not determined. ^b Isolated yield by crystallization in CH₂Cl₂. For experimental details, see: Section 7.4.1.4 of Chapter Seven. ^c Reactions were stopped and worked up at 16 h, but the reaction was not complete yet. It was then exposed to the same conditions for more 8 h until no **16a** could be detected by TLC.

In contrast to the large-scale investigations employing neat conditions (Table 4.1), the data in Table 4.3 shows that the reproducibility of the reaction is greatly improved in the presence of mineral oil. The relative deviation in the yields of **9a** for each set of reactions is significantly smaller in mineral oil, and in addition, the reaction time can be reduced to 24 h without compromising the yield (entry 4).

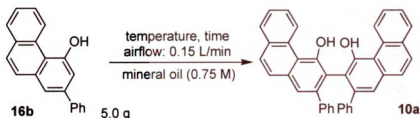
4.5 Preparation of VAPOL with mineral oil as solvent

The original procedure^{17b} for the preparation of VAPOL *via* the oxidative coupling under neat conditions on large scale was problematic for the same reasons that the original synthesis of VANOL was problematic. With a simple and high yielding procedure using mineral oil in hand for the synthesis of VANOL (Table 4.3), effort was turned to extend the same protocol for dimerization of **16b** and the synthesis of VAPOL.

4.5.1 Preparation of VAPOL on small scale: conditions optimization

Of course, the extent to which the findings concerning VANOL were pertinent to the synthesis of VAPOL remained to be determined. Hence, an exploratory reaction was performed. Upon exposing a mixture of **16b** and mineral oil to air at 190 °C, racemic VAPOL was observed to form as a yellow slurry as the reaction proceeded. The workup of the reaction was carried out in the same manner as VANOL synthesis, and VAPOL was isolated as yellow crystals in good yield (entry 1, Table 4.4).

Mineral oil was believed to disperse the materials in the reaction mixture and ensure homogeneity and thereby lead to the successful improvement in the VANOL synthesis. This experience proved to be true again in the case of VAPOL synthesis. A direct benefit emanating from this was the fact that the reaction could be finished without unnecessary interruptions. Furthermore, the quality of the crude product was greatly improved. Importantly, the reactions could now be conducted using conventional heating with an oil bath that greatly simplifies the operational procedure.^{17b,11}

Table 4.4 Temperature effects on the oxidative coupling of **16b** in mineral oil

Entry	Scale of 16b (g)	Temperature ^a (°C)	Time (h)	Crude yield of 10a (%)	Yield of 10a (%)
1	4.31	190	32.5	86.1	84.3 ^b
2	5.00	180	35.5	93.4	69.5 ^c
3	5.00	170	35.5	94.9	83.8 ^c

^a Oil bath temperature. For experimental details, see: Section 7.4.2.1 of Chapter Seven. ^b

Crystallized from CH₂Cl₂. ^c Crystallized from ethyl acetate.

With the promising result in hand (Table 4.4, entry 1), a set of reactions were conducted to probe the optimum temperature. As discussed above (Figure 4.2), high temperatures (190 °C) were required for the reaction to proceed at a synthetically useful rate largely due to radical production was slow. There were some concerns for the oxidative stability of **16b** and thus performing the reaction under milder conditions could therefore be desirable. As summarized in Table 4.4, temperatures as low as 170 °C were effective to drive the reaction to completion at a reasonable rate (entry 3).

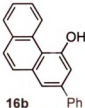
4.5.2 Large-scale preparation of VAPOL

With the methods described in Table 3.4 of Chapter three, an abundant supply of the precursor **16b** is readily available, and the synthesis of VAPOL on large scale was now attainable and the results are collected in Table 4.5.

The oxidative coupling of **16b** in mineral oil produced racemic VAPOL reliably on 50 g scale in excellent yield (Table 4.5, entry 1). A small amount of monomer

16b (1.8 g) was recovered from the reaction after 24 h (Table 4.5, entry 1). The reaction gained full conversion when it was maintained under the same conditions for 36 h (entry 2 and 3), which was essential to ensure best yield.

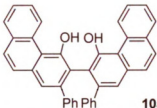
Table 4.5 Large-scale preparation of VAPOL in the presence of mineral oil



16b

170 °C, time
airflow: 0.15 L/min
mineral oil (0.75 M)

→



10a

Entry	Scale of 16b (g)	Time (h)	Crude product		10a after crystallizations ^a	
			Yield (%)	Mp (°C)	Yield (%)	Mp (°C)
1	50.0 ^b	24	90.5	293-6	80.9 ^c	310-1
2	50.0 ^b	36	97.5	297-9	88.8	308-9
3	50.0 ^b	36	91.1	296-9	92.7	306-9
4	48.0 ^d	36	99.5	300-1	97.1	310-1

^a From 1 L toluene; for experimental details, see: Section 7.4.2.2 of Chapter Seven. The reported mp of **10a**^{17b,c} is >250 °C. ^b **16b** is from Table 3.4 of Chapter three. ^c 1.8 g of **16b** was recovered.

^d **16b** is from the CAEC cascade reaction of **17b** and **63a** in entry 2, Table 3.12 of Chapter Three.

Next, this reaction was applied to **16b** from the CAEC cascade pathway (Table 4.5, entry 4). In fact, it turned out that this reaction was equally applicable to the substrate.

4.6 Scope and limitations of the coupling reaction using mineral oil as solvent

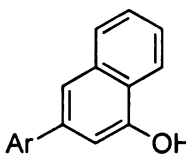
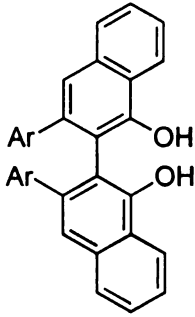
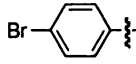
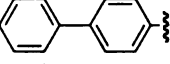
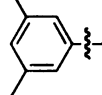
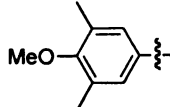
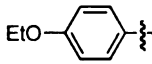
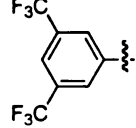
The oxidative coupling reaction was originally designed for α -naphthols with a substituent *meta*- to the hydroxyl functionality. While it has only been applied to the synthesis of VANOL and VAPOL up until now, it may become more widely used with the current interest in these ligands. With the optimal conditions identified, the stage was set for the screen of a variety of substrates to test the

generality of the reaction.

4.6.1 Electronic effects

In collaboration with other group members, the scope of this reaction was examined with regard to substrates with different electronic properties as exerted by various substituents on the aromatic ring (Table 4.6).

Table 4.6 Preparation of VANOL derivatives *via* the phenol coupling reaction

		$\xrightarrow[\text{mineral oil, 24 h}]{160\text{ }^{\circ}\text{C, airflow}}$		
16c–h				9c–h
Entry	Monomers	Ar	Dimers	Yield (%) ^a
1	16c		9c	56
2	16d		9d	40
3	16e		9e	69
4	16f		9f	67
5	16g		9g	60
6	16h		9h	0

^a Dr Zhenjie Lu's Results

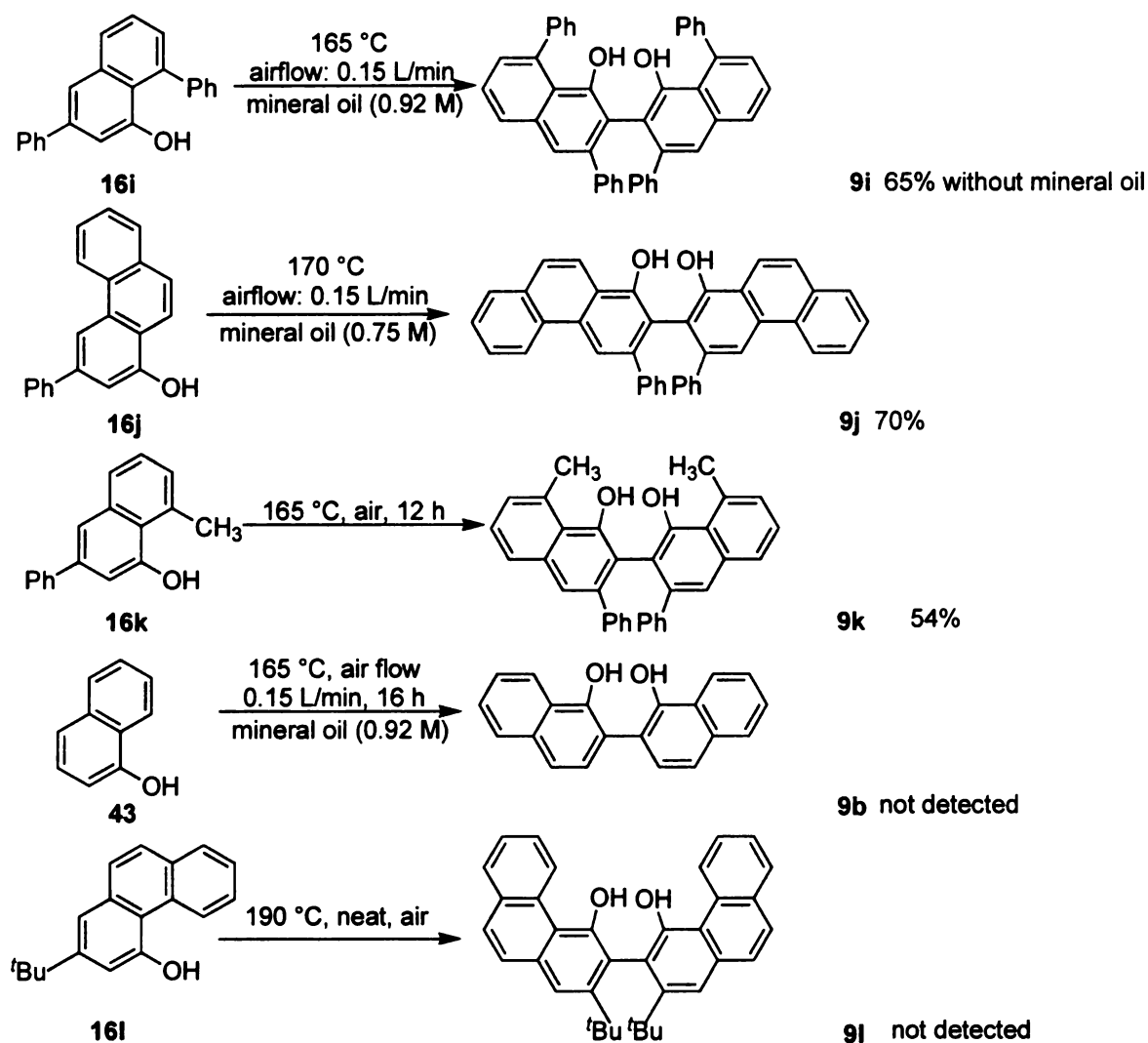
Dr Zhenjie Lu found that the reaction accommodated both electron-donating and slightly electron-withdrawing substituents on the 3-aryl residues of VANOL (Table 4.6, entries 1 to 5).^{18f} The strongly electron-deficient monomer **16h** was

not a suitable substrate, and did not provide any detectable product (entry 6). At this stage it was suspected that the reaction failed because the trifluoromethyl groups significantly remove electron density from the naphthol ring, and accordingly increase the energetic barrier for the oxidative formation of the phenol radical. If true, this method would not be useful for electron-poor naphthols and perhaps future experiments will confirm this limitation.

4.6.2 Steric effects

Other substrates were also subjected to the phenol coupling reaction to map the compatibility with different structural features and the results are summarized in Scheme 4.8.¹⁴⁴ Mr. Desai found that this method works well for the 3,8-diphenyl-1-naphthol **16i**, however, isolation of **9i** from mineral oil was not possible even with multiple silica gel chromatography columns due to their extremely close polarity. Cognizant of this, it is anticipated that other high boiling point solvents such as diphenyl ether (bp = 259 °C) or ethylene glycol (bp = 196-198 °C) could facilitate this reaction to eliminate the separation issues associated with mineral oil.^{131,144a} Fortunately, Mr Desai found that the oxidative coupling of **16i** under neat conditions (without mineral oil) was successful, yielding ligand **9i** in 65% yield.^{144a,b} The solvent-free conditions were found suitable for **16k** as well; in this case, moderate yield of **9k** was obtained on small scales, but the mineral oil protocol was not attempted on this substrate.^{144b}

Scheme 4.8 Steric effects of the oxidative coupling reaction



The high level of conversion observed for the oxidative coupling of **16i** to give **9i** demonstrated that the oxidative dimerization could proceed satisfactorily with sterically demanding substrates. However, substrates lacking the *meta*-substituent simply failed to generate substantial amounts of the dimeric product. For example, applying this procedure to 1-naphthol **43**^{145,138b} resulted in the formation of hard lumps, which were difficult to break up and to transfer out of the flask. On the contrary, for sterically crowded monomers such as **16l**, no dimeric product **9l** was detected.^{17b,c}

The results described above represent efforts to achieve a better understanding of the interplay of the many reaction variables. However, the scope of the reaction is still not fully elucidated, although the preliminary data begin to define the extent of the scope of the reaction. Considering that biaryl structural motifs are often an integral feature of pharmacologically and biologically active compounds,¹³⁹ these efforts offer an opportunity to formulate more broadly applicable procedures for their syntheses.

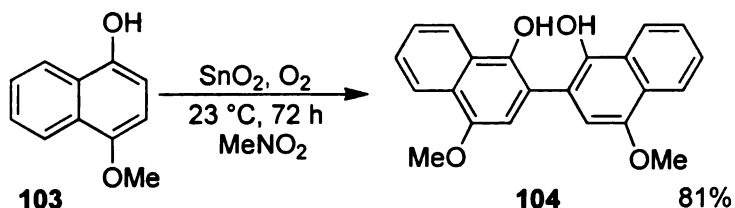
4.7 Future perspective

As impressive as it is, the oxidative self-coupling of 1-naphthol derivatives using air is a simple and effective synthetic method for the VANOL and VAPOL ligands. The remarkable effectiveness of mineral oil as solvent has been developed for this process as a natural progression of these investigations. Whilst understanding the chemistry behind what ultimately controlled the reaction allowed for the process to be operated at lower temperature, it is still too high¹³¹ to be germane for the ultimate goal of asymmetric phenol coupling. Therefore, one future goals in pursuing asymmetric syntheses of the VANOL and VAPOL ligands is to liberate radical generation from the tyranny of demanding high temperatures or to eliminate the formation of radical altogether. In fact, by using copper-based oxidant, the synthesis of VANOL via oxidative coupling of **16a** has been successfully realized at lower temperature (140 °C).¹¹²

Catalysis, offers potential solutions to these inherent drastic conditions of the phenol coupling reaction by lowering the activation energy and by allowing reactions to be conducted at lower temperatures. Indeed, a variety of methods to

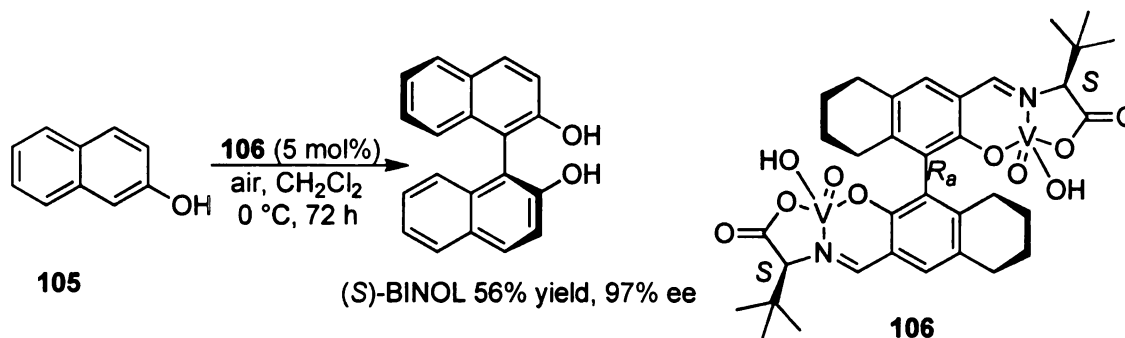
generate chiral biaryls by using metal-mediated oxidants has been extensively explored.^{146,138,131} A recent observation on the oxidative coupling of **103** using SnO₂ as catalyst (Scheme 4.9) illustrates this possibility.¹⁴⁷

Scheme 4.9 Efficient oxidative dimerization of **103** to **104**¹⁴⁷



For our purposes, the asymmetric catalytic coupling of 2-naphthol exemplified by the reaction in Scheme 4.10^{137b} provides an important consideration in future efforts with respect to the development of analogous methodology for the synthesis of VANOL and VAPOL ligands.

Scheme 4.10 Chiral vanadium(V) catalysts for the oxidative coupling of **105**^{137b}



4.8 Concluding remarks

A method for the high-yield production of the racemic VANOL ligand by oxidative self-coupling has been investigated. Under solvent-free conditions, the phenolic coupling delivered the binaphthol ligand VANOL using air as oxidant. However, precipitation of the product during the course of the reaction rendered the stirring difficult and greatly slowed the reaction. This necessitated the periodic interruption of the reaction and removal of the product VANOL from the crude

reaction mixture. This made the process inefficient and tedious.

These problems have been tackled very efficiently by inclusion of mineral oil as the reaction media. Thus, the products are formed as finely dispersed particles, which dramatically enhanced the reaction rate. With significant improvement in the quality of the crude product, downstream workup and purification steps are simplified. All these factors facilitate throughput during the course of the whole processes. The reaction tolerates a diversity of functional groups in the monomeric precursors. With the arrival of this new methodology, rapid access to various VANOL / VAPOL derivatives should be feasible.

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**VANOL AND VAPOL CHEMISTRY: NEW METHODOLOGIES,
LARGE SCALE SYNTHESIS, DERIVATIVES, AND
SYNTHETIC APPLICATIONS**

VOLUME II

By

Zhensheng Ding

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Chemistry

2009

CHAPTER FIVE

UNRAVELING THE RESOLUTION OF THE VANOL AND VAPOL LIGANDS

Along with the establishment of elegant and effective synthetic processes of racemic VANOL and VAPOL, the introduction of the proper configuration about the chiral axis in these dimeric ligands is the final requirement. However, the absence of methods for the asymmetric formation of the biaryl bonds by default leaves classical resolution as the crucially important source of the enantiopure ligands. As a result, the next task is to develop a reliable procedure for conducting the resolution *via* the formations of diastereomeric salts and also to liberate both of the ligands from their salts.

5.1 Introduction

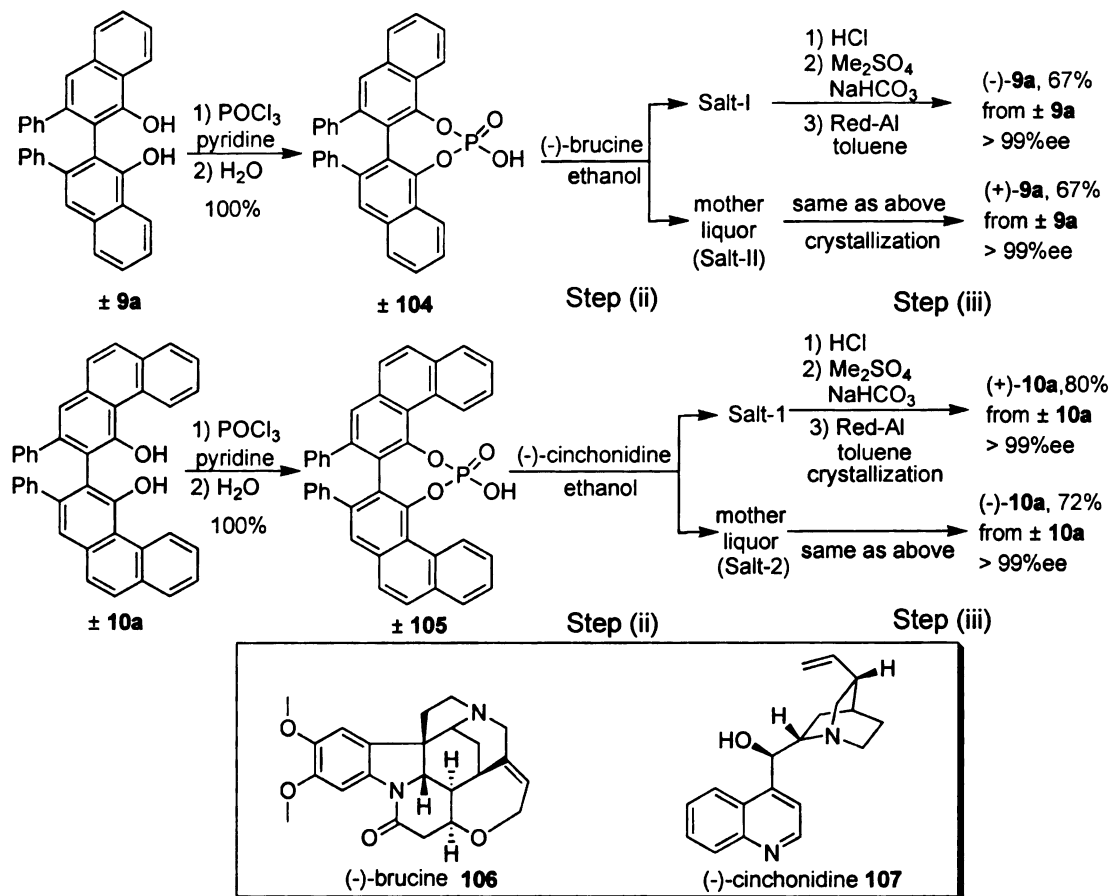
Resolution *via* diastereomeric salt formation involves the acid-base reaction of a racemate with an enantiopure resolving agent.¹⁴⁸ This furnishes two diastereomers, which differ in physical properties. A difference in solubility is often used to separate the diastereomers. Because both isomers of the ligands are desired, this renders resolution as the ideal method of choice.

In general, the critical analysis of a resolution procedure with the purpose of finding an economically viable process can be dissected into the following steps: (i) selection of a resolving agent that forms readily separable diastereomers with the target racemate; (ii) finding a suitable method for diastereomer separation; (iii) purification of the separated diastereomer or the enantiomer prepared therefrom.

The basic procedure for the resolution of the VANOL and VAPOL ligands have been defined (Scheme 5.1). However, the conditions have to be modified

owing to the low efficiency of the procedure on large-scales. Thus the starting point for further development has efforts directed being to optimize steps (ii) and (iii) in the hunt for an efficient resolution process for both VANOL and VAPOL.

Scheme 5.1 The published procedure for the resolution of **9a** and **10a**



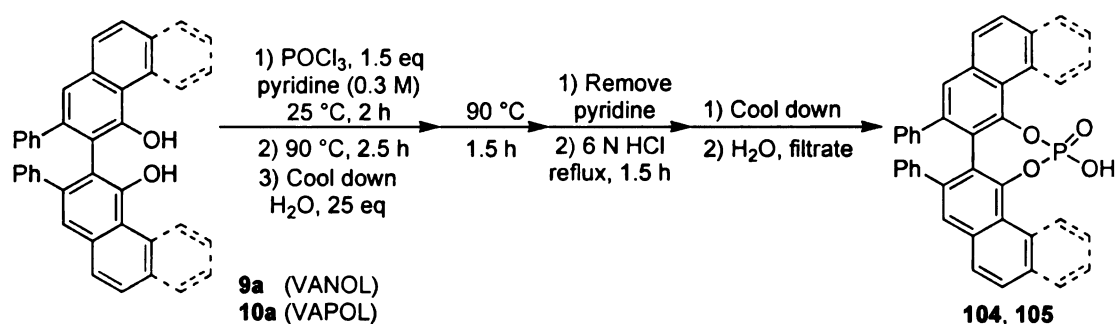
5.2 Preparation of VANOL– and VAPOL–phosphoric acid

To resolve VANOL and VAPOL, they were first converted to the corresponding phosphoric acids **104** and **105**. The published methods for the synthesis of these acids (**104** and **105**) were first repeated under the conditions that are described in the literature.^{17b} This involves the reaction of the free ligands with POCl_3 in refluxing pyridine. The intermediate phosphoryl chloride

was then hydrolyzed in boiling water followed by quenching with refluxing 6 N HCl (Table 5.1).

While successful, this process suffers from the relatively harsh reaction, tedious temperature variations and solvent transfers. The utilization of vast excesses of the reagents also induces cost and safety concerns.

Table 5.1 Preparation of **104** (from VANOL) and **105** (from VAPOL) via the reported^{17b} procedure ^a



Entry	Substrate	Scale (g)	Pyridine (mL)	Yield (%)	Product
1	VANOL 9a	10.0	80	100	104
2		30.0	250	100	
3		30.0	250	95.3	
4		50.0	400	100	
5		100.0	800	99.0	
6		100.0	800	97.0	
7		103.8	800	100	
8	VAPOL 10a	40.3	250	87.8	105
9		45.0	250	94.6	
10		46.0	350	100	

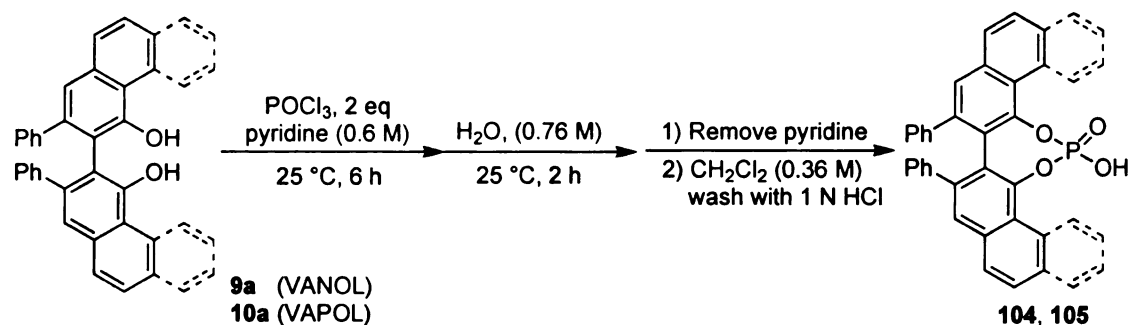
^a For experimental details, see: Sections 7.5.1 and 7.5.2 of Chapter Seven.

Another concern of this process is the way in which the product is isolated from the crude reaction mixture and the way in which it is dried. This is important because the phosphoric acids are obtained by precipitation from HCl as finely dispersed particles, which can block the filter paper and lead to a very slow filtration on-scale. Moreover, it is difficult to dry the products since they are

precipitated directly from water. Hence, the entire procedure was reevaluated, beginning with a literature search that was aimed at unraveling alternative operational options.

After the literature screening, Mr. Aman Desai found that the harsh conditions of the original procedure were not necessary to synthesize **104** and **105**.¹⁴⁴ The same results were afforded under much milder conditions (Table 5.2). The major advantage, however, was offered by the opportunity to conduct the synthesis in one pot. A further upside to this procedure is that the concentration of the substrates (**9a** and **10a**) in pyridine could be raised from 0.3 M to 0.6 M, allowing the use of less pyridine.

Table 5.2 New procedure to prepare **104** (from VANOL) and **105** (from VAPOL) ^a



Entry	Substrate	Scale (g)	Pyridine (mL)	Yield (%)	Product
1	VANOL 9a	0.92	3.0	100	104
2		40.0	150	96.4	
3		40.0	150	100	
4		40.7	150	100	
5		38.8	150	100	
6	VAPOL 10a	30.9	170	100	105

^a For experimental details, see: Sections 7.5.1 and 7.5.2 of Chapter Seven.

Implementation of these changes resulted in an appreciable throughput improvement, which was largely attributed to performing the sequence in a one-pot scenario. Furthermore, the product was obtained by washing the CH_2Cl_2

solution of the crude reaction mixture with HCl (1N). This was not only much milder, but also eliminated the time-consuming filtration protocol. This new procedure is now also being used in the synthesis of optically pure VANOL and VAPOL phosphoric acids,¹⁴⁴ which have been demonstrated as effective chiral Brønsted acid catalysts.²²

5.3 Resolution of VANOL–phosphoric acid 104: 1st generation method

As described in the previous section, an efficient procedure for the synthesis of the racemic VANOL-phosphoric acid **104** has been developed. We then moved to the resolution of this compound by using (-)-brucine **106** to generate diastereomeric salts.

5.3.1 Introduction

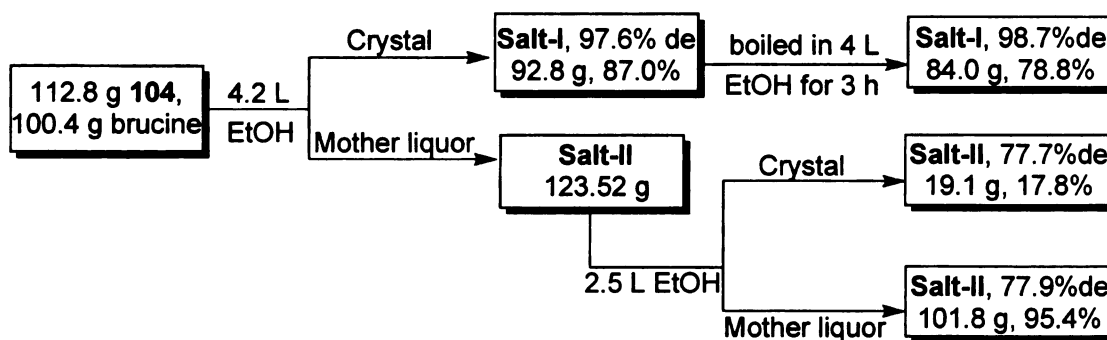
To be able to realize such a scheme, several variables had to be considered: (i) the optimum conditions for diastereomer separation (solvents, concentration, temperature, etc.); (ii) the procedures to liberate of both enantiomers of the free ligands; and finally, (iii) the method to determine optical purity (ee) of the salts.

In view of the low cost and bulk availability of (-)-brucine, and particularly its success in the resolution of VANOL-phosphoric acid in early investigations,^{17b} we decided to continue the studies with one equivalent of this resolving agent. Reductive cracking of the diastereomeric salts by Vitride® (i.e. Red-Al) was the method of choice to release the optically enriched VANOL ligand. The ee of VANOL could be easily determined by HPLC on a Pirkle D-phenylglycine column (see Section 7.5.3.1 of Chapter Seven for details). Thus, the efforts were focused on optimization of the conditions.

5.3.2 Investigations of crystallization solvents for the resolution of **104**

The reported procedure involves boiling a mixture of **104** (27 g) and brucine in 1 L of ethanol.^{17b} It was first repeated on larger scale (112.8 g of **104**, Figure 5.1; see Section 7.5.3.1 of Chapter Seven for experimental details). Shockingly, the solid did not completely dissolve in 4.2 L ethanol even after refluxing for 3 h. As a result, upon cooling to 25 °C and collection of the solid, the ee (97.6%ee) of the first salt (salt-I) was lower than reported. This salt was refluxed with another 4 L ethanol, but still failed to completely dissolve, and only a slight improvement in ee was observed (98.7%ee). On the other hand, the diastereomeric salt in the mother liquor (salt-II, 123.5 g, 77.9%ee) is much more soluble in boiling EtOH. After removal of the solvent from the mother liquor, the residue could be completely dissolved in 2.5 L of boiling ethanol. Unfortunately, this procedure failed to enhance the optical purity of this material as indicated by the identical ee values of the salt in the crystal and in the mother liquor (Figure 5.1).

Figure 5.1 Resolution of **104** on 112.8 g scale using EtOH



The failure to reproduce the published resolution procedure was clearly linked to the low solubility of the salt-I in EtOH. To test this idea, dissolution of racemic **104** alone (53 g) in boiling EtOH was attempted before brucine was added.

However, it was found that the solubility of **104** (7 g/ L) was also unacceptably low. Consequently, boiling ethanol was deemed unsuitable for large-scale resolution.

The previous studies on resolving **104** relied heavily on ethanol as the solvent.^{17b} Considering that solvents can have a marked impact on solubility and thus on the efficiency of resolution, the solubility behavior of both salts (salt-I and II) in different solvents was subsequently subjected to investigation (Table 5.3). This solvent screen indicated that chlorinated solvents such as CH₂Cl₂ and 1,2-dichloroethane (DCE) were good solvents for solubilizing salt-I but not for salt-II. It is more inspiring to observe that for salt-II, crystals formed from either of these two solvents upon cooling the boiling saturated solutions to ambient temperature.

Table 5.3 Solubility tests of the diastereomeric salts formed by **104** and brucine ^a

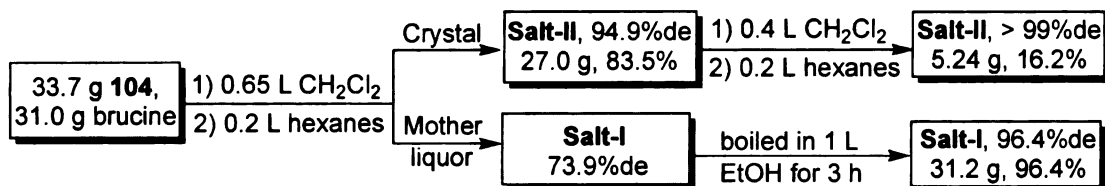
Salt	DCM	DCE	EtOAc	Acetone	Hexane	Toluene	MeOH	iPrOH
I	✓	✓	X	✓	X	✓	foam ^c	X
II	cryst ^b	cryst ^b	X	✓	X	✓	foam ^c	X

^a Procedure: the pure salt (0.5 g) was heated to reflux with solvent (up to 20 mL) until dissolution, then it was cooled down to 25 °C. ✓: highly soluble; X: not soluble. ^b Crystals formed upon cooling to 25 °C. ^c Dissolved but foam formed upon cooling.

We then attempted to reverse the order of isolation and precipitate salt-II first by using CH₂Cl₂. Operationally, the resolution was performed by first dissolving the mixture of the *rac*-**104** (33.7 g) and 1 equiv of brucine in boiling CH₂Cl₂ (650 mL; it was noticed that the use of CH₂Cl₂ alone did not lead to sufficient precipitation upon cooling). Hexanes (200 mL) was slowly added to this refluxing solution over a period of 30 min. Salt-II precipitated rapidly from the hot solution (less than 2 min) with good d.e. (94.9%) in 83.5% yield (Figure 5.2; for

experimental details, see: Section 7.5.3.2 of Chapter Seven).

Figure 5.2 Resolution of **104** in CH₂Cl₂/ hexanes



In this new resolution sequence, salt-I (74% d.e.) stayed in the mother liquor, which was isolated by removal the solvents in vacuo. To upgrade its optical purity, it was boiled with 1 L EtOH for 3 h. After cooling to room temperature, filtration of the resulting slurry yielded the brucine salt with (S)-**104** (salt-I) in 96.4% yield and with 96.4%de.

However, it was a frustrating situation that both diastereomeric salts were optically impure at this point. Therefore, alternative methods for purification of the primary products (the salt-I and salt-II) of the above-described resolution had to be devised and will be discussed in the following sections.

5.3.3 Strategies for the purification of the diastereomerically impure salts

Because the optical purities of both salts were not acceptable, we had two options:

(1) Recrystallization of each diastereomeric salt to an acceptable level of optical purity.

These two salts could be further recrystallized to improve the optical purity, to the point where enantiomerically pure free VANOL could be gained.

(2) Perform the cleavage on the impure salts followed by crystallizing the free VANOL ligand to optical purity.

Since selective precipitation of racemic VANOL from an enantiomerically enriched mixture has been used for enhancing its enantiomeric purity (see section 5.8.2), it seems reasonable to cleave these salts and purify the free VANOL ligand as a method to obtain optically pure ligand. This, however efficient, would add extra steps to the process and decrease material throughput. Moreover, it has been observed that the pure enantiomers of VANOL are less stable than the racemic form, thus these extra steps would risk decomposition. Given these issues, enrichment of the free ligands was deemed unfavorable as a final procedure.

Thus, strategy (1) was adopted and efforts were directed to explore for the optimal conditions to produce optically pure VANOL ligands. Attention was first focused on salt-I. When working in pure ethanol, salt-I was not sufficiently soluble. However, it was revealed by the data in Table 5.3 that CH_2Cl_2 was suitable for solubilizing salt-I. Therefore, it was used as the co-solvent to dissolve and upgrade the purity of salt-I. Experimentally, salt-I (22.5 g, 96.4% de) was dissolved in a minimum amount of boiling CH_2Cl_2 (70 mL), and to this solution was added 100 mL EtOH at a rate such that refluxing could be maintained. A solid crashed out at this point and more EtOH (900 mL) was added and reflux was continued for 3 h. This solution was cooled to 25 °C, the crystals were filtered, and identified as pure salt-I (>99%de, 21.7 g, 96.4% recovery).

It should be noted that the rate of addition of EtOH was critically important to ensure acceptable diastereomeric integrity of salt-I. In fact, after taking this precaution with this procedure, purification of salt-I can be achieved on material

with purity as low as 26%de (82.8 g) to give excellent results (>99% de, 34.8 g, 66.7% recovery) after crystallization with same conditions.

To optically upgrade salt-II, the recrystallization of the salt-II with CH₂Cl₂/hexanes seemed promising. However, this protocol proved to be troublesome.

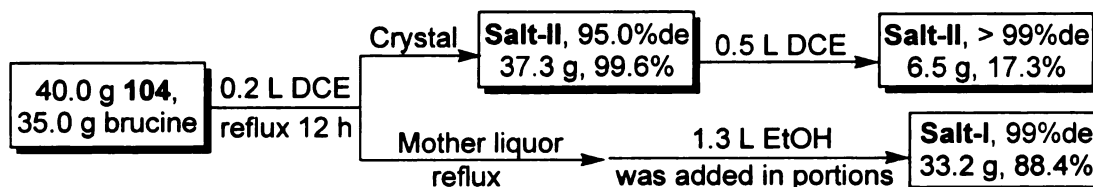
The salt-II (27.0 g 94.9%de, Figure 5.2) was dissolved in a minimum amount of boiling CH₂Cl₂ (400 mL) and then hexanes (200 mL) was added in four aliquots. This crystallization worked as expected, yielding crystals of salt-II with >99%de. Unfortunately, this process was much less efficient: the yield was only 16.2%.

5.4 Resolution of 104 by using 1,2-dichloroethane (DCE)

Surprisingly, the yield of salt-II was much better when DCE was used as solvent for the resolution (Figure 5.3). Thus, following a protocol similar to that for CH₂Cl₂/ hexanes (Figure 5.2), a mixture comprising **104** and brucine was heated to boil in DCE. While the mixture was being heated, a homogeneous solution formed and then a white solid crashed out. This material could not be dissolved even if the solution was maintained at the boiling point for an extended period of time. The solution was cooled, salt-II was collected and found to be 95%d.e., which was further purified by crystallization from DCE as follows. The crystals of salt-II (37.3 g, 95% de) were heated to reflux in DCE and it was found that 500 mL was required for complete dissolution. Cooling to room temperature gave only a 17.3% recovery (6.5 g, >99% de). Attempts to decrease the amount of DCE and increase the time for dissolution were not investigated. Meanwhile, salt-I (99% de) could be obtained by adding 1.3 L EtOH in three aliquots, after each

addition the solution was brought back to reflux. Solid crashed out when 1 L EtOH was added. It was first cooled to 25 °C then to -20°C overnight, solid was collected to get salt-I (33.2 g, 88.4%) as light yellow powder.

Figure 5.3 Resolution of **104** in 1,2-dichloroethane (DCE)



In principle, the yield of the diastereomeric pure salt-II could be raised by further crystallizing the residue from the mother liquor. However, it is very likely to be unacceptably protracted based on the low recovery observed. Therefore, it was easily recognized that this process was far from being ideal as a method for ensuring the long-term supply of enantiomerically pure *R*-VANOL, and no attempts were undertaken to explore this further.

The experiment outlined in Figure 5.3 suggests that the optical quality of the first crop of salt-II must be high such that any further enrichment is not needed. To achieve this goal, the rate of precipitation of salt-II had to be reduced. After extensive investigations, the best way to do this was envisaged to involve the maintenance of a low concentration of brucine. This would be operationally difficult for the two-solvent system (CH₂Cl₂/ hexanes) that was previously employed since both brucine and **104** are insoluble in hexanes. These facts suggest that the optimization of salt-II should be continued with DCE.

5.5 Resolution of VANOL–phosphoric acid: 2nd generation method

As witnessed by the results obtained in the previous section, we were still far

from an ideal procedure. Initial results on the attempted resolution of *rac*-**104** with the revised procedure involving CH₂Cl₂/ hexanes (Figure 5.2) were not encouraging in view of the fact that both salts were diastereomerically impure. However, the success of the initial screens using CH₂Cl₂ as solvent fostered new ideas, and offered some hope that by a systematic variation of the solvent, the pure diastereomer containing the (*R*)-VANOL (i.e. salt-II) could be attainable.

5.5.1 Introduction

The preferential precipitation of salt-II from hot DCE solution yielded a 99.6% recovery with 95% d.e. (Figure 5.3). The high propensity for precipitate of salt-II was welcomed, but to a limited extent. This is because if the precipitation is too quick, lower optical purity will result. Therefore, the experimental conditions had to be carefully controlled. It was blatantly clear that the rate at which salt-II reached the saturation point was concentration dependent. Therefore, these considerations led to the prediction that slow addition of the resolving agent (brucine, **106**) to a refluxing solution of **104** would be ideally suited for the precipitation of salt-II.

The manner in which the racemate and the resolving agent are combined seems to be a trivial matter, but it turns out to be of prime importance for the success of the resolution of VANOL. When brucine and acid **104** are mixed together with DCE and then brought to reflux, crystallization of salt-II gave reduced enantiomeric purity. Mixing the components that were dissolved separately in the same solvent might give better results since the concentration of the resolving agent could be controlled. This would serve to define the rate of

the formation of the salts and thus may improve the optical purity.

5.5.2 Initial optimizations of the resolution using DCE on small scale

After unsuccessful preliminary experiments conducted in various solvents, attention was focused on DCE in regard to its higher boiling point and its ability to solubilize both brucine and racemic VANOL phosphoric acid **104**. Most importantly, crystals of salt-II were easily precipitated as shown in Figure 5.3. Operationally, the modified procedure was preformed by slowly adding the DCE solution of 1 equiv of brucine over 60 min to the solution of *rac*-**104** (2.0 g) in boiling DCE, followed by slowly cooling to ambient temperature overnight. Filtration of the resulting slurry yielded salt-II. The diastereomeric purity was determined by HPLC after reductive cleavage of this salt to the free VANOL ligand, and the results are shown in Table 5.4.

Table 5.4 Resolution of **104** in DCE by slowly adding brucine solution: small scale

Entry	DCE for 104 (mL)	DCE for brucine ^a (mL)	Total DCE (mL)	Salt-II (<i>R</i> -VANOL) Yield (%)	de (%)
1 ^b	15	16	31	85	98.5
2	7	23	30	70	99.0
3	7	13	20	70	99.6
4	7	3	10	72	90.6
5 ^c	7	3	10	79	98.7

^a Brucine (98% purity) was used unless otherwise mentioned. ^b Technical grade (-)-brucine

(92.6% purity) was used. ^c Performed under a N₂ atmosphere.

Technical grade brucine (Aldrich: batch #: 367869, lot #: 06017EX) was used to establish the initial condition because of its lower price (Table 5.4, entry 1). A homogeneous solution was obtained from which the diastereomeric salt-II quickly crystallized after 1 h. After ageing for 12 h, excellent yield of salt-II was afforded with marvelously good de.

In addition to the pronounced solvent effect, one variable that caught our attention was the presence of an insoluble component in brucine during the course of dissolving and transferring this material. To minimize its impact on the resolution, a higher grade brucine (98%) was examined under the same conditions (Table 5.4, entry 2). This improved the d.e. of salt-II but gave lower yield. Performing the resolution at a higher concentration (entry 3) did not improve the resolution, while a significant drop of d.e. was observed when the total volume of the DCE was decreased to 10 mL (entry 4).

As a matter of possible chemical relevance, another incidence stood out and caught our attention: over-exposure of the DCE solution of brucine to air gave rise to a white precipitate, and this was thought to have resulted from the reaction of brucine with CO₂.^{144b} The effect of this material on the resolution were not clear; however, its removal would be desirable at a minimum to favor consistency of the process. Consequently, the resolution in entry 4 of Table 5.4 was repeated under an N₂ atmosphere (Table 5.4, entry 5), and better results were furnished in terms of yield and d.e. All resolutions discussed in the remainder of this chapter were all carried out under a N₂ atmosphere.

5.5.3 Effects of the purity of brucine on the resolution of **104**

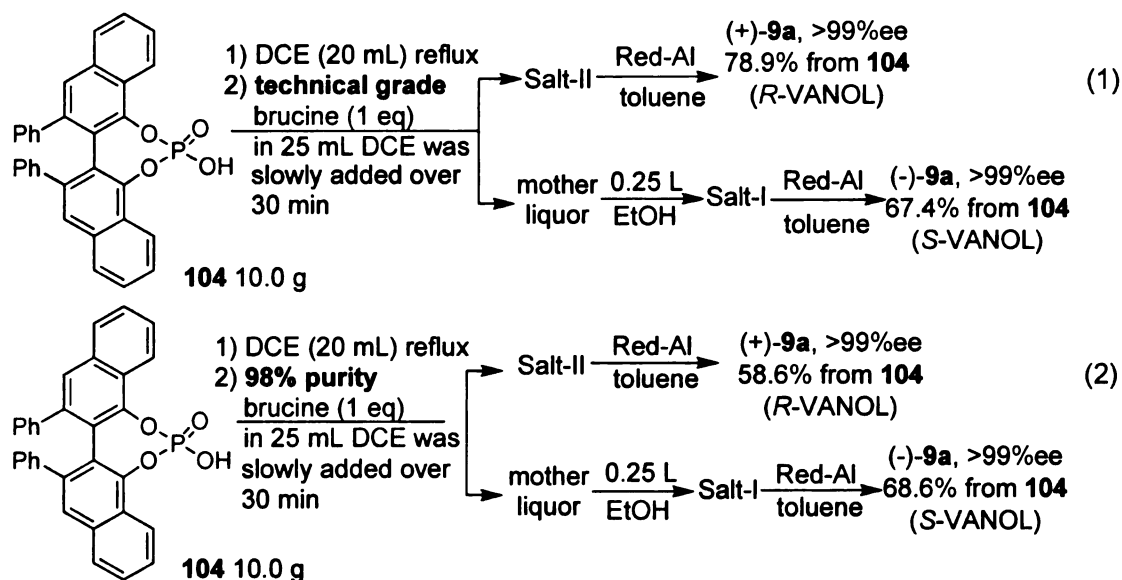
The yields of salt-II obtained in Table 5.4 were generally lower than 80% using 98% brucine. Most likely the insoluble component in technical brucine played some role, perhaps to provide a seeding surface for crystal growth. This could account for the improvement of the yield of the salt-II with the lower quality brucine (Table 5.4, entry 1).

Being so close to a solution, it was decided to continue the optimization using technical grade brucine. It was believed that the root cause of the failure of resolution (i.e. the diastereomeric purity of salt-II was less than 99% de. See: Table 5.4, entry 1) was the overly fast formation of the salt.

Therefore, the two components were separately dissolved in DCE in different flasks. Racemic phosphoric acid **104** (10 g) was dissolved in boiling DCE (20 mL), and to this refluxing solution was added a DCE (25 mL) solution of brucine *via* syringe pump over 30 min (Figure 5.4). Having become aware of the presence of impurities in the resolving agent, extra care was taken in transferring the brucine solution by syringe to ensure that any solids remained in the flask. After liberation of the free ligand by Red-Al, this gave *R*-VANOL in 78.9% yield with >99%ee (Figure 5.4, Eq. (1)).

This endeavor was additionally rewarded when it was shown that pure salt-I could be easily obtained by simply bringing the mother liquor to reflux followed by the addition of EtOH in five aliquots (50 mL each). Complete reduction of this salt (salt-I) by Red-Al produced *S*-VANOL (>99% ee) in 67.4% yield from racemic acid **104** (Eq. (1), Figure 5.4).

Figure 5.4 Effects of the purity of brucine on resolution of **104**



Interestingly, a side-by-side resolution using 98% brucine under identical conditions (Figure 5.4, Eq. (2)) also cleanly gave both salts but with a much lower yield of **(+)-9a** (*R*-VANOL) from salt-II. Thus, we focused on the development of methods to resolve the VANOL ligand with technical grade brucine.

5.6 Summary of the optimization of the resolution of phosphoric acid **104**

Unsatisfied with the obtained results by following the original report,^{17b} the resolution of racemic **104** in CH₂Cl₂ / hexanes gave the desired Salt-II in good yield with <99%de. Unlike CH₂Cl₂, DCE does not require hexanes to precipitate salt-II, and at the same time it is capable of dissolving salt-I while allowing precipitate of salt-II. Therefore, DCE was the solvent of choice as it also offered expediency in further explorations.

The key parameter for the success for resolution of **104** was found to be the rate of formation of the crystals of the salts. Armed with this information, brucine was dissolved in DCE and slowly added to a refluxing DCE solution of **104**. This

protocol worked well for brucine with 98% purity and gave moderate yields of salt-II, but surprisingly it worked even better with the lower grade technical brucine. The presence of impurities in the technical grade brucine appears to have a negative effect on the de of salt-II (See: Table 5.4, entry 1). Therefore, it may be prudent to remove these impurities before addition of brucine to phosphoric acid **104**. Furthermore, salt-I could be isolated by simply adding EtOH to the boiling mother liquor. In this way, both diastereomeric salts could be obtained in excellent yields with high optical purity.

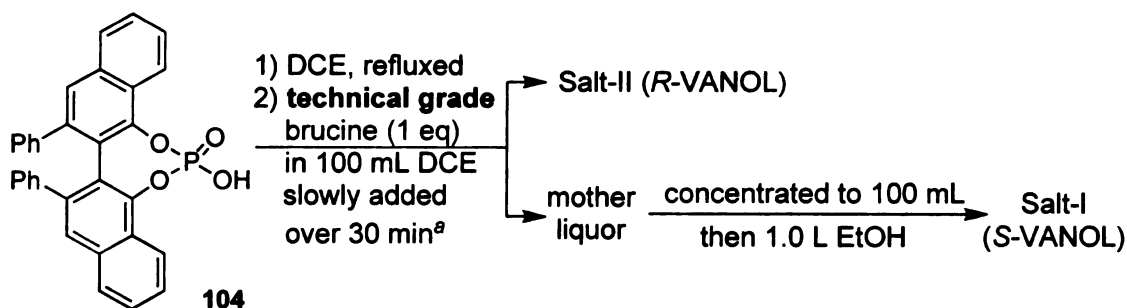
5.7 Large scale resolution of VANOL–phosphoric acid **104**

The combination of above observations led to the development of the conditions chosen for scale-up. The resolutions were performed in DCE, with a brucine solution slowly added to a refluxing solution of **104**. These conditions delivered salt-II in a diastereomerically pure form. The whole process was carried out under a N₂ atmosphere, and the insoluble impurities in the brucine solution were excluded during the transfer by syringe to ensure an acceptable stereochemical purity of the crystals. Salt-I remained in the DCE solution and could be efficiently and selectively precipitated by simply adding EtOH to the refluxing solution of the mother liquor.

Brucine with 98% purity was first examined for purposes of comparison, and once again as on small scale gave a low yield of salt-II (Table 5.5, entry 1). The de of salt-II in entry 2 was lower owing to the higher concentration of the both reactants. This highlighted the importance of rigorous control of the conditions during crystallization.

Pure salt-II could be obtained as follows: the DCE solution of brucine was added slowly to a boiling DCE solution of **104**. Once the saturation point of salt-II in DCE (0.12 g/ mL) was reached, the addition of brucine was suspended and the mixture was refluxed for 15 min to ensure complete precipitation. The addition of the brucine solution was then resumed (see Section 7.5.3.3 of Chapter Seven for details). This operational change brought about a consistent and reproducible 99% de with >80% yields of salt-II on large scale, while salt-I from its antipode stayed in solution (entries 3 to 5, Table 5.5).

Table 5.5 Resolution of acid **104** using technical grade brucine on large scale



Entry	104 (g)	Brucine (g)	Impurities ^b (g)	Salts	Yield of 1 st crop		de (%)
					(g)	(%)	
1	46.3	36.5 ^{c,d}	nd ^e	Salt-II	22.8	55	> 99
				Salt-I	38.5	93	> 99
2	45.0	38.0	1.71	Salt-II ^c	35.7	85	96.0
				Salt-I	37.2	89	> 99
3	42.3	35.7	1.37	Salt-II	32.4	83	> 99
				Salt-I	34.8	89	> 99
4	45.2	38.0	1.69	Salt-II	36.3	87	> 99
				Salt-I	34.8	83	> 99
5	46.7	40.3	0.6	Salt-II ^c	37.1	89	> 99
				Salt-I	34.1	78	> 99

^a Procedure: for salt-II, 100 mL DCE was used to dissolve brucine (technical pure) and this solution was added to the solution of **104** in 200 mL boiling DCE over 30 min. The DCE in the mother liquor was removed and the residue was re-dissolved in 100 mL boiling DCE, to which EtOH (1 L) was added in portions. The de of the salts was determined by HPLC (see Section

7.5.3.3 of Chapter Seven for details). ^b Insoluble impurities in the brucine solution were not transferred by syringe. ^c Brucine was dissolved in 120 mL DCE, and another 100 mL DCE was used to dissolve **104**. ^d 98% brucine was used. ^e nd = not detected.

The enrichment of the salt-I was accomplished by adding EtOH in portions to the boiling mother liquor (see: Section 7.5.3.3 of Chapter Seven). This simple maneuver reliably gave pure salt-I in excellent yields. (Table 5.5, entries 1 to 5).

Overall then, the procedures for large-scale resolution of VANOL were established. As noted above, technical grade brucine was preferable to higher grade brucine in terms of both price and the fact that it gave better yields of salt-II. Both of the diastereomerically pure salts could be obtained in excellent yields with only one crystallization for each. This process secured the long-term supply of both isomers of the enantiopure VANOL ligands, and the total solvent consumption for the whole process was only 300 mL DCE and 1 L EtOH.

5.8 Resolution of VAPOL–phosphoric acid **105**

The original procedure for the resolution of VAPOL has been explored on different scales.^{17b,144d} However, the impressive efficiency exhibited in the resolution of VANOL described in the previous section kindled the investigation of alternative procedures for VAPOL. Identifying better conditions to get optically pure salts in the most efficient manner has continued for years.

5.8.1 Introduction

The original procedures to resolve VAPOL phosphoric acid **105** was published in 1996 by Dr Bao and other group members, where (-)-cinchonidine was chosen to be the resolving agent.^{17b} EtOH was used as the solvent for precipitating both diastereomeric salts (salt-1 and salt-2). The most informative

and diagnostic structural feature of these two salts is the chemical shift of the bay-proton doublet in the ^1H -NMR spectra. They are at 9.7-9.8 ppm in the free ligand. In the salts formed from **105** and (-)-cinchonidine, however, it is shifted upfield and differentiated into two sets of doublets: 9.9-10.0 for salt-1 and 10.0-10.1 for salt-2, respectively. This differentiation is distinctive enough to be used for determination of the diastereopurity of the two salts.

This resolution procedure is severely hampered by its low efficiency set by salt-2, for which disappointingly low yield is achieved in EtOH with variable de's.¹⁴⁴ⁱ The repercussions this has for a practical resolution are considerable, and hence, an alternative was needed.

At this late stage of the project, the basic idea was to change the method as little as possible to avoid introducing too many unknowns, and thus shifting to other solvents was the obvious approach. Dr Hu and Dr Wu had discovered that a mixture of 2-propanol and acetone was a good solvent for inducing crystal growth for salt-2.^{144e} This solvent change significantly improved both the optical quality and the yield of salt-2 and greatly facilitated the resolution process.

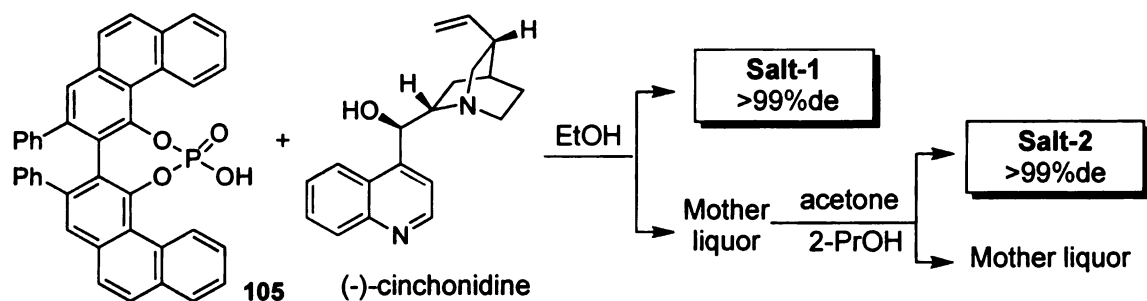
5.8.2 Large-scale resolution of VAPOL phosphoric acid **105**

From the outset, the resolution began with crystallization from EtOH to produce the salt-1. This was done by directly adding solid (-)-cinchonidine (1 equiv) to a boiling suspension of **105** (40 g) in 2 L ethanol which gave a homogeneous solution, from which fine crystal grew on the wall of the flask after cooling to 25 °C overnight (Table 5.6).

An interesting discovery was made that after crystals of salt-1 formed and had

settled to the bottom of the flask, there was a small amount of a fine solid that was dispersed in the solution. During filtration, these impurities formed a thin layer of solid on the filter paper. Consequently, there was a considerable risk that this material (0.5 to 2.0 g) would end up in the final product. Thus, the solution was filtered without disturbing the crystals of salt-1 until most of the liquid was filtered through a Buchner funnel. The filter paper was then replaced with a new one, and then the crystals of salt-1 (17.6 g, 58%, entry 1, Table 5.6) were filtered and collected to give material with >99%de based on ¹H-NMR analysis.

Table 5.6 Large-scale resolution of **105** in EtOH and acetone/ 2-PrOH^a



Entry	105 (g)	Salt-1 ^b 1 st crop	Salt-2 1 st crop	Salt-1 2 nd crop	Salt-2 2 nd crop	Salt-1 3 rd crop	Salt-2 3 rd crop	Total (%) ^c
1	40	58%	-	31%	-	10%	-	99
		-	87%	-	12%	-	-	99
2	47	60%	-	26%	-	5%	-	91
		-	77%	-	15%	-	7%	99
3	51	45%	-	41%	-	6%	-	92
		-	69%	-	26%	-	4%	99
4	35 ^d	38%	-	33%	-	- ^e	-	71
		-	70%	-	6%	-	-	76

^a The de of the crystals of the salts of each crop is >99%; see Section 7.5.4 of Chapter Seven for details. ^b An impurity was isolated on the filter paper, which weighed: 1.01 g, 1.67 g, 0.48 g, 1.68 g, respectively for entries 1 to 4. ^c The overall yields. ^d **105** was obtained by the new method; see entry 6, Table 5.2. ^e A mixture of the salts was obtained (5.05 g, 19%, 0%de).

All EtOH was removed from the mother liquor and then residue was boiled

with 2 L 2-propanol, to which acetone was added slowly until all solids dissolved (ca. 500 mL). The solution was cooled until spontaneous crystallization set in. Crystals (26.1 g, 87%, entry 1 of the 1st crop of salt-2, Table 5.6) was harvested and ¹H-NMR spectrum proved it was pure salt-2. The solvents from the mother liquor were removed and this process was repeated on the residue with small modifications (see: Section 7.5.4 of Chapter Seven) until all salts were collected (usually 3 crops for each salt, Table 5.6). This process was virtually infallibly and reliably produced diastereomerically pure salt-1 and 2 in good overall yields.

5.8.3 Summary

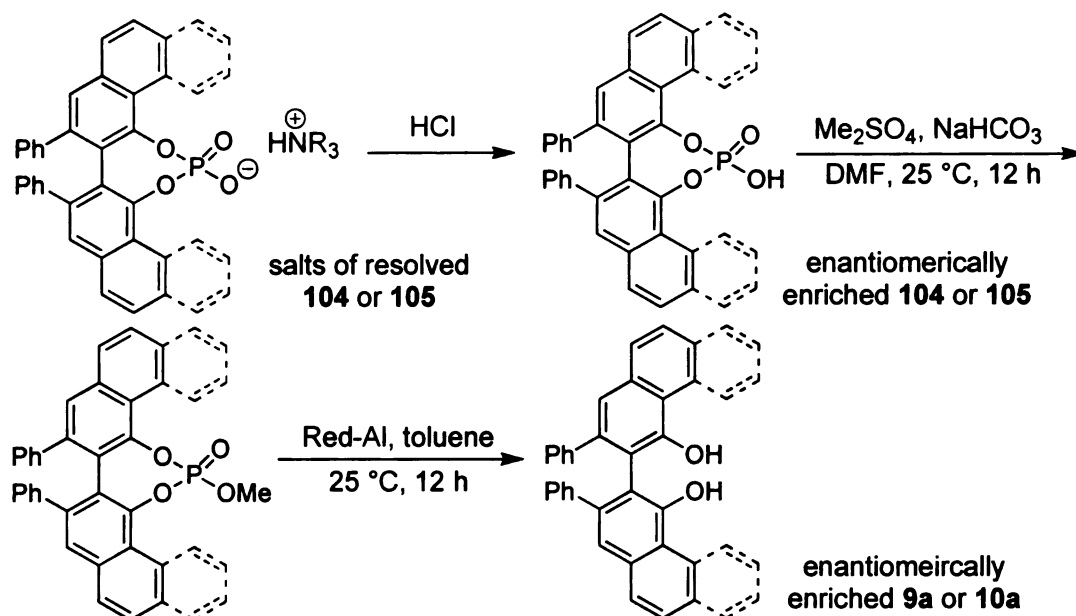
Early work on the resolution of VAPOL in EtOH produced protocols that suffered from low efficiency.^{17b} Incorporation of 2-propanol and acetone as the solvent for crystallization of salt-2 remarkably improved the efficacy, and the outcome of the resolution was a big step forward. Apart from the high yield and diastereomeric excess, this procedure was particularly practical to scale up in a reproducible manner. These methods to produce both optically pure salts in the resolution step paved the way for the final access to enantiopure VANOL and VAPOL ligands. Thus, the next challenge to address is the search for an effective way to decompose these salts to liberate the optically active ligands.

5.9 Liberation of the optically enriched VANOL and VAPOL from the salts

With sufficient quantities of the diastereomerically pure salts in hand, attention was turned to their cleavage to release the optically pure VANOL and VAPOL ligands. In the published method,^{17b} the optically enriched salts were first decomposed by strong acid (HCl) to give the phosphoric acids, which was

subsequently converted to their methyl esters. These esters were then reduced by Red-Al (Vitrade®, Scheme 5.2) to produce the enantiomerically enriched VANOL / VAPOL ligands.

Scheme 5.2 Published procedure to liberate **9a** / **10a** from the resolved salts^{17b}



While successful, the reductive cleavage of the O-P bonds to unmask the hydroxyl groups of the ligands was not optimized in terms of mildness of conditions and the efficiency of the overall process. Moreover, because the phosphoric esters were harvested from aqueous medium, they had to be thoroughly dried prior reductive cleavage; otherwise, a violent reaction of Red-Al with residual water would ensue.

To circumvent these problems, we began investigating the optimization of direct cleavage of the optically enriched salts without prior liberation of the phosphoric acids. In unpublished work, this direct reduction of the salts with Red-Al had been shown to be feasible by Dr Gang Hu and Dr Chunrui Wu. Performing this conversion in a one-pot process was very tempting for obvious

reasons, as this would eliminate the need for functional group manipulations and the accompanying yield penalty.

5.9.1 Reductive cleavage of optically pure salts of VANOL and VAPOL

The key issue of directly conducting reductive cracking of the salts was deemed to be conditions control to release the safety constraints. Hence, the reaction was performed at 0 °C. The rate of Red-Al addition could also be used to modulate the rate of the reaction. Therefore, the rate of addition was kept low in order to control the temperature and H₂ evolution. This turned out to work fine on small scale, albeit in low yields (entries 1 & 2, Table 5.7). The low yields on small scale were found to be due to the fact that an old bottle of Red-Al was used. Fortunately, the yields could be recovered by using a newer sample of Red-Al. Large-scale cleavages were also performed and proved to be equally workable and reliable in generating VANOL in good yields (Table 5.7, entries 3 to 8).

Table 5.7 Reductive liberation of optically enriched VANOL from the salts of **104**

Salt-I or Salt-II

1) Red-Al, 3.5 eq toluene (0.2 M)
0 to 25 °C, 12 h
2) 6 N HCl, 0 °C

S-9a (from Salt-I)
R-9a (from Salt-II)

Entry	Salts (g)	Toluene ^a (mL)	VANOL (9a)	
			Yield ^b (%)	% ee
1	8.7	50	34.8 ^c (29.6)	> 99 (S)
2	7.4	50	50.0 ^c (36.2)	93.8 (R)
3	84.0	500	97.1 (80.0)	98.1 (S)
4	23.8	125	60.1 (46.9)	> 99 (R)
5	52.7	250	88.0 (45.4)	> 99 (R)
6	25.6	125	85.5 (71.0)	> 99 (R)
7	25.3	150	81.6 (67.7)	> 99 (S)
8	20.4	100	89.6 (59.7)	> 99 (R)

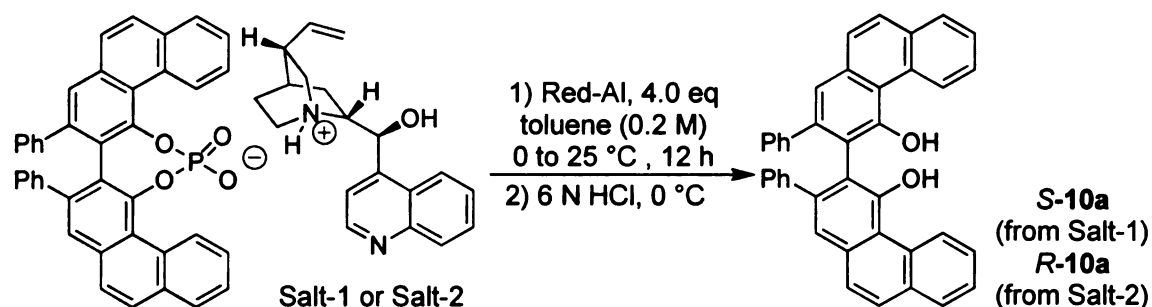
^a Reagent grade toluene was used. For details, see Section 7.5.5.1 of Chapter Seven for details.

^b The yields in parentheses are from racemic **9a** over three steps. ^c Old bottle of Red-Al (not titrated) was used.

The same method was extended to the liberation of VAPOL as well, and excellent yields of both enantiomers were isolated after reduction using Red-Al (Table 5.8).

The major drawback of above procedure arises from Red-Al, which is not a reagent with a long shelf life. Had this procedure been the subject of continued development, further work would have focused on finding more stable reducing agents.

Table 5.8 Reductive liberation of optically enriched VAPOL from the salts of **105**



Entry	Salts ^a (g)	Toluene ^b (mL)	VAPOL (10a)	
			Yield ^c (%)	% ee
1	29.9	165	57.7 (51.5)	97.7 (S)
2	31.3	165	88.1 (82.3)	> 99 (R)
3	32.2	180	96.0 (82.6)	> 99 (S)
4	35.6	200	96.2 (91.5)	> 99 (R)
5	36.3	200	90.8 (86.1)	> 99 (S)
6	38.5	210	90.3 (89.8)	> 99 (R)

^a Combination of the 3 crops of the entries 1 to 3 of Table 5.6. See Section 7.5.5.2 of Chapter Seven for details. ^b Reagent grade. ^c The yields in parentheses are from racemic **9a** over 3 steps.

5.9.2 Methods for the purification of non-racemic enantiomeric mixtures

Even successful resolutions sometimes yield enantiomerically impure

products; therefore it is important to find methods for the purification of the primary product of a resolution. Fortunately, non-racemic mixtures of most enantiomers can be purified by recrystallization,¹⁵⁰ and the enhancement of the optical purity of both VANOL and VAPOL by crystallization is described herein.

1) Purification of S-VANOL

To a sample of optically impure S-VANOL (30.0 g, 68.4 mmol, 96% ee) was slowly added CH₂Cl₂ until all solid dissolved. To this solution was added 3 L hexanes (volume not optimized), which was slowly concentrated on rotary evaporator until small amount of solvent was (ca. 500 mL) left. This mixture was flushed with N₂ and allowed to stand overnight before the light yellow solid was filtered, which was enantiopure S-VANOL (28.3 g, 64.5 mmol, >99% ee). The ee of the S-VANOL ligand (0.85 g, 1.94 mmol) in the mother liquor was 35% ee.

In contrast to CH₂Cl₂/ hexanes,^{144c} when ethyl acetate/ hexanes is used to crystallize optically impure S-VANOL,^{18e} enantiopure S-VANOL will be enriched in the mother liquor by precipitation of racemate. The procedure is as follows: To a 2 L round bottom flask was added S-VANOL (40 g, 91.2 mmol, 98% ee). Ethyl acetate from washing bottle was carefully added and the flask was swirled until the solid dissolved. Hexane (1.5 L) was added and the flask was manually shaken for two minutes. A white solid appeared and it was then cooled to -20 °C overnight. The solid (30.0 g, 68.4 mmol, 96% ee) was filtered off, and the ee of the S-VANOL ligand in the yellow mother liquor was found to be >99% ee by HPLC. It was concentrated *in vacuo* to afford 10.0 g (22.8 mmol) S-VANOL as a light yellow foam-like solid with >99% ee.

It should be noted that the optically pure VANOL ligand obtained directly after removal of the solvent is an amorphous solid and is vulnerable to oxidative decomposition over time. To address this problem, the amorphous solid is dissolved in CH_2Cl_2 (3 mL/g), to which hexanes (30 mL/g) is added. Upon swirling this homogeneous solution manually under a nitrogen flow, crystals form within a few minutes (ca. 10 to 15 min). Slow removal of the solvent in *vacuo* results in a more stable crystalline material that is stable under argon in a refrigerator. In general, this procedure is necessary, particularly for VANOL, and provides increased stability toward storage.

2) Purification of S-VAPOL

Racemic VAPOL has extremely low solubility in most solvent systems. Therefore, it can be preferentially precipitated from enantiomerically impure solutions. Optical enrichment of S-VAPOL from a non-racemic mixture is accomplished as follows: a sample (10.4 g, 97.7% ee) is combined with 75 mL CH_2Cl_2 and the mixture is stirred under argon for about 5 min. The solid (0.53 g, 53% ee) is isolated by filtration and enantiopure S-VAPOL (9.0 g, > 99% ee, 86.5% recovery) can be afforded as fine crystals from the filtrate after slow removal of the solvent in *vacuo*. Like most phenols, enantiomerically pure VAPOL is somewhat air sensitive and should be stored under an inert atmosphere.

5.10 Concluding remarks

Recent years have witnessed an explosion of interest in the development of resolution protocols for the separation of the enantiomers of chiral compound.¹⁴⁹

As a result of these endeavors, a substantial amount of work has been published that offer practically useful levels of stereoselectivity in resolutions. Prompted and assisted by the accumulation of knowledge in this area, the VANOL and VAPOL ligands were successfully and efficiently resolved.

The continuous search for the optimal conditions for the resolution is primarily driven by the idea that it is most advantageous to bring VANOL and VAPOL to complete optical purity *via* their diastereomeric salts of their phosphoric acid derivatives with chiral amines rather than late-stage ee upgrade of the free ligands. Quickly achieving good yields of the both (*R*)- and (*S*)-VANOL and VAPOL ligands in enantiomerically pure form from the racemate reflects the practical consequence of an effective resolution. With these new conditions established, the resolution of these ligands would be more competitive with other methods (such as desymmetrization strategy^{142, 18e, 144d}).

CHAPTER SIX

STRUCTUALLY MODIFIED VANOL AND VAPOL: DESIGN AND SYNTHESIS

In a given organic reaction, the substrates encompass an enormous molecular diversity and therefore demand similar diversity in the structures of catalysts to effect their transformations. Thus, the need for structurally diverse catalysts would appear endless. In this regard, access to catalysts with a broad scope remains highly desired but in reality are limited in numbers.⁷ Moreover, existing catalysts provide powerful nexus for defining future structural modifications for continued optimization because their preparations and diversification elements have already been well investigated.

On the other hand, catalysts specifically designed for a given class of reactants usually have optimum potency and selectivity for recognition of the substrate. For these reasons, methods allowing facile access to these catalysts with high efficiency are desirable for maintaining successful synthetic programs.

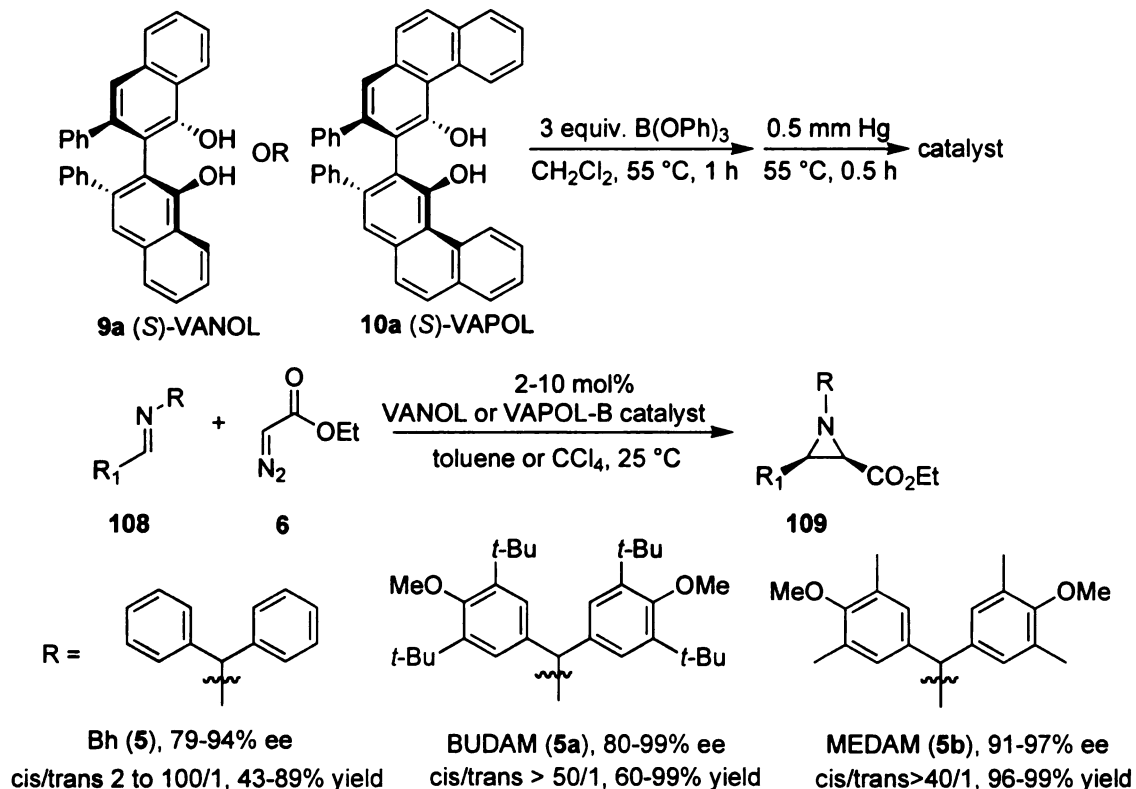
Although ligandless catalysts are also known,¹⁵⁰ it is widely accepted that the ancillary ligation to the metal center plays a crucial role in dictating the efficiency of a catalytic system. Generally speaking, the major role of ligands in a catalyst for asymmetric organic synthesis is that they not only tune the electronics of the active site, but also define the chiral environment of the catalyst. Consequently, a flexible collection of structurally related ligands offers the maximum possibilities to find the best platform for transforming a given substrate. These considerations ensure significant impetus to diversify the VANOL and VAPOL ligands by backbone revisions, which is vital for the tuning of their properties for reaching

the optimum performance for a given transformation.^{19b,144}

6.1 Introduction

Properly *N*-protected imines will bind to catalysts generated from either VANOL or VAPOL ligand and B(OPh)₃ and then upon reaction with ethyl diazoacetate are converted into aziridines; this process is called the Wulff aziridination reaction (Scheme 6.1).^{12,18} Consequently, two contiguous stereogenic centers are simultaneously formed in a highly strained 3-membered heterocycle in a highly efficient manner, both in terms of yield and enantioselectivity. From a historical standpoint, such spectacular reactions were deemed only possible with enzymes, and chemists could once only envy such an exquisite level of molecular manipulation.

Scheme 6.1 Aziridination reactions using VANOL/VAPOL as ligands^{12,18}



Parallel to the work of optimization of the imines, the search for a follow-up optimized ligand based on the VANOL structural platform aims at improvement of efficacy and universality. Practically, the yield of the aziridination reaction is limited by both the efficiency of the reaction and the efficiency of product separation. Thus, the efforts directed to identifying optimal conditions for this reaction mainly focus on two aspects: 1) methods to facilitate the isolation of the product, and 2) the hunt for successively better and better ligands to improve the selectivity and the yield with the ultimate goal to find the “best-in-class” catalyst.

6.1.1 Reasons for synthesis of derivatives VANOL and VAPOL

Traditionally, the ligand (VANOL or VAPOL) used for the asymmetric aziridination reaction is released from the catalyst upon workup, and removal of the ligand from the products post-reaction is achieved by means of chromatography.^{12,18} While practically feasible, it does require careful control even for routine separations owing to the close mobility of the product and the ligand on silica gel. The popularity of immobilized ligands¹⁵¹ suggests an obvious answer to this separation problem: having the catalyst and the product in different phases. This idea is operationally attractive, and therefore it constitutes the first part of this chapter.

One of the beauties of the aziridination reaction is the existence of a relatively high degree of mechanistic understanding, which is a result of the Wulff's group continuous investigations.^{18,144} This understanding enables reasonable explanations for the observed outcomes. More importantly, it provides an ideal platform to rationally design a specific ligand for a particular situation. In addition,

this design is aided by the crystallization and X-ray diffraction analyses of the chemzyme-substrate complexes.^{144f} These crystal structures also confirm the commutative properties between the catalyst and the substrates previously proposed solely on the basis of their enantioselective outcomes.^{18f}

In this regard, further optimization of the aziridination reaction would require various analogues of VANOL and VAPOL ligands to evaluate structural features that contribute to the selectivities. These needs, coupled with the limited availability of such derivatives from synthetic sources, motivated us to devise synthetic approaches to VANOL and VAPOL and this will constitute the second part of this chapter.

6.1.2 Methods to derivatize the VANOL and VAPOL ligands

There are three general approaches to the modification of the VANOL and VAPOL ligands: (a) by the synthesis of a substituted monomer prior to the oxidative coupling to give a substituted ligand;^{18c,f,19b} (b) by replacing a hydrogen atom(s) in one of the rings of a pre-existing ligand with different functional groups through aromatic substitution reactions;^{144a} or (c) by replacement of the oxygen ligating groups with other heteroatoms either before or after the ligand is synthesized.¹⁵²

While method (b) is strategically more favored, adoption of path (a) allows for bypassing the hurdles and limitations associated with aromatic substitution (electrophilic or nucleophilic) reactions. Therefore, in the following sections of this chapter, the preparation of derivatives of VANOL and VAPOL will always start with approach (a) that is also known as '*de novo*' synthesis.

6.2 Approaches to the preparation of immobilized VANOL and VAPOL ligands

Continuous demand for practical and facile synthetic methods has evoked a constant interest in developing polymer-bound catalysts.¹⁵¹ This is because immobilized reagents offer a number of advantages over conventional solution-phase chemistry. Ideally, they can be separated and recovered from the reaction mixture by simple filtration thereby avoiding product contamination. As a result, they can be recycled which increases their commercial value. Therefore, a solid-supported catalyst is perfectly suitable for our purpose in facilitating product purification in the aziridination reaction.

6.2.1 Introduction

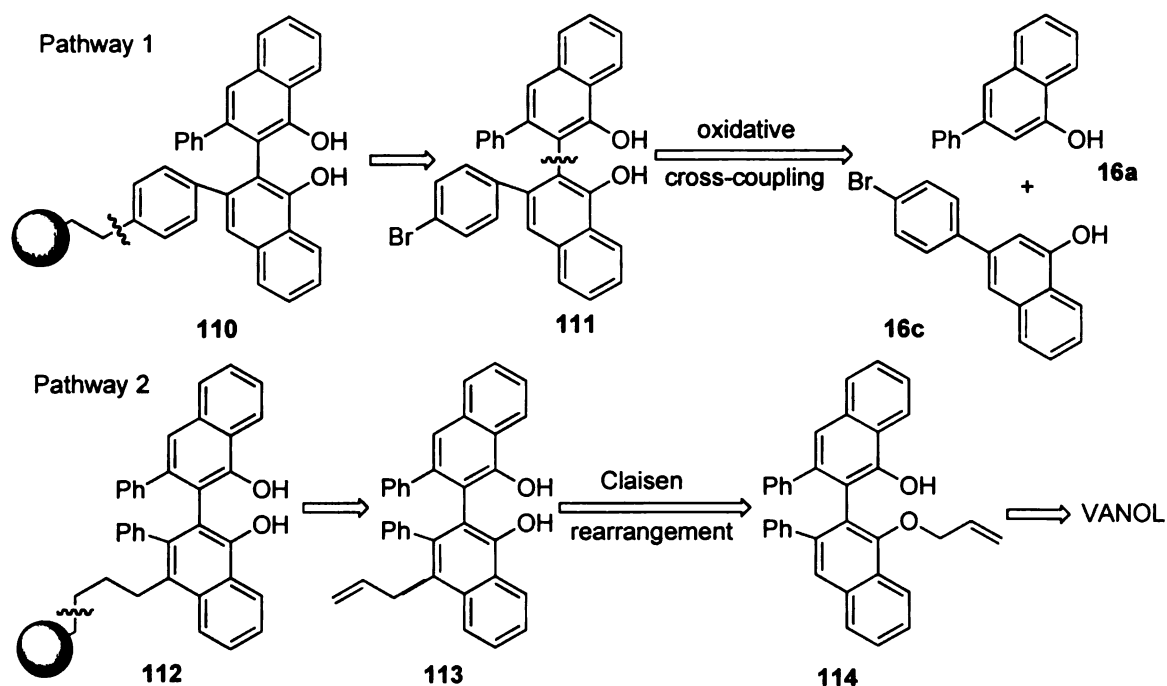
In order to maintain the maximum activity and selectivity of the free catalyst, certain key design criteria for immobilized VANOL ligand have to be met. First, the local molecular structure of the active centers (around the two oxygen ligating atoms) should mimic precisely the structure of the catalyst prepared from the free VANOL ligand. This argument requires that the linker should be as far as possible from the active center to avoid interruption of the catalytic process. In addition, the degree to which it perturbs the electronic properties of the ligand should be minimized.

Second, VANOL should be attached to the support through a single flexible linkage to minimize any conformation change in the catalyst. The introduction of a single linker breaks the C_2 -axis of the ligand. As a result, it induces certain synthetic challenges. Third and lastly, the attachment of VANOL ligand to the

support should be achieved in a reasonably facile manner. This is because enantiomerically pure VANOL should be attachable to the resin under mild conditions in order to limit the possibility of racemization,^{17b} leading to a loss of asymmetric induction during the course of a reaction.

Polymer-supported VANOL and VAPOL can be prepared in a variety of ways (Scheme 6.2). From the chemistry point of view, however, attachments either on the 3-phenyl group (pathway 1) or at the 4-position (pathway 2) of the naphthalene ring are the methods of choice, both having their potential merits. The advantage of connecting at the 3-phenyl group is that the immobilization is far from the active center, therefore minimizing adverse effects on moving from homogeneous to heterogeneous catalysis. In contrast to ligand **110**, ligand **112** should be much easier to access by direct substitution at the 4-position of the naphthalene ring of VANOL.

Scheme 6.2 Pathways to prepare solid-supported VANOL ligands



As for the polymer support, the styrene-based polymers are suitable for our purpose.¹⁵¹ Being hydrocarbon like, these polymers are compatible with organic solvents and typical organic reagents. Because they are abundantly used, the type and the degree of cross-linking has been extensively studied. Finally, apart from being inexpensive, the polymers are not degraded by most chemical reagents under ordinary conditions and can withstand the chemical treatment and physical handling required in sequential synthesis.

6.2.2 Preparation of immobilized VANOL via oxidative cross-coupling reaction

To minimize risk of failure, the decision was made at outset to link the VANOL ligand to the resin at the 3-phenyl group. This idea led to the advanced intermediate **111** (Scheme 6.2) with a halide group on the 3-phenyl substituent, which would be used to create a covalent attachment to the resin in the proceeding steps. Since methods to selectively functionalize such an inactivated phenyl ring in VANOL would appear to be quite limited,¹⁵³ it was deemed to wise to prepare **111** via an oxidative cross-coupling reaction of the modified VANOL monomer **16c** with the unsubstituted monomer **16a** (Scheme 6.2).

The most efficient synthesis of the VANOL monomer **16a** involves the conversion of 4-chloro-1-naphthol (**42**) to 3-phenyl-1-naphthol (**16a**, Table 2.20, Chapter Two) in benzene in the presence of AlCl_3 . It was reported¹⁵⁴ that substituted benzenes (e.g. chlorobenzene) behave similarly in the presence of AlBr_3 , and 3-(4-chlorophenyl)-1-naphthol was obtained by reacting **42** with PhCl (Entry 1, Table 6.1), and toluene condenses readily with **42** to form 3-(4-tolyl)-1-

naphthol. Thus, spurred on by this accomplishment, the point of departure entailed the condensation reaction of **42** with bromobenzene in the presence of AlBr_3 as Lewis acid (Entry 3, Table 6.1). Ideally, this would result in the desired modified VANOL monomer **16c**, which could be subsequently coupled with **16a** to generate the precursor for solid supported ligand.

In contrast to the reported results¹⁵⁴ where **42** condensed smoothly with chlorobenzene to yield **16m**, an attempt to condense **42** with PhCl produced a complex mixture (entry 2, Table 6.1), from which it failed to isolate pure **16m**. Although a venetian red coloration of the solution of this mixture might indicate the presence of an arenium cation **48** (see below and also Scheme 2.31), the reaction of the cation appeared to give a mixture with **16m** as the major product based on crude $^1\text{H-NMR}$ analysis.

Table 6.1 Attempted preparation of VANOL monomer derivatives from **42**

Oc1ccc(Cl)cc2ccccc12 (42, 0.25 M) $\xrightarrow[3 \text{ eq AlBr}_3, 25^\circ\text{C}]{\text{PhX (solvent)}}$ Oc1ccc(cc2ccccc12)-c3ccc(X)cc3 (16c, 16m or 16n)

Entry	42 (g)	X	Time ^a (h)	Product	Results ^b
1	0.50	Cl	3.5	16m	87% ¹⁵⁴
2	0.50	Cl	8	16m	Mixture ^d
3	0.51	Br	8	16c	Mixture ^c
4	0.54	OCH_3	72	16n	nd ^e
5 ^f	3.24	Br	1h	16c	Mixture ^g

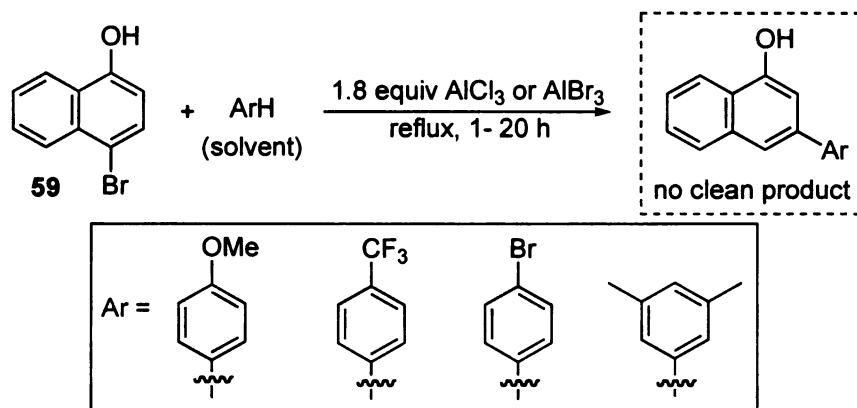
^a Not optimized; for experimental details, see Section 7.6.1.1 of Chapter Seven. ^b Obtained after workup and attempted isolation. ^c After column chromatography on silica gel (hexanes: ethyl acetate = 10:1) and crystallization from hexanes/ CH_2Cl_2 . ^d After column chromatography (hexanes: ethyl acetate: CH_2Cl_2 = 20:1:2) and crystallization from $\text{CH}_3\text{CO}_2\text{H}$. ^e nd = no reaction

detected; starting material was recovered.^f AlCl_3 was used, and the mixture was heated to 90 °C (oil bath temperature) for 1 h.^g After column chromatography (hexanes: ethyl acetate: CH_2Cl_2 = 20:1:2) and crystallization from toluene.

In order to investigate the scope of the condensation reaction, several substituted benzenes (PhX, Table 6.1) were tested. The reactions attempted by using solvents other than benzene always gave mixtures of products as indicated by TLC and ^1H -NMR analyses. All efforts to isolate and purify the products from this reaction (silica gel columns and crystallizations, sublimations) ended with unidentifiable mixtures. One should keep in mind that solvent PhX is also a reactant, which would nucleophilically attack the intermediary arenium ion **48**. An attempt aiming at decreasing the Lewis acidity by using AlCl_3 instead of AlBr_3 (entry 5, Table 6.1) was also unsuccessful.

In addition, similar results were also reported by Dr Zhenjie Lu,^{18f} when she examined the related reaction of 4-bromo-1-naphthol (**59**, Scheme 6.3) with substituted benzene. No products were detected; either the starting material was recovered or complex mixtures were observed.

Scheme 6.3 Attempted preparation of VANOL derivatives from naphthol **59**

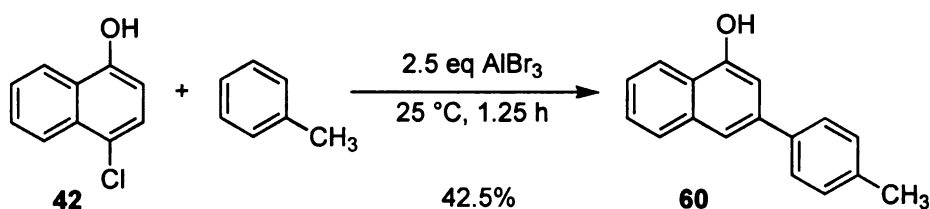


In view of the high electrophilic nature of AlBr_3 , successful condensations

might depend on the delicate balance between the coordinating ability of PhX with AlBr_3 and the nucleophilicity towards carbocation **48**. Thus, substrates (PhX) with electron-withdrawing groups may simply inhibit the reaction, while substrates bearing electron-releasing moieties having heteroatoms may not react because of coordination with AlBr_3 . This results in electron density loss on PhX. These effects dramatically destabilize intermediate **48a** in the alkylation step of the condensation reaction (Scheme 2.30) and thereby prevent the key C-C bond forming reaction.

These observations highlight the unique property of toluene as a nucleophile in this transformation, which is an electron-neutral yet a non-coordinating nucleophile. Thus, compound **42** was smoothly consumed in toluene with 2.2 equiv of AlBr_3 at ambient temperature (Scheme 6.4; for experimental details, see Section 7.6.1.5 of Chapter Seven). The corresponding product was detected, isolated and later confirmed to be the desired 3-(4-tolyl)-1-naphthol **60**. This is in agreement with the prediction made in Chapter two that a narrow window for the condensation reaction of **42** with PhX exists.

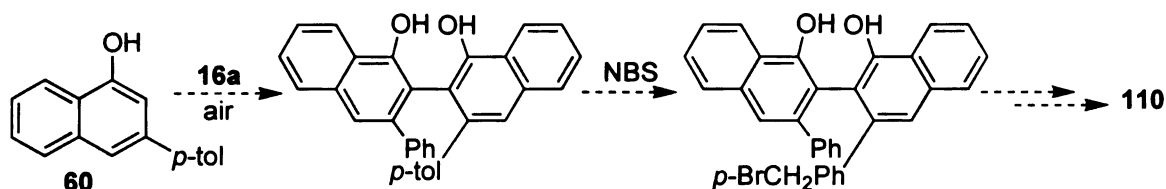
Scheme 6.4 Synthesis of **60** using toluene as alkylation agent



As a common solvent, toluene is capable of delivering the structurally modified VANOL monomer **60**, which at last represents a possible approach to immobilized VANOL ligands since it should be possible to functionalize the

benzylic methyl group (Scheme 6.5).

Scheme 6.5 Proposed pathway to prepare polymer-bound VANOL **110** from **60**



While the methyl group in naphthol **60** could ultimately serve as an anchor point for a linker, the attractiveness of introducing a more directly functionalizable anchor prompted a more thorough investigation of an introducing a p-bromophenyl group in the construction of 4-bromo-1-naphthol with bromobenzene (Scheme 6.3) and these results are shown in Table 6.2. Unfortunately no conditions were found that led cleanly to **16c**.

At this point, it was painfully clear that this approach was not going to viable, and thus attention was directed toward finding a different approach, in which various functional groups could be tolerated. Thus, the Wulff-Dötz benzannulation reaction was investigated as a method to access **16c**.

Table 6.2 Attempted preparation of **16c** from **59** with expanded conditions

Entry	59 (g)	Conditions ^a	Results
1	0.66	25 °C, 3.5 h	Mixture ^b
2	0.81	80 °C, 1 h	Tar ^c
3	0.68	-20 to 25 °C, 3.5 h	Tar ^c
4	0.60	-20 to reflux, 2.5 h	Tar ^c
5	0.60	-20 to 60 °C, 3 h ^d	Mixture ^b
6	0.60	-20 to 25 °C, 24 h ^{d,e}	Mixture ^b

^a PhBr was washed in turn with H₂SO₄, H₂O and aq. NaHCO₃. It was dried over MgSO₄ and

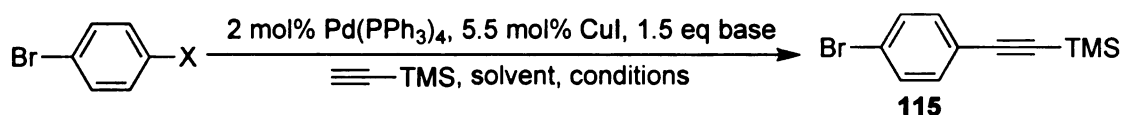
distilled from CaH_2 . AlBr_3 was from a newly opened bottle. For experimental details, see Section 7.6.1.1 of Chapter Seven. ^b After column chromatography on silica gel (hexanes: ethyl acetate: DCM = 20: 1: 2). ^c Workup was not performed. ^d AlCl_3 was used. ^e PhI was used in stead of PhBr.

6.2.3 Preparation of **16c** with benzannulation reaction

Although the condensation of **59** with bromobenzene failed to generate **16c**, from a chemistry perspective, **16c** is still a promising synthon for further development toward a solid-supported VANOL ligand. This is because the halogenated arenes are popular substrate for subsequent manipulations *via* cross coupling reactions.¹³⁸ Hence, a slightly more circuitous route, namely the Wulff-Dötz benzannulation reaction, was developed to avoid subjecting any of the intermediates to electrophilic condensation conditions (For experimental details, see Section 7.6.1.2 of Chapter Seven).

The synthesis started with the generation of the key alkyne intermediate **63b**, the preparation of which was achieved *via* the Sonogashira reaction.¹⁵⁵ To compensate for the higher cost of this strategy, *p*- $\text{BrC}_6\text{H}_4\text{Br}$ was used instead of *p*- $\text{IC}_6\text{H}_4\text{Br}$ in favor of its ready availability and low price (Table 6.3). Only a trace amount of **115** was detected in neat *i*- Pr_2NEt (entry 1), and in THF the coupling reaction gave **115** in moderate yields (entry 2), which could not be enhanced by slow addition of TMS-acetylene (entry 3).

Given the low yields with 1,4-dibromobenzene ($\text{X}=\text{Br}$, Table 6.3), it was decided to turn to 4-iodobromobenzene ($\text{X}=\text{I}$, Table 6.3) to effect the cross coupling. The advantage of the greater reactivity of 4- $\text{IC}_6\text{H}_4\text{Br}$ was evident in the cross coupling reactions, where the product was uniformly obtained in much higher yields (entries 4 to 6, Table 6.3).

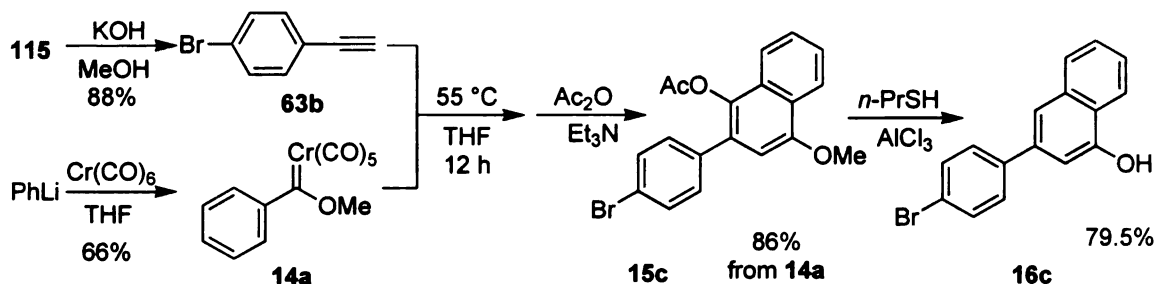
Table 6.3 Synthesis of **115** by Sonogashira reaction

Entry	X	Base	Solvent	Conditions ^a	Yield (%)
1	Br	<i>i</i> -Pr ₂ NEt	<i>i</i> -Pr ₂ NEt ^b	25 °C, 12 h	Trace ^c
2	Br	<i>i</i> -Pr ₂ NEt	THF	25 °C, 12 h	41.0
3	Br	<i>i</i> -Pr ₂ NEt	THF	12 h, 25 °C ^d	32.2
4	I	Et ₃ N	THF	25 °C, 12 h	99.0
5	I	Et ₃ N	THF	0 °C, 30 min; 25 °C, 36 h	95.7
6	I	Et ₃ N	THF	0 °C, 30 min; 25 °C, 24 h	98.4

^a For experimental details, see Section 7.6.1.2 of Chapter Seven. ^b *i*-Pr₂NEt was used as solvent.

^c Detected by ¹H- and ¹³C-NMR spectroscopy. ^d TMS-acetylene was added slowly over 12 h.

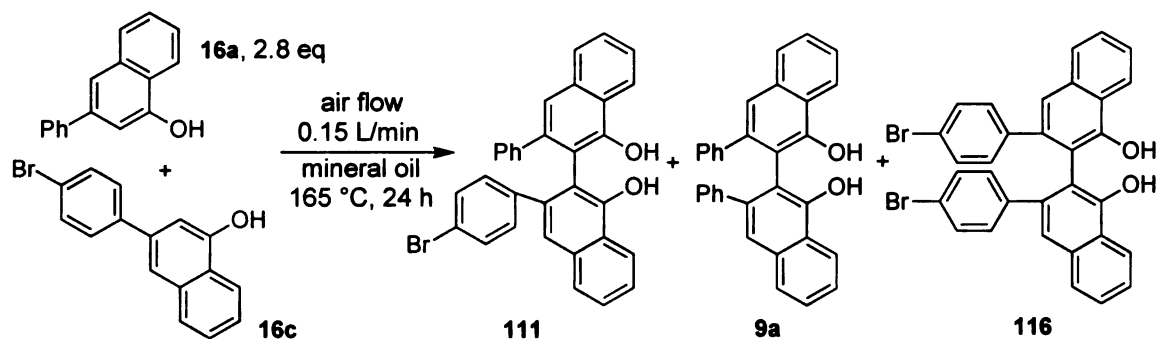
With alkyne **115** in hand, the methods employed to finish the synthesis were straightforward and as illustrated in Scheme 6.6 expediently provide naphthol **16c** in sufficient amounts for subsequent experiments (3.0 g of **16c** from 3.7 g **63b**).

Scheme 6.6 Preparation of **16c** by Wulff-Dötz benzannulation reaction

With the monomer **16c** in hand, the development of strategies for forging the biaryl linkage in **111** (Scheme 6.7; for experimental details, see Section 7.6.1.3 of Chapter Seven) could now be addressed. The procedure that had been developed for the oxidative coupling of phenol **16a** (Chapter four) was then attempted in a cross coupling of **16a** and **16c**. This reaction can of course also produce the homo-coupled products **9a** and **116** indicated in Scheme 6.7. One method to bias the

outcome is to dilute the more precious monomer **16c** with excess **16a**. Success in this approach may depend on the succeeding isolation step. It can be foreseen that the three products may have very similar properties. As a result, achieving efficient separation may be simultaneously the most daunting challenge in the synthesis of **111**.

Scheme 6.7 Oxidative cross-coupling reaction of **16a** with **16c** to prepare **111**

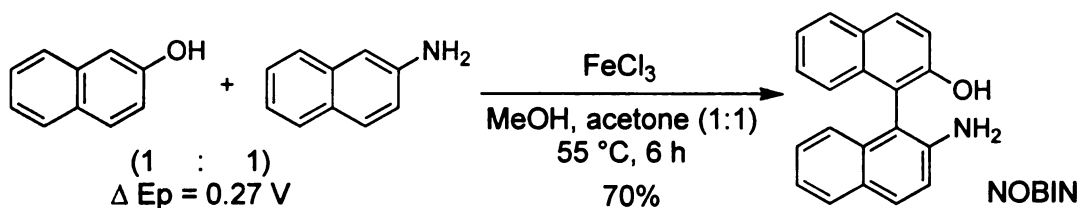


Not surprisingly, complete consumption of both substrates was attained upon exposure of a 2.8:1 mixture of **16a** to **16c** to the standard oxidative coupling conditions (see: Table 4.3). Only a single spot could be observed on the TLC plate even though theoretically at least three compounds were present. Attempts to separate this reaction mixture using crystallization, column chromatography on silica gel and preparative TLC all failed, which posed a tremendous concern for the analysis of the reaction outcome. A plausible solution to this problem is to attach a long-chain functionalized carbon linker in place of the bromine in **16c** with the hope that the three different coupling products would have different mobility on silica gel. However, this approach remains to be explored in future work in this area.

It was evident that a method for facilitating the reaction of **16a** and **16c** in a selective manner would be of immense benefit. Indeed, examples of simple,

highly selective oxidative cross-coupling of aromatic compounds have been known for over 15 years exemplified by the practical synthesis of NOBIN using 2-naphthol and 2-aminonaphthalene with FeCl_3 in water by Ding (Scheme 6.8).^{156a} The high efficiency of this reaction can be explained by a sufficient difference of the redox potentials of the two coupling partners (i.e., if $\Delta E_p \geq 0.25 \text{ V}$).^{156b} Active intermediate generated by preferential oxidation of one of the partners is captured by another partner with higher redox potential, and the reaction proceeds when this condition is met. Otherwise, mixtures would form when the redox potentials of the individual partners are similar. With this in mind, it may be possible that VANOL monomers with appropriately different redox potentials may lead to the selective construction of substituted VANOL ligand that could be useful for preparing solid supported ligands.

Scheme 6.8 Preparation of NOBIN via oxidative cross-coupling reaction

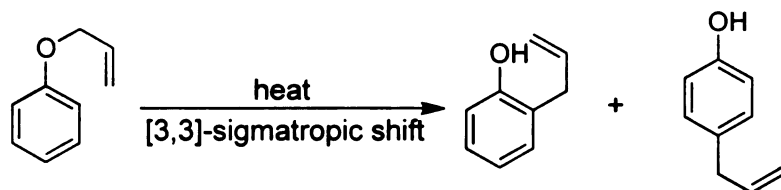


6.2.4 A modular approach to the synthesis of immobilized VANOL ligands

The above-described methodology to construct the unsymmetrical brominated VANOL derivative **111** is straightforward. However, the major weakness is the requirement to incorporate a non-selective coupling step into the synthesis, which in turn is complicated by a very difficult separation. Other potential routes starting from VANOL were then examined which rely on modifications of unsubstituted VANOL since effective methods for the syntheses of VANOL have already been established. The appealing feature of the strategy

outlined in pathway 2 in Scheme 6.7 is that it allows for a simple method to introduce various functionalities on optically pure VANOL, thereby opening avenues to expeditious preparation and screening. For this purpose, the [3,3]-sigmatropic rearrangement reaction (Scheme 6.9)^{72b} is particularly attractive.

Scheme 6.9 Claisen rearrangement of allyl phenyl ether

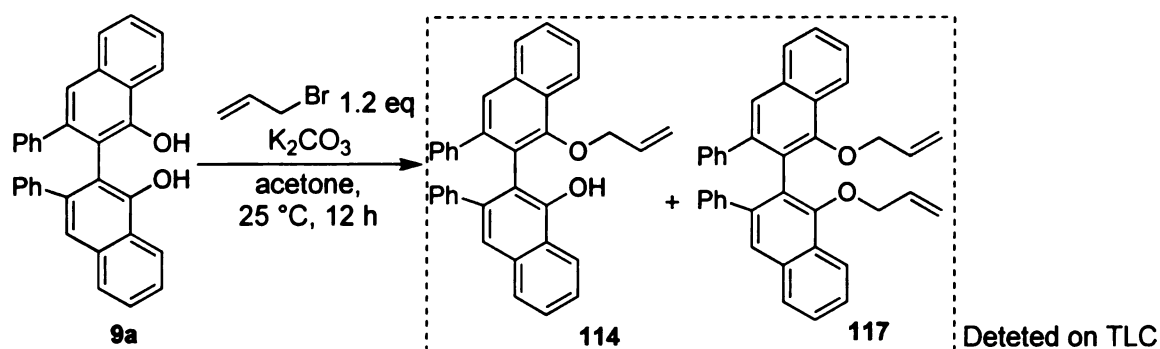


At elevated temperatures, allyl aryl ethers can undergo an intriguing reaction where the olefinic appendage is transposed onto either the *ortho*- or *para*-positions of the aromatic ring. Mechanistically, this transformation is normally referred to as the Claisen rearrangement.^{72b} Regarding the Claisen rearrangement of VANOL allyl ether, the only accessible positions are the *para*-carbons since both *ortho*- positions are blocked.^{72b} Thus, this methodology has promise for the specific generation of 4-alkylated VANOL precursor and an elegant direct entry to solid-supported VANOL ligands.

A challenge in this strategy is to selectively mono-alkylate one of the two identical phenolic hydroxyl groups in VANOL, as attachment of VANOL to polymer through a single linker is preferred. During the course of a study on the direct lithiation of VANOL, it was found that a singly methylated VANOL was predominately formed when treated with CH₃I in the presence of K₂CO₃ in acetone (see Section 6.4.2).¹⁶⁷ The mono-alkylation of VANOL with allylbromide under the same conditions was then examined (Scheme 6.10; for experimental details, see Section 7.6.1.4 of Chapter Seven). As expected, the reaction gave

rise to two different products; however, attemptive isolation by silica gel column chromatography led to decomposition, which seemingly resulted from their vulnerability to the acidic media. Although the apparent instability of the allyl ethers **114** and **117**, the significant potential application to the synthesis of solid-supported VANOL may make further investigation of this approach worthwhile.

Scheme 6.10 Attempted synthesis of mono-allylated VANOL (**114**) using K_2CO_3



6.2.5 Summary

In an attempt to avoid the necessity of separating the products from the ligands in the aziridination reaction, we recognized that solid-supported VANOL ligands hold promise for solving this problem.

Two different methods were attempted to prepare the advanced precursors (**111** and **113**, Scheme 6.2) for incorporation into polymer-bound VANOL. After evaluating these routes, it is clear that the modular synthesis using the Claisen rearrangement is the most promising as a scalable process. From the preliminary results, one can see that the appealing features are: 1) the ready availability of the starting materials, and 2) the establishment of a selective single-alkylation protocol. Even though solid supported VANOL has not yet been prepared and evaluated, the need to do so will become increasingly important with the ever-increasing drive to develop more environmentally benign and economically

proficient synthetic methods. The development of polymer-bounded VANOL will greatly simplify the workup and increase the attractiveness of catalytic processes with VANOL.

6.3 *De novo* synthesis of the VANOL derivatives

The second way to improve the aziridination reaction is to optimize the reaction itself. Previous work on the structure of the catalyst and on the mechanistic aspects of how the catalyst activates this reaction has generated important information. This information can be used to guide synthetic modifications of the catalyst, leading to improved catalyst performance.

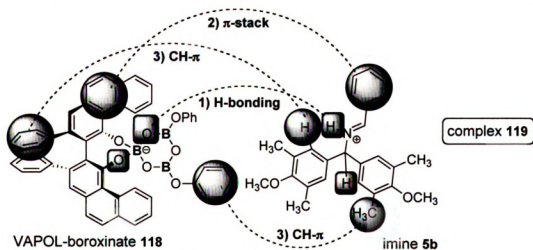
6.3.1 Introduction

The successful launch of the VAPOL/VANOL family of ligands has resulted in the development of many asymmetric reactions, the most prominent of which is the aziridination reaction.^{12,18} This asymmetric catalytic aziridination reaction (Scheme 6.1) is general for both aryl and alkyl aldimines using a catalyst made from either the VAPOL or VANOL ligand with B(OPh)₃ (Scheme 6.1). The process involves the reaction of N-benzhydryl imines **5** and ethyl diazoacetate **6** to afford aziridines **109** with high cis diastereoselectivity (> 40:1) and up to 98% ee. Moreover, by simply changing the protecting group on the imine nitrogen, the ee can be improved up to 99% using aryl BUDAM-imine (**5a**) as substrates.^{18e}

To elucidate the mechanism of the aziridination reaction, efforts were carried out to investigate the interactions between the substrate and the catalyst in more detail. Dr Gang Hu obtained crystals of the VAPOL-B(OPh)₃ complex (**118**) with various Lewis bases and the crystal structure with the protonated MEDAM imine

(**5b**, $R_1 = \text{Ph}$) is depicted in Figure 6.1 as an example.^{144f} As shown by X-ray crystallography, the complex consists of a protonated imine (**5b**) and a chiral counterion in the form of the VAPOL boroxinate (**118**). A variety of non-covalent catalyst-substrate interactions could be identified: 1) H-bonding between the hydrogen of the protonated imine and one of the oxygens of the boroxine ring; 2) π - π stacking interaction between the phenyl group of the protonated imine and the central ring of the phenanthrene of the catalyst; 3) CH- π interactions and a CH-O interaction between the methine hydrogen of the benzhydryl group and the oxygen of VAPOL.

Figure 6.1 Crystal structure of the complex generated from the **118** and imine **5b**



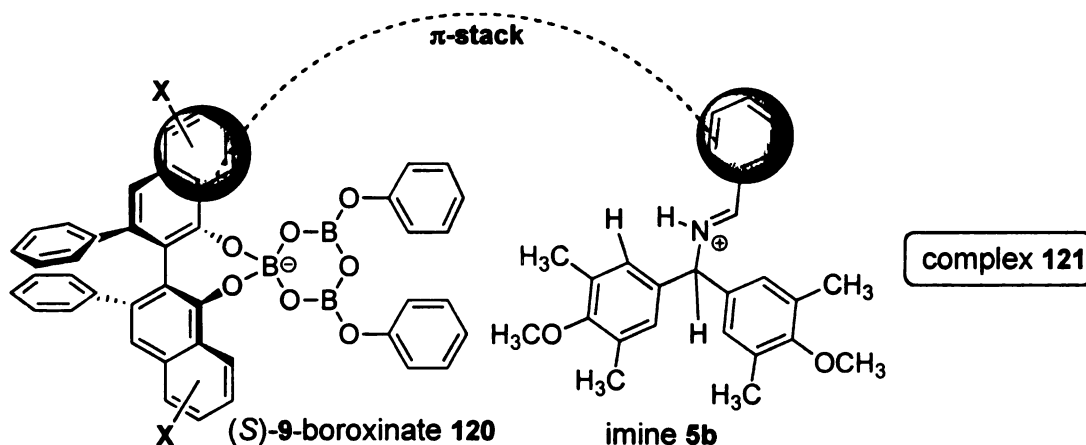
Among the recognition patterns listed above, the study of 1) (the H-bonding) and 3) (the CH- π interactions) have been extensively carried out by Dr Zhenjie Lu,^{18c,f} which benefited greatly from the successful establishment of the different methods for the synthesis of VANOL outlined in Chapter Two. Another important feature of this catalyst-substrate interaction is the presence of the aromatic ring of the imine and its π - π stacking interactions¹⁵⁷ with the catalyst as revealed by

the X-Ray analysis. With the development of the CAEC method (Figure 3.2) for the preparation of VANOL, VAPOL and their derivatives, an investigation was undertaken to determine if this method could be used to prepare VANOL derivatives that would be useful in probing the π -stacking interactions.

6.3.2 Synthesis of the VANOL derivatives using the CAEC cascade reaction

Since VANOL and VAPOL give nearly identical ee's in the aziridination reaction over a range of substrates, we decided to evaluate the π - π stacking interactions by using VANOL derivatives as models. This decision was made on the basis that, the π - π stacking interaction of the imine **5b** with the central ring of the phenanthrene of VAPOL should also be present in the VANOL ligand (Figure 6.2).^{18c} Thus, the π - π stacking interaction can be studied by perturbing the electronic properties of VANOL through introduction of different substituents into this ligand.

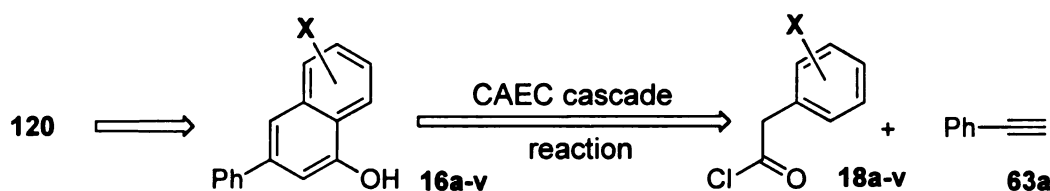
Figure 6.2 Study of π - π stacking by using modified VANOL ligand (S)-9



The proposed preparation of these electronically modified VANOLs with the CAEC cascade reaction as the key step is shown in Scheme 6.11. Therefore, The CAEC cascade method to prepare the VANOL/ VAPOL family of ligands is

distinct from all other methods for several reasons. The first unique feature is the high efficiency made possible by the short number of steps and the typically good yields for each step. Beyond these considerations, the ability of delivering a diversified family of VANOL ligands bearing different electronic and steric functionalities^{18f} by this method is truly impressive, making it the most important general method for the synthesis of VANOL derivatives.

Scheme 6.11 Retrosynthetic analysis of VANOL derivatives **120**



An extensive investigation of reaction conditions with a range of bases, solvents, and trapping agents led to the establishment of the optimized conditions described in Chapter Two and Three of this thesis. Guided by the outcome of these studies, the scope and generality of this process was next explored using substrates with various functional groups and the results are summarized in Table 6.4.

A wide variety of substituted phenylacetyl chlorides participated in the reaction; a noteworthy point is that some electron-withdrawing substituents could be tolerated (entries 3 to 5), giving naphthols that are difficult to access using other existing methods. A *p*-methoxy group can survive the reaction as well and generate **16r** in decent yield (entry 6). Unexpectedly, the more electron-enrich dimethoxyl substrate **18t** failed to afford a detectable amount of the desired product upon complete consumption of starting material (entry 8). The failure of the reaction with **18s** is thought to be due to the bad quality of the starting

material, and thus this reaction should be re-examined in the future (entry 7).

Table 6.4 Preparation of electronically modified VANOL monomers

Entry	Reactant	X	Product	Yield ^a (%)	Byproduct	Yield ^a (%)
1	18a	H	16a	70.0	92a	nd
2	18b	C ₄ H ₄ ^b	16b	80.7	92b	7.9
3	18o	<i>p</i> -F	16o	75.9	92o	nd
4	18p	<i>p</i> -Br	16p	48.7 ^e	92p	nd
5	18q	<i>o</i> -Br	16q	83.9	92q	nd
6	18r	<i>p</i> -MeO	16r	67.9	92r	18.5
7	18s	<i>p</i> -AcNH ^c	16s	mixture ^d	92s	mixture ^d
8	18t	<i>o</i> , <i>p</i> -di-(MeO)	16t	mixture ^d	92t	mixture ^d
9	18u	<i>p</i> -NO ₂	16u	mixture ^d	92u	mixture ^d
10	18v	<i>p</i> -CF ₃	16v	mixture ^d	92v	mixture ^d

^a Isolated yields by after column chromatography on silica gel. nd = not detected. For experimental details, see Section 7.6.2 of Chapter Seven. ^b 2-naphthylacetyl chloride. ^c This substrate was found to have decomposed subsequent to starting the reaction. ^d A mixture of components was produced which could not be separated by silica gel chromatography. ^e The low yield was possibly due to bad stirring conditions.

Nitro substituted substrate (**18u**, entry 9, Table 6.4) also failed to give the cyclized product although this reaction was reported to be successful by other researchers.¹⁵⁸ This difference might be attributed to the forcing conditions used during basic workup, and thus, this reaction should be further investigated with alternative workup procedures. Alternatively, this problem could easily be circumvented by using protected amine substituents in the reaction, which could be oxidized to -NO₂ in a later stage of the synthesis.¹⁵⁹

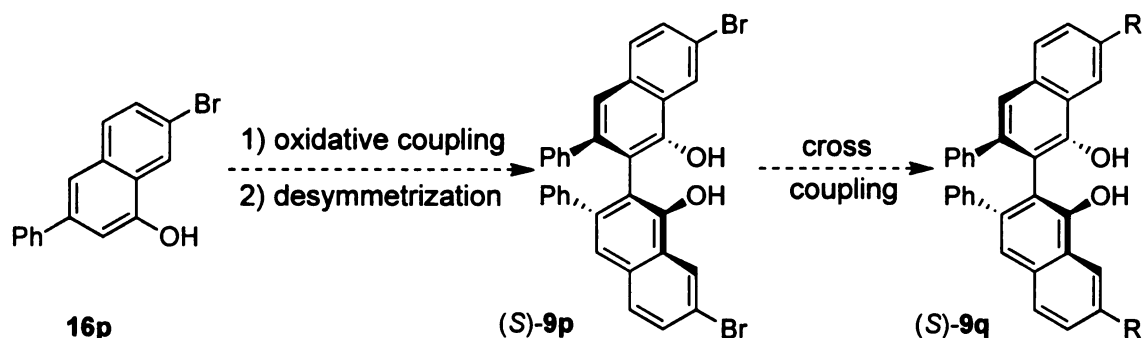
Notably, the only phenylacetic acid derivative that gives rise to the double

alkyne-insertion byproduct is the *p*-methoxy substrate **18r** (entry 6, Table 6.4). With respect to the synthesis of 6- and 8-substituted VANOL monomers, it was rationalized that the use of this method would be problematic since a mixture of regioisomers could be produced, thus, the corresponding *meta*-substituted phenylacetyl chlorides were not explored.

6.3.3 Proposed synthesis of VANOL derivatives by cross coupling reaction

The ability to incorporate halogen substituents makes the above-depicted method particularly appealing, since these moieties can be used for further synthetic manipulations.¹³⁸ In particular, transition metal mediated crossing coupling reactions of aryl halides provide significant and versatile methods to diversify aryl compounds, and can serve in the synthesis of VANOL derivatives that are not amenable to the CAEC cascade conditions (Scheme 6.12).

Scheme 6.12 Proposed synthesis of modified VANOL by cross coupling reaction

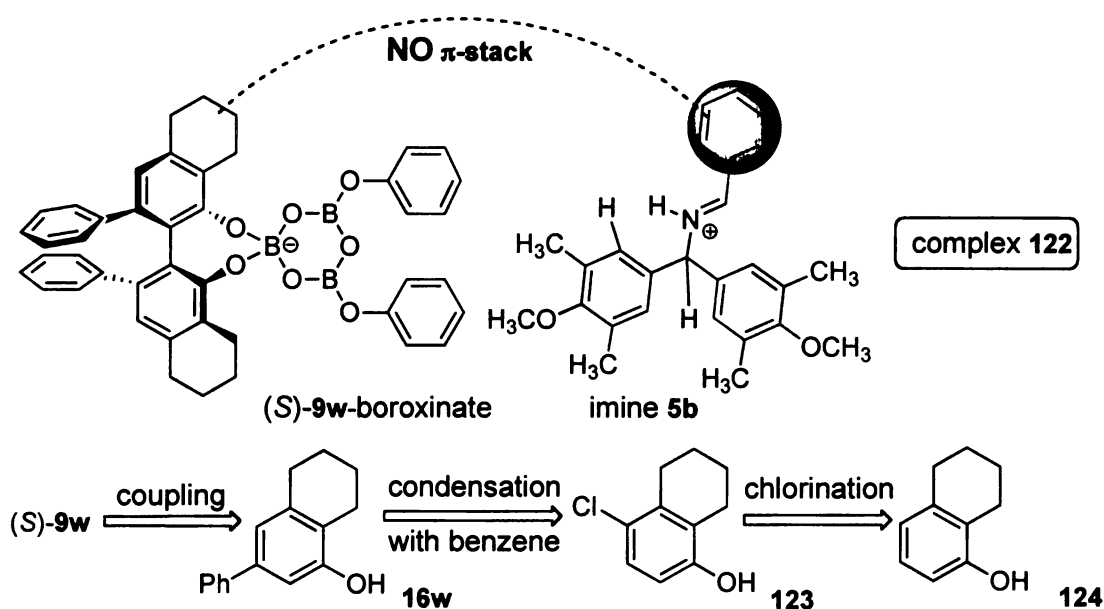


Aryl halides have been at the forefront of recent developments in coupling reactions and thus there are wide variety of methods that can be brought to bear in the synthesis of VANOL derivatives of the type **9q** (Scheme 6.12). An advantage of this approach would be its convergence. After oxidative coupling of the bromonaphthol **16p** and its resolution or deracemization to give optically pure **9p**, a diversity of substituents could be introduced in the last step.^{19b}

6.3.4 Attempted preparation of H8-VANOL *via* condensation reaction

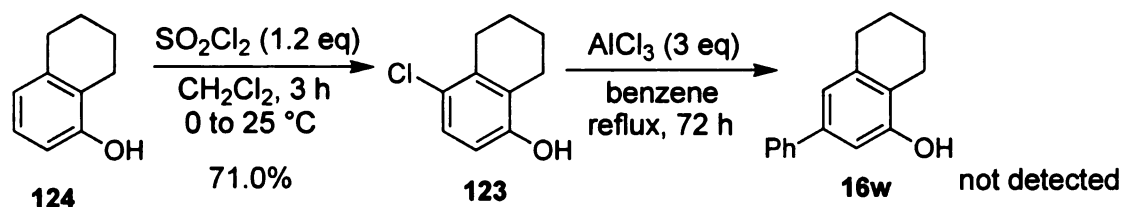
Another way to tackle the π - π stacking effect (Figure 6.1 and Figure 6.2) in the aziridination reaction is to probe the reaction by using VANOL (or VAPOL) derivatives lacking π -bonds on the ring that stacks with the arene ring in imine **5b** (complex **122**, Figure 6.3). To reach this goal, ligand **9w** was designed, in which one of the aromatic rings of the naphthol residue in VANOL has been reduced (H8-VANOL, i.e. 5,5',6,6',7,7',8,8'-octahydro-3,3'-diphenyl-[2,2'-binaphthylene]-1,1'-diol). It was predicted that for a boroxinate derived from **9w**, the π - π stacking effect with imine substrates would be rendered unimportant in the aziridination reaction with this ligand. This in turn should decrease the face selectivity in the addition to imine **5b** and thus the asymmetric introduction in the aziridination reaction. The synthesis of this ligand is proposed to start from the commercially available phenol **124** (Figure 6.3) by using the condensation protocol as the key step which is described in Chapter Two (Table 2.20).

Figure 6.3 H8-VANOL **9w** and the retrosynthetic analysis



The preparation of **123** via chlorination of **124** proceeded smoothly and generated phenol **123** in good yield (Scheme 6.13). However, the condensation reaction with benzene in the presence of AlCl_3 was extremely sluggish. The desired product **16w** was not detected even after refluxing for 72 h (Scheme 6.13). In view that **123** is a substrate analogous to 4-chlorophenol, which failed in its condensation with benzene under similar conditions.⁸⁵ In the end, this discouraging scenario gave way to other more modular pathways to access this class of new ligands (Scheme 6.23).

Scheme 6.13 Attempted synthesis of **16w** by condensing **123** with benzene



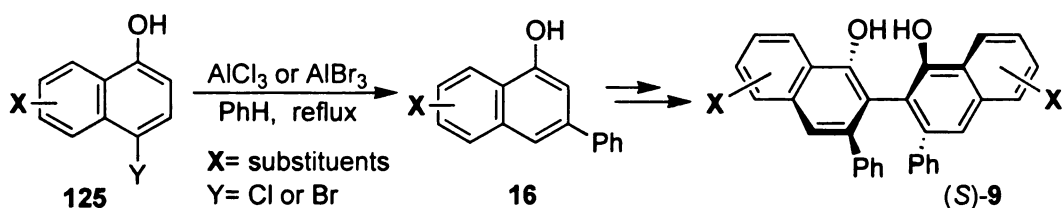
6.3.5 Summary of the *de novo* method to derivatize VANOL monomers

Collectively, and in connection with a program devoted to the elucidation of the mechanism of Wulff's aziridination reaction, the preparation of several VANOL derivatives bearing different substituents is needed. The CAEC cascade reaction of ketenes with alkynes offers the best chance of ultimately leading to the production of a diverse set of VANOL ligands since it posits advantages of inherent regioselectivity, brevity and starting material availability. Furthermore, it can serve as a relay for the synthesis of additional VANOL derivatives by Pd-catalyzed cross coupling of halogenated ligands.^{19b} Thus as a whole, this approach provides considerable opportunity for the regiospecific construction of polysubstituted VANOL derivatives. As a result, these findings are currently under exploitation for the tailoring of chemical properties of suitable VANOL

derivatives to aid in the mechanistic investigation of the asymmetric aziridination reaction.

However, since the condensation of naphthols of type of **125** (Scheme 6.14) has not been investigated yet,¹⁶⁶ one should bear in mind the possibility of preparing VANOL derivatives of the type (S)-**9** (See also Figure 6.2) according to the approach shown in Scheme 6.14 should not be ruled out.

Scheme 6.14 Possible ways to prepare (S)-**9** by condensing **125** with benzene



6.4 Modular synthesis of the VANOL derivatives

Chemically modified VANOL and VAPOL ligands would be expected to exhibit different on various asymmetric reactions than the parent ligands due to steric and electronic changes in the biaryl backbone.^{19b,144a} Therefore, quick accessibility to a large number of such compounds is crucial for rapid screening purposes. However, it maybe expected that *de novo* design of chiral VANOL and VAPOL derivatives would be treacherous due to the inherent difficulty in predicting applicability of the standard oxidative coupling conditions (Table 4.3). Therefore, a modular synthesis by direct functionalization of the VANOL/VAPOL ligands appears attractive: since the convergence is greatly increased, this is a proposition that makes the synthetic aspects of the project intriguing.

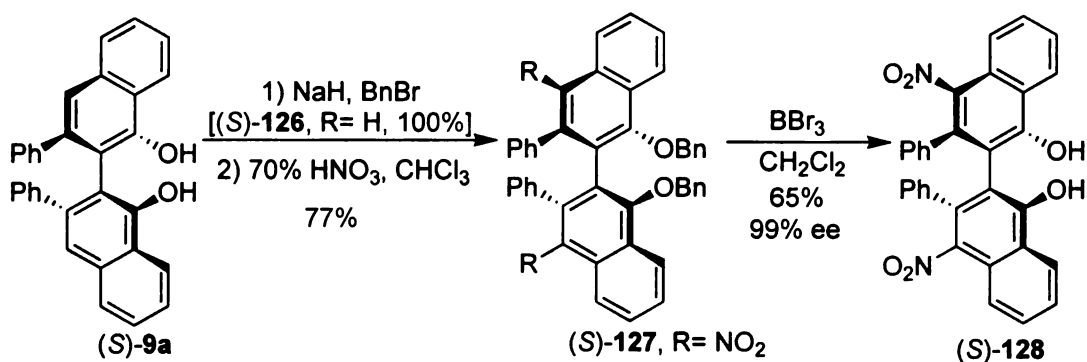
6.4.1 Introduction

Catalysts based on BINOL ligands are popular in asymmetric synthesis. This

is due partly to the fact that various derivatives can be readily prepared from BINOL ligand itself,¹⁶⁰ allowing the ligand to be tailored to a specific catalytic process. Similarly, due to the relative ease of the synthesis of the enantiopure VANOL/VAPOL ligands, it is obvious that facile variations in the structure of these two ligands should be investigated. In turn, this allows for rapid screening to find the optimal ligand for a specific substrate.

The naphthol moieties of VANOL can be conveniently functionalized in various positions; the most frequently functionalized are the 4,4'-positions as they are activated by the OH groups toward reaction with electrophiles.¹⁴⁴ The 4,4'-disubstituted VANOL derivatives that have been prepared are those associated with tuning the electronic characteristics of the binaphthol system.^{144g} An example is 4,4'-dinitro VANOL shown in Scheme 6.15.

Scheme 6.15 Preparation of 4,4'-dinitroVANOL (S)-128 by Dr Gang Hu^{144g}



On the other hand, the majority of 8,8'-modified VANOL ligands that have been prepared were intended to sterically modulate the environment associated with a given asymmetric processes.^{19b,144a} Their behavior is often principally different from structurally related complexes with VANOL ligands.^{144b} With this in mind, a better understanding of the stereoelectronic properties of 8,8'-

disubstituted VANOL derivatives on various asymmetric processes should prove beneficial.

Unlike the 4,4'-disubstituted VANOLs, however, the preparation of 8,8'-disubstituted VANOLs by directly incorporating different functional groups onto VANOL has not been studied yet. Therefore, their anticipated distinctive reactivity and the unique structural features of 8,8'-disubstituted VANOL derivatives have provided the impetus for the exploratory studies described herein.

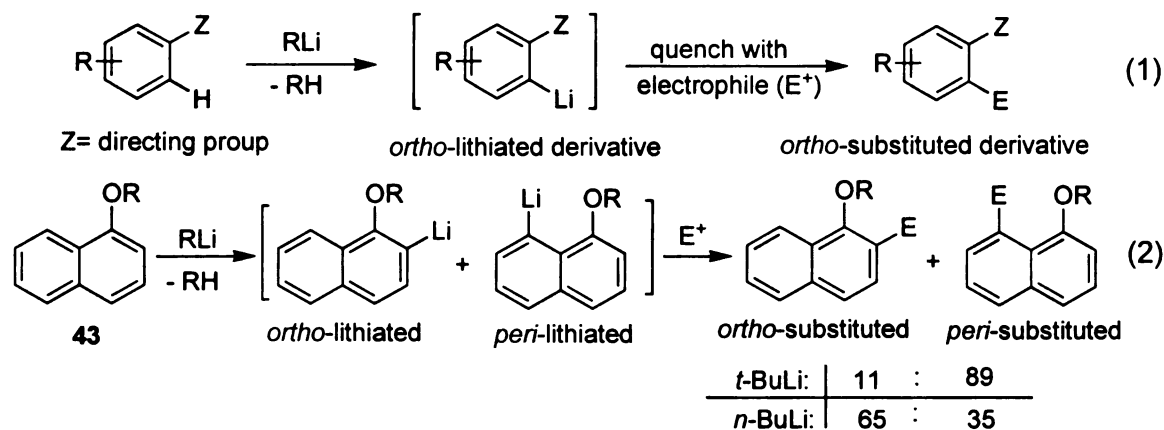
6.4.2 Attempted synthesis of 8,8'-disubstituted VANOL by direct lithiation reaction

For the reasons given above, the development of routes to expedite the preparation of 8,8'-disubstituted (i.e. *peri*-positions) VANOL ligands is necessary to promptly assess their utility in organic synthesis. Being aware that the *peri*-substituted groups reside on electronically non-activated rings of the naphthol moieties, the introduction of substituents in the 8 and 8' positions is not easily attainable by means of electrophilic aromatic substitution. Luckily, the two *peri*-hydrogens of VANOL are in close proximity to hydroxyl functions and thus functionalization *via* metallation of the naphthalene moiety^{72c} could provide a convenient strategy for the synthesis of 8,8'-derivatives of VANOL.¹⁶¹

Directed *ortho*-lithiation^{72c} is the metallation of an aromatic ring adjacent to a heteroatom-containing functionality (directing group, eq (1), Scheme 6.16). This typically involves deprotonation of a substituted aromatic ring by an organolithium species such as *n*-butyllithium. This process is thermodynamically viable, as butane is ten orders of magnitude less acidic than benzene. The reaction is

generally regioselective, as lithiation occurs at the *ortho*-positions to the directing group.

Scheme 6.16 Directed *ortho*-lithiation reaction of heteroatom substituted arenes

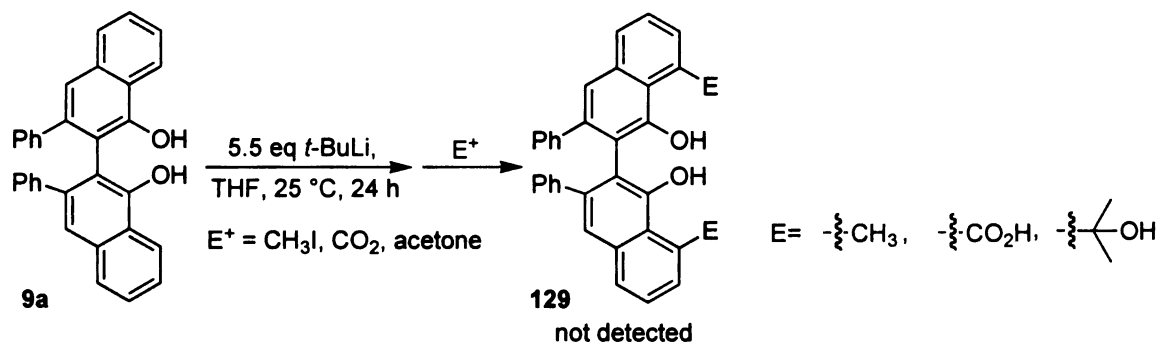


When applied to α -naphthol derivatives,¹⁶¹ the directed lithiation can result in functionalization at either the *ortho*- or *peri*- positions, and thus poses selectivity concerns (eq (2), Scheme 6.16). In the case of VANOL, the *ortho*-position is not accessible and thus this structural feature should ensure by default exclusive *peri*-selection in the lithiation reaction. Stimulated by these considerations, we tested the conjecture that deprotonation of the two *peri*-hydrogens in VANOL would result in the corresponding carbanions, a process which, upon trapping with various electrophiles, would fall under the term of modular VANOL syntheses.

As illustrated in Scheme 6.17, *t*-BuLi was examined in the synthesis of 8,8'-disubstituted VANOL derivatives **129** since it was reported that this base attacked preferentially at the *peri*- position of 1-naphthol derivatives,^{161c} while *n*-BuLi predominantly generated 2-lithiated products. Thereupon, the lithiation reaction of racemic VANOL was initially examined in different solvents. After

quenching with various electrophiles, however, the reactions unexceptionally led to recovery of starting material. Given that VANOL possesses relatively acidic protons on the hydroxyl group, it was thought that this might have a detrimental effect on the metalation step. This is because the reaction was carried out in the presence of a strong base, which not only resulted in wasting two equivalents of base but also increased the negative charge on the naphthalene rings and thus perhaps retarded the metallation. Therefore, metalation of a protected form of VANOL was deemed to be more compatible with the directed lithiation reaction. The subsequent unmasking of –OH groups to release the functionalized VANOL could then be effected after trapping the carbanions by electrophiles.

Scheme 6.17 Attempted directed lithiation-substitution of unprotected VANOL

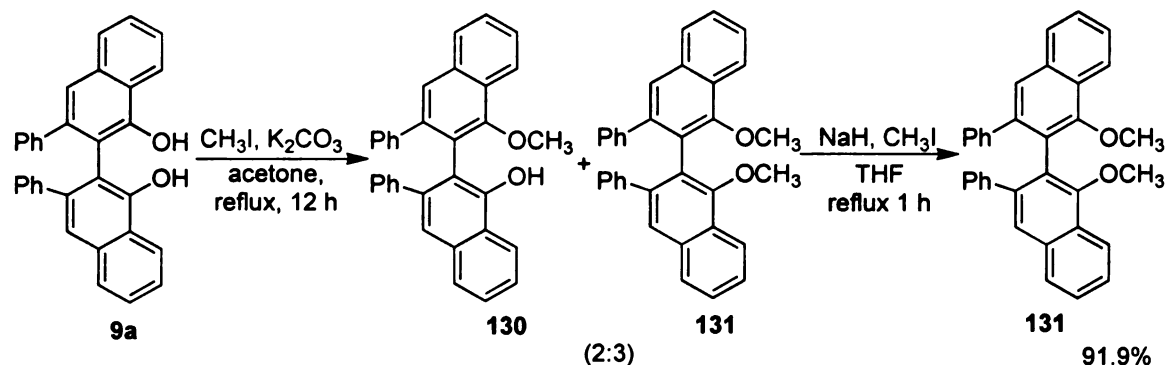


With these ideas in mind, attention was then focused on the synthesis of bis-O-methyl VANOL which starts with a base-mediated deprotonation of VANOL to furnish the corresponding dianion followed by treatment with MeI (Scheme 6.18; for experimental details, see Sections 7.6.1.4 and 7.6.3 of Chapter Seven).¹⁶² Unfortunately, efforts to generate a fully protected VANOL using K_2CO_3 in acetone in the presence of MeI led to incomplete conversion. One of the products was the monomethylated VANOL derivative **130**, and the ratio of this compound over the dimethylated VANOL **131** was 2:3 based on the integration of

the methyl groups on ^1H -NMR spectrum.¹⁶⁷ In contrast, deprotonation of VANOL with the stronger base NaH furnished the fully protected ligand in good yield.

From this preliminary study, we concluded that as a weak acid, there was a chance that VANOL could be selectively monoalkylated using a milder base like K_2CO_3 under properly controlled conditions. This would be important when the formation of mono *O*-alkylated VANOL was desired and an example would be in the synthesis of solid supported VANOL (Scheme 6.10). In this case, the fully alkylated VANOL would be a byproduct, but perhaps the yield of the mono-alkylation product could be improved by controlling the steric effects of the alkylation reagents.

Scheme 6.18 *O*-methylation of VANOL by CH_3I under different conditions

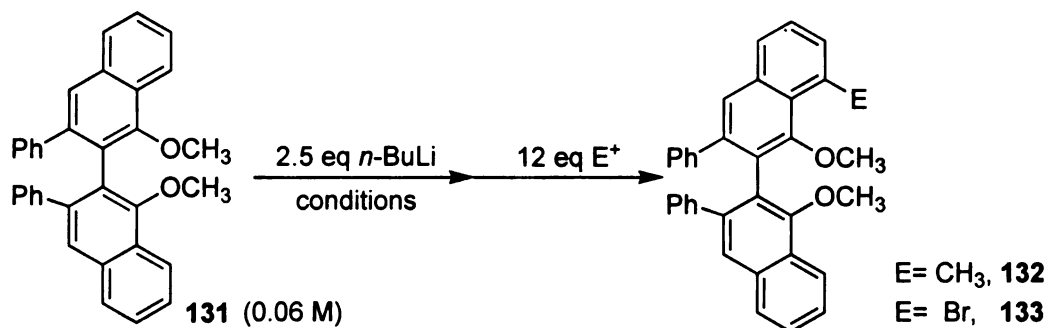


One potential problem in converting VANOL to O,O'-dimethylVANOL **131** is that the bay area of this ligand is more crowded, which would make *t*-BuLi a less favored base for the lithiation reaction than *n*-BuLi. Consequently, it was judged that it might be easier to prepare **129** by a similar procedure where the less sterically demanding *n*-BuLi is utilized (Table 6.5).^{161c}

Quite disappointingly, no reaction was detected when the substrate **131** was exposed to *n*-BuLi at ambient temperature (Table 6.5, entry 1). These conditions

only resulted in full recovery of the starting material. Simply heating the reaction to 45 °C led to trace amount new compounds that could only be detected in the ¹H-NMR spectrum (entry 2).^{161a} Under more forcing conditions (entry 3), a complete conversion of **131** to a new compound (based on ¹H-NMR spectrum) was achieved.

Table 6.5 Directed mono *peri*-lithiation reaction of **131**



Entry	E ⁺	Solvent	E	Conditions	TMEDA (eq)	Yield (%) ^c
1	CH ₃ I	Ether	CH ₃	25 °C, 35 h	0	nd ^a
2		Ether		45 °C, 2 h	0	40 ^b
3		Ether		50 °C, 24 h	0	100 ^b
4		Ether		25 °C, 24 h	2.5	44.2 (100 ^b)
5		Hexanes		25 °C, 24 h	2.5	nd
6	BrCH ₂ CH ₂ Br	Ether	Br	25 °C, 3 h	2.5	31.4 (65 ^d)

^a nd=not detected, **131** was recovered. For experimental details, see Section 7.6.4 of Chapter Seven. ^b Conversion, which was based on ¹H-NMR spectrum. ^c Isolated yield by chromatography on silica gel. ^d **131** (34.8%) was recovered.

One major drawback of using RLi in deprotonation processes is that they form aggregates in solution that kinetically deactivated these reagents.¹⁶³ This significantly limits their usefulness unless a chelating agent such as TMEDA is present.^{163b} Gratifyingly, with TMEDA as additive, **131** underwent lithiation smoothly and cleanly, and a single new compound was isolated upon exposure to MeI with the remainder of the mass consisting of only the unreacted starting

material.

Amazingly, this newly formed compound was assigned to be the 8-methylated product **132**. This claim could be supported by the disappearance of one of the bay protons doublets and the complete differentiation of the two naphthalene moieties in ^1H -NMR spectrum. Thus assignment was further confirmed by mass spectroscopy. To account for this observation, it is proposed that the highly hindered environment at the bay area, created by the two fused benzene rings and two methoxyl groups, is such that after the first metallation the resulting organolithium species in combination with ligands on the lithium (TMEDA) created a total steric environment that inhibits attack by the second *n*-BuLi.

An interesting result was that bromine could also be introduced to one of the *peri*-carbons (**133**) when 1,2-dibromoethane was used to quench the aryllithium intermediate (entry 5). This discovery opens new horizons for further transformations, since bromine should be easily convertible to other functional groups.^{19b}

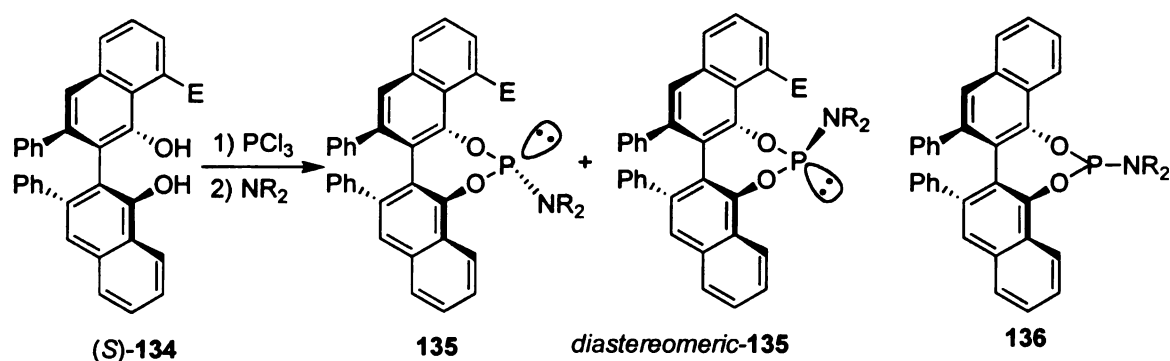
For future work, it is planned to investigate the possibility to apply these conditions listed in Table 6.5 on unprotected VANOL to avoid the protection and deprotection of the hydroxy groups in VANOL ligand.

6.4.3 C_1 - and C_2 -symmetric ligands: possible applications of 8-substituted VANOL

Noticeably, this modification of the VANOL backbone described above resulted in a new class of binaphthol compounds bearing two distinctive aryl units (Scheme 6.19, (*S*)-**134**). In these new structures, C_2 symmetry no longer holds.

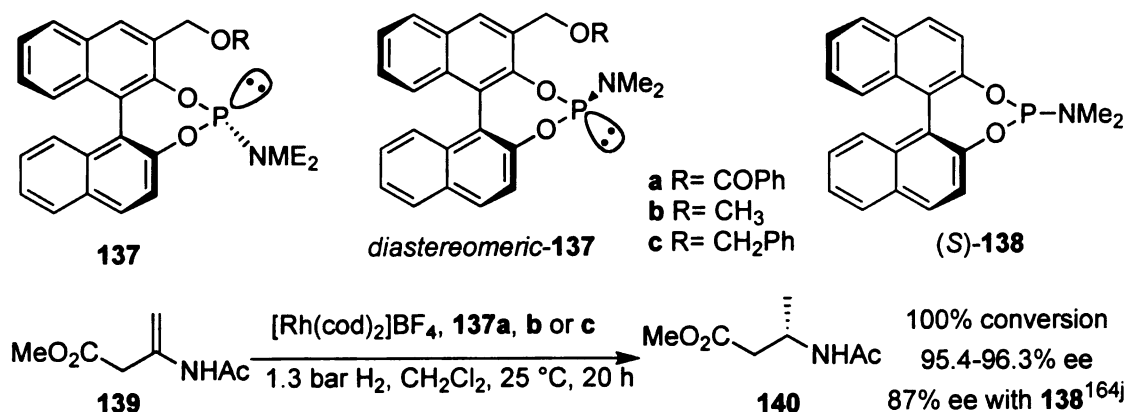
Moreover, when (S)-**134** is bound to a phosphorous fragment, the phosphorous center is rendered diastereomeric (Scheme 6.19). This means that the P atom in phosphoramidites **135** (and other derivatives such as phosphates and phosphonites) become stereogenic centers (P_R or P_S). This gives rise to two diastereomers, which upon coordination of the lone-pair to a metal center, the chirality is positioned much closer to the active site (compared with (S)-**136**, Scheme 6.19). Therefore, they should exert special effects in different asymmetric transformations.¹⁶⁴

Scheme 6.19 Novel VANOL-derived monodentate ligands with P stereogenic center



For example, when only one naphthyl moiety in phosphoramidite ligand **137**^{164a} is modified (Scheme 6.20), it becomes sterically and electronically non-symmetrical (C_1 symmetry). Therefore, these ligands exhibit excellent activities in rhodium-catalyzed olefin hydrogenation of **139**, which give distinctly better results in the generation of **140** (>95% ee) than that from the parent C_2 -symmetric phosphoramidite (S)-**138** (87% ee).^{164j}

Scheme 6.20 Applications of monodentate ligands with P stereogenic centers

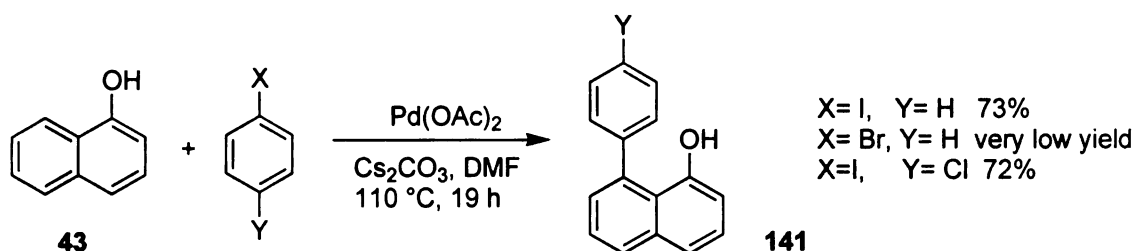


In many applications, C_1 symmetry ligands had made valuable contributions and often display superior results to the more conventional C_2 ligands.¹⁶⁴ However, the area of C_1 VANOL ligands with modified backbones had not previously been explored in any context.^{19g} Accordingly, this should open an active area of research.¹⁶⁴ The success of C_1 -symmetrical BINOL derivatives in the past few years demonstrates that this 8-substituted-VANOL represented an appealing complement to the existing C_2 -symmetrical derivatives. Opportunities may exist in fields in which its better-known C_2 -symmetrical relatives (VANOL and derivatives) might fail.

6.4.4 The 8,8'-disubstituted VANOL ligands: future perspective

The initial objective of this project was to devise new pathways to access the 8,8'-disubstituted VANOL ligands, since the direct lithiation methodology failed to do so. However, these sterically more demanding ligands present an opportunity to inspect the possible asymmetric synthetic applications of catalysts requiring deeper chiral pockets. The success of analogous 3,3'-disubstituted BINOL ligands in asymmetric catalysis suggests that a close examination of the preparation of 8,8'-disubstituted VANOL derivatives is merited.

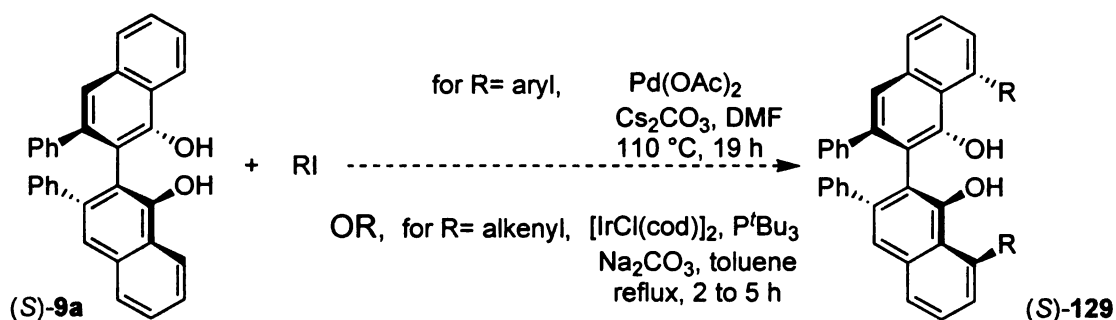
Scheme 6.21 Regiospecific arylation of **43** mediated by palladium catalysis



Miura^{165a} developed a one-pot sequential *peri*-palladation-arylation reaction of 1-naphthol (Scheme 6.21). This new method consists of heating a mixture of 1-naphthol **43**, PhI (1.2 equiv), and 2.5 mol% Pd(OAc)₂ in DMF, and provided the 8-phenyl-1-naphthol **141** in good yield (73%).

This new method, when applied to VANOL (Scheme 6.22), has the clear advantage over the direct lithiation strategy in that protection and deprotection of -OH groups is not necessary. Additionally, no strong bases are involved that would be of immense benefit in regard to safety, operational facility and particularly for functional group compatibility. Furthermore, a recent extension of this work with an iridium catalyst makes it possible to introduce various alkenyl groups at the *peri*-positions of 1-naphthol **43**.^{165b} The extension of this reaction to the synthesis of 8,8'-VANOL derivatives is currently an ongoing project in our lab.

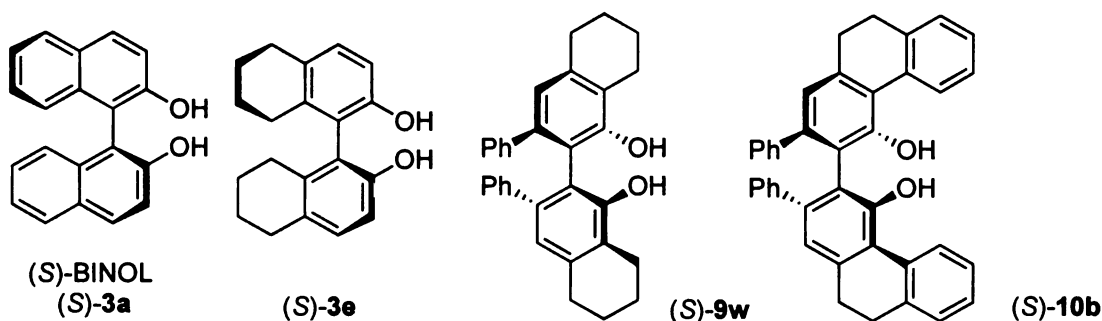
Scheme 6.22 Proposed synthesis of (S)-**129** via Miura's protocol^{165a,b}



6.4.5 Proposed modular synthesis of H8-VANOL (H4-VAPOL) *via* reduction

During the course of the studies to unravel the mechanism of Wulff's aziridination reaction, the H8-VANOL ligand **9w** (Figure 6.4) was identified as a ligand to test the proposed π - π stacking interactions. The introduction of the sp^3 carbons in **9w** would be expected to result in more conformational flexibility in the ligand, more broadly it might be expected that chiral catalysts derived from **9w** may exhibit different features for asymmetric reactions due to the steric and electronic modulation in the biaryl backbone. In support of this contention, a recent re-evaluation of BINOL **3a** and its octahydro analogue **3e** (H8-BINOL, Figure 6.4) has revealed subtle differences in their asymmetric inductions of various reactions and in many instances H8-BINOL **3e** has given higher enantioselectivity than the corresponding BINOL derived catalysts.¹⁶⁸ These observations directed our interests to the synthesis of the novel H8-VANOL ligand **9w** with a partially hydrogenated aromatic backbone.

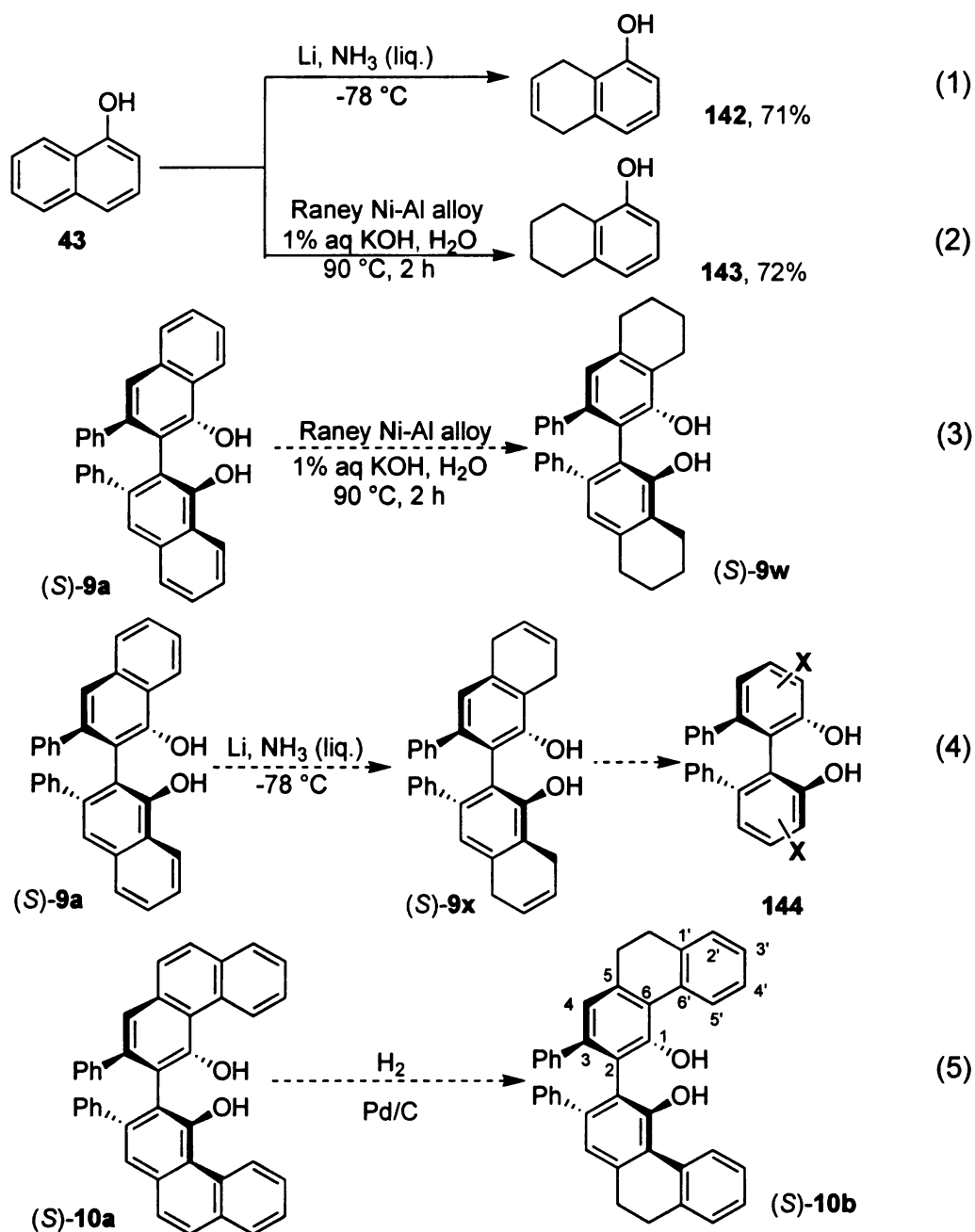
Figure 6.4 BINOL, H8-BINOL, H8-VANOL and H4-VAPOL ligands



The adventurous synthesis of **9w** shown in Scheme 6.13 relied on a condensation reaction of **123** with benzene to produce monomer **16w**, which unfortunately did not bear fruit. Hence, alternative synthetic options were considered which were aimed at identifying more convergent methodologies from

enantiopure (*S*)-VANOL **9a**. The synthetic challenge posed by **9w** reflects the fact that the structural modification of parental VANOL takes place on the electronically non-activated ring of the naphthol residue. Thus, a new route was conceived by using Birch type reduction as the key step (Scheme 6.23).

Scheme 6.23 Proposed methods to access hydrogenated VANOL and VAPOL



For example, 1-naphthol **43** has been selectively hydrogenated to generate

partially (**142**, Route (1), Scheme 6.23) or fully (**143** Route (2)) saturated derivatives under different conditions.¹⁶⁹ On the basis of this precedent, it is reasonable to propose that the formation of 8H-VANOL (S)-**9w** from reduction of (S)-**9a** should be feasible (Route (3)). Moreover, in view of the fact that olefins are substrates for a rich array of synthetic transformations, the presence of carbon-carbon double bonds in (S)-**9x** (Scheme 6.23) provides other possibilities to further diversify the VANOL ligand (**144**, Route (4)).

The known facile reduction of phenanthrene derivatives into 9,9'10,10'-tetrahydrophenanthrene¹⁷⁰ invites the development of a novel route to new ligand (S)-**10b** ((S)-H4-VAPOL, Figure 6.4). In this regard, it is proposed that (S)-**10b** can be produced from (S)-**10a** by exposing it to H₂ in the presence of Pd (Route (5), Scheme 6.23).^{170e} For (S)-**10b**, the firm rigidity demanded by the aromaticity in the parental VAPOL ligand (S)-**10a** is partially released but still the rotation around the 6C-6'C single bond between the two phenyl groups in (S)-**10b** is still confined by the ethylene linkage. This feature may introduce some new reaction modes to VAPOL chemistry.

6.4.6 Summary of the modular preparation of VANOL derivatives

To sum up, 8-mono-substituted VANOL derivatives have been serendipitously prepared by direct lithiation of O,O'-diprotected VANOL using strong base. The result is attractive and distinguished in that it directly produces a VANOL derivative with a C₁ skeleton from a C₂ symmetrical parent ligand. To the best of our knowledge, the synthesis of 8-substituted VANOL derivative is unprecedented. As discussed previously, the construction of a C₁ symmetrical

VANOL ligand *via* a cross coupling reaction is inherently problematic, which makes the present accomplishment more impressive. Difficulties encountered in performing the double lithiation of VANOL has so far prevented the direct conversion of VANOL to its 8,8'-substituted derivatives, and work towards accessing these derivatives is ongoing.

6.5 Concluding remarks

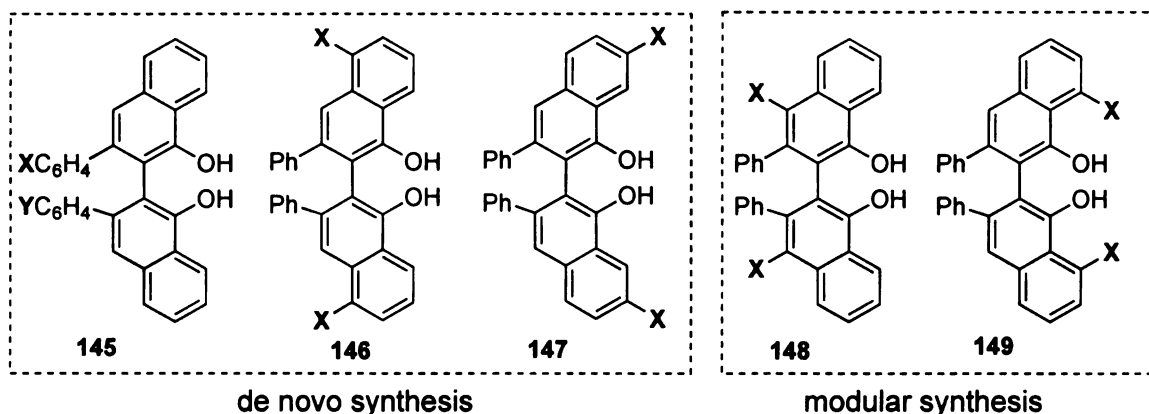
Initially driven by the desire to operationally and mechanistically improve the efficiency of the aziridination reaction, the derivatization of the VANOL ligand was considered for two different purposes: the synthesis of solid-supported catalysts and the synthesis of skeleton modified VANOL derivatives. All of these efforts were rewarded with success to some extent, and the impact of this research on organic transformations was highlighted by the way that it enabled access to different 'finely tuned' VANOL ligands for elucidation of the mechanism of the aziridination reaction.

Depending on the subclass of a chiral VANOL derivative that is desired, it is likely that at least one strategy would be relevant of various strategies presented here. The *de novo* methods using CAEC cascade reaction generally excelled at producing 3,3'- (**145**), 5,5'-(**146**) and 7,7'-(**147**) substituted VANOL ligands with various electronic properties (Figure 6.5).

On the other hand, the modular method was overwhelmingly superior at functionalizing VANOL at 4,4'- (**148**, by electrophilic substitution)^{144b} and 8,8'-positions (**149**, by direct metalation). The promising feature of the modular method, apart from being strategically more efficient, was its capability of delivery

of C_1 symmetric VANOL derivatives, which are hard to access otherwise yet highly favored to provide catalysts with new properties in view of the recent developments in unsymmetrical BINOL derivatives.

Figure 6.5 Pathways to produce skeleton-modified VANOL ligands



It is unrealistic to expect that one particular ligand will exert perfect enantiocontrol in many different reactions for many different substrates. Therefore, when developing new ligands for stereospecific synthetic processes, it is crucial that the synthesis is flexible and simple enough to allow structural optimization of a ligand for a particular application. We detailed the case of the derivatization of VANOL; this ligand is rich in its applications to chemical reactions, and improved routes to access various VANOL derivatives could serve as models for diversifying VANOL ligands, and open up new opportunities for discovery in asymmetric synthesis.

CHAPTER SEVEN

EXPERIMENTAL PART

All reagents were obtained from commercial suppliers and used without further purification unless otherwise indicated. The following compounds were distilled under N₂ atmosphere: THF, toluene, Et₂O and benzene (from sodium metal); Triethyl amine and CH₃CN (from CaH₂); Diisopropylethylamine and TMEDA (from KOH). The following compounds were distilled under one atmosphere pressure (in air): Oxalyl chloride (61-3 °C); CHCl₃ (61-2 °C); SO₂Cl₂ (69-70 °C) and CH₃I (42-3 °C). The following compounds were distilled under vacuum: Ethyl bromoacetate (80 mmHg/ 80-2 °C); 1-bromonaphthalene (0.5mmHg/ 95-6 °C); Dimethyl sulfate (75 mmHg/ 67.5-80 °C); Phenylacetylene (80 mmHg/ 81-2 °C); Isobutyric anhydride (4 mmHg/ 40-1 °C); 1, 2-dibromoethane (30 mmHg/ 44-5 °C); Bromobenzene (75 mmHg/ 88-9 °C). 1-naphthol was sublimed under high vacuum (3 mmHg/ 70 °C). Cr(CO)₆ was crystallized in 1, 2-dichloroethane (DCE).

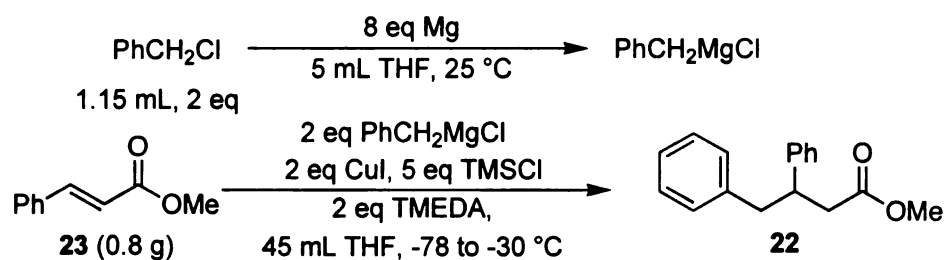
Melting points were determined on a Thomas Hoover capillary apparatus and were uncorrected. Infrared spectra were recorded on a Nicolet IR/42 FTIR spectrophotometer. ¹H-NMR spectra were recorded on Varian Gemini-300, Varian Inova-300, Varian VXR-500 and Varian Unity-plus 500 instrument (at 300 and 500 MHz). ¹³C-NMR spectra were obtained on Varian Unity-plus 300 or 500 instruments at 75 MHz. GC spectra were performed on a HP 5890 Series II GC in

tandem with a Trio-1 MS instrument, which was also used to record low-resolution mass spectra with direct-probe inlet. High-resolution mass spectra were recorded on a JOEL-AX505 mass spectrometer (resolution 7000) at Mass Spectrometry Service Center of Michigan State University. Elemental analyses were done on PerkinElmer Series II CHN/O Analyzer 2400. Compounds were separated *via* flash chromatography using 230-400 mesh silica gel. Chiral HPLC chromatography was obtained on a Varian chromatograph using a Pirkle covalent D-phenylglycine column.

7.2 Experiments of Chapter two

7.2.1 Preparation of 16a *via* Michael addition reaction pathway (Section 2.2)

7.2.1.1 Preparation of 22 and 21 on different scales

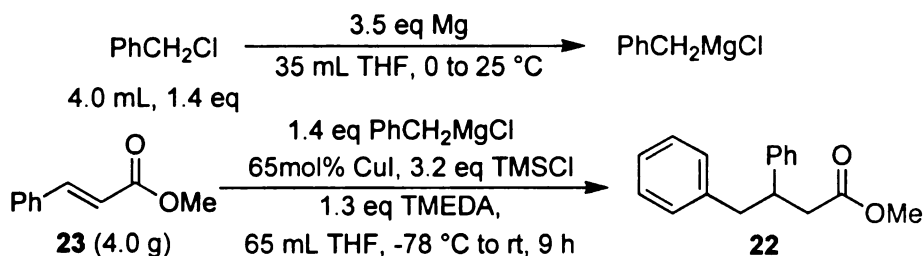


Preparation of 22 following the literature procedure.³⁰ Benzyl chloride (1.15 mL, 10 mmol) was slowly (ca. 1 h) added to Mg turnings (0.98 g, 40 mmol) and in dry THF (5 mL) at room temperature under an argon atmosphere and kept stirring for another hour.

To an oven-dry round bottom flask was added CuI (1.90 g, 10 mmol, purified according to reference³⁷) and dry THF (40 mL). The flask was then sealed with a

rubber septum, flushed with argon and dry TMEDA (1.66 mL, 11 mmol) was added. After the contents were stirred at room temperature for 10 minutes the flask was cooled to -78 °C and the THF solution of BnMgCl was injected followed by stirring at -78 °C for 15 minutes. TMSCl (3.2 mL, 25 mmol) and **23** (0.98 g, 40 mmol), as a solution in dry THF (5 mL), was then injected and stirring continued while the temperature was allowed to rise to -30 °C over a period of 24 h. The mixture was poured into a separatory funnel containing a saturated NH₄Cl in NH₄OH solution (40 mL) and extracted with diethyl ether (2x50 mL). The combined ether extracts were then washed with 50 mL brine, dried over MgSO₄ and filtered. Upon removal of solvent by evaporator, residue was dissolved in minimum amount of CH₂Cl₂ and loaded to a silica gel column, eluted with a 1:20 mixture of EtOAc: hexane to give 1.12 g of **22** (4.40 mmol, 88.0%) as white solid.

Spectral data for **22**: white wax-like solid; mp = 38-40 °C (lit. value: not found); *R_f* = 0.36 (1:9 EtOAc/hexane). ¹H-NMR (CDCl₃, 300 MHz) δ 2.63 (dd, 1H, *J* = 6.9, 20.1 Hz), 2.67 (dd, 1H, *J* = 7.2, 20.1 Hz), 2.84-2.97 (m, 2H), 3.37-3.47 (m, 1H), 3.52 (s, 3H), 7.03 -7.28 (m, 10H); ¹³C NMR (CDCl₃, 75 MHz) δ 39.89, 42.85, 43.79, 51.90, 126.07, 126.49, 127.35, 128.12, 128.30, 129.13, 139.39, 143.34, 172.58; mass spectrum, *m/z* (% rel intensity), 254 M⁺ (40), 223 (50), 181 (85), 180 (100), 121 (100), 91 (100), 59 (84).

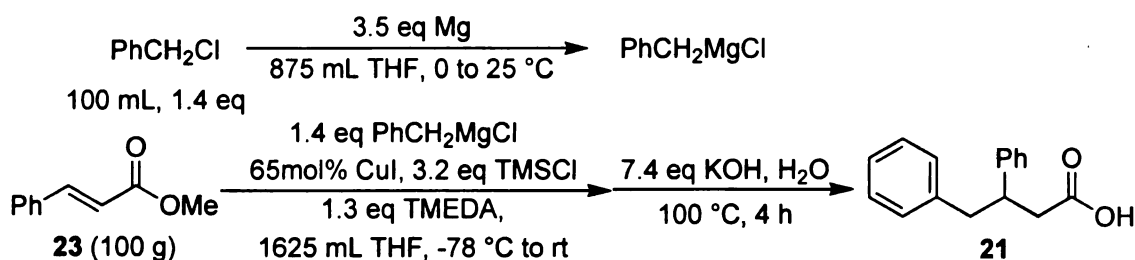


The final optimized procedures to prepare 22 before scaleup. While stirring in a 100 mL flask, benzyl chloride (4.0 mL, 34.7 mmol, 1.4 eq) in 5 mL dry THF was slowly (ca. 1 h) added to Mg turnings (4.0 g, 164.6 mmol, 6.6 eq) in dry THF (30 mL) at 0 °C under N₂ and kept stirring for another hour at 25 °C.

To an oven-dried round bottom flask was added CuI (3.01 g, 15.8 mmol, 63.6mmol%, reagent grade, dried at 90 °C under 5 mmHg vacuum overnight), sealed with a rubber septum, and then filled with argon. Dry THF (50 mL) was added followed by TMEDA (5.0 mL, 33.1 mmol, 1.33 eq). The color of the solution changed from white to brown. After the contents were stirred at room temperature for 10 minutes the flask was cooled to -78 °C and the THF solution of BnMgCl was added followed by stirring at -78 °C for 15 min. The color of the suspension changed from brown to yellow. TMSCl (10.0 mL, 78.8 mmol, 3.16 eq) and **23** (4.04 g, 24.9 mmol), as a solution in dry THF (15 mL) under argon, was then injected. The color changed to red immediately, then to dark red as reaction underwent. Stirring continued while the temperature was allowed to rise to 25 °C over a period of ca. 9 h (the crude ¹H-NMR spectrum indicated that the reaction was complete). The mixture was quenched with a saturated NH₄Cl in NH₄OH

solution (100 mL) and extracted with diethyl ether (3x50 mL). The combined ether extracts were then washed with H₂O (50 mL) and dried over MgSO₄. Upon removal of solvent by evaporator, residue was loaded to silica gel column and eluted with a 1:20 mixture of EtOAc: hexane to give 6.02 g of **22** (23.5 mmol, 95.0%) as white wax-like solid, with bibenzyl (0.67 g, 3.67 mmol) as byproduct.

For more conditions, see **Section 2.2.2, Chapter two**.



The final procedures to prepare 22 on large scale. To a 2 L round bottom flask was added 25 g Mg turnings (1.0 mol) and 750 mL dry THF. The flask was flushed with N₂ and cooled down to 0 °C. To this mixture benzyl chloride (100 mL, 0.87 mol) in 125 mL dry THF was slowly added. After one quarter of the solution was added, another 28 g of Mg turnings (1.15 mol) was added. Addition of benzyl chloride was then resumed and added over 1 h. The ice-water bath was then removed to raise the temperature to room temperature and stirred for 1.5 h.

To a 5 L oven-dried 3-neck round bottom flask was added CuI (75 g, 0.39 mol) and a large stirrer bar. The flask was equipped with and a 1 L pressure compensating addition funnel and the other two necks were sealed with rubber septum. The top of the addition funnel is vented to a bubbler. The flask was then

flushed with N₂ through one of the neck. Dry THF (1.25 L) was added followed by 65 mL TMEDA (0.43 mol). After stirring at room temperature for 15 min, the color changed to brown. The flask was cooled to -78 °C for 30 min. The PhCH₂MgCl solution was transferred *via* a cannular. The color changed to yellow and solid formed. It was stirred for 10 min before TMSCl (250 mL, 1.98 mol) and **23** (100 g, 0.625 mol) in 375 mL dry THF was added *via* the addition funnel over a period of 10 min. The color changed to red immediately. It was kept stirring allowing the temperature to increase to 25 °C. The reaction was quenched by 2.5 L of the saturated NH₄Cl in NH₄OH, and air was bubbled into the flask for 2 h through one of the neck and all solid dissolved to form two layers with the top one being the THF layer. It was collected; the blue aqueous layer was extracted with ether (500 mL×3). The combined organic layer was washed by water (400 mL×3), dried over MgSO₄ and filtered. Upon removal of solvent by evaporator, a wax-like white solid (181.6 g, mixture of **22** and bibenzyl) was afforded in a 2 L round bottom flask, which was used for the next step (hydrolysis) without further purification.

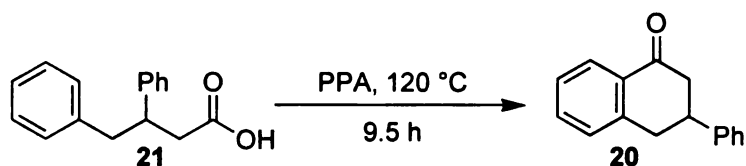
To this flask was added aq. KOH (255 g, 4.55 mol in 700 mL H₂O) and a stirrer bar. It was refluxed for 3.5 h. Upon chilling down to rt, the solution was washed with hexanes (200 mL×3) to remove bibenzyl (16.4 g, 88 mmol). Water layer was acidified by 6 N HCl (1.5 L) till pH~0, and extracted by ether (400 mL×4). The organic layer was dried over MgSO₄ and filtered. The filtrate was stripped of solvent by rotary evaporator and then dried at 0.5 mmHg vacuum overnight to

afford 150.0 g (0.62 mol, 100 %) of **21**. Both mp⁵⁰ and ¹H-NMR spectrum indicated it was pure, no further purification was performed.

Spectral data for **21**: white solid; mp = 91.0-92.5 °C (lit value⁵⁰ 95-6 °C); *R_f* = 0.24 (1:20 EtOAc/hexane). ¹H-NMR (CDCl₃, 300 MHz) δ 2.63 (dd, 1H, *J* = 8.3, 15.9 Hz), 2.68 (dd, 1H, *J* = 6.9, 15.9 Hz), 2.89 (d, 2H, *J* = 6.6 Hz), 3.38 (p, 1H *J* = 7.8 Hz), 7.00-7.03 (d, 2H, *J* = 9.9 Hz), 7.12-7.30 (m, 8H), 11.4 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 40.00, 43.80, 44.10, 126.24, 126.71, 127.47, 128.23, 128.40, 129.25, 139.30, 143.18, 179.90; mass spectrum, *m/z* (% rel intensity), 240 M⁺ (15), 181 (38), 180 (100), 149 (85), 108 (100), 91 (100), 77 (73), 65 (40).

Spectral data for bibenzyl: white solid; mp = 45-48 °C (lit value²⁵ 50-3 °C); *R_f* = 0.60 (1:20 EtOAc/hexane). ¹H-NMR (CDCl₃, 300 MHz) δ 2.95 (s, 4H), 7.19-7.29 (m, 10H). ¹³C NMR (CDCl₃, 75 MHz) δ 39.00, 125.62, 128.00, 128.18, 141.52.

7.2.1.2 The standard procedures to prepare **20** on large scale.⁵¹



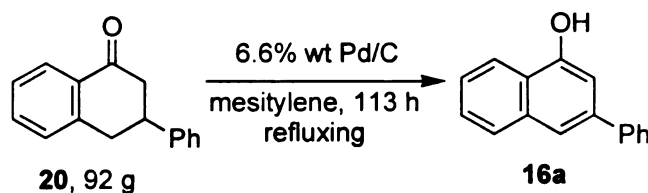
Polyphosphoric acid (i.e. PPA, 300 g) was magnetically stirred and heated in a 120 °C oil bath in a 1 L round bottom flask. Well-ground **21** (150 g, 0.62 mol) was added slowly, and the temperature was maintained for 4.5 h. The flask was put under vacuum (2 mmHg) for 3 h at the same temperature to remove the excess water. Vacuum was then removed by filling the flask with argon and was kept at

120 °C for another 2 h. The crude mixture was cooled down to rt and H₂O (400 mL) was added to quench the reaction, which was stirred overnight. It was diluted by another 400 mL H₂O, and then extracted by ether (400 mL×4). Ether layer was washed in turn by 400 mL water, 400 mL of 10% aq. NaHCO₃, and 400 mL water. Organic layer was dried over MgSO₄ and filtered. Upon removal of solvent, a red solid (136 g) was isolated after drying on high vacuum. This material was pure **20** (0.61 mol, 95.8%) according to ¹H-NMR, which was used for the next step without further purification. Further purification of this material on small scale could be performed as follow: crude **20** (1.4675 g, 6.60 mmol) was dissolved in minimum amount of CH₂Cl₂ and loaded onto a silica gel column, which was eluted by a 10:1 mixture of hexanes and EtOAc to get 1.3190 g (5.93 mmol, 89.8% yield) pure **20**.

Spectral data for **20**: white solid; mp = 63.1-63.7 °C (lit. value:⁵⁰ 65 °C); *R_f* = 0.07 (1:9 EtOAc/hexane). ¹H-NMR (CDCl₃, 300 MHz) δ 2.62-2.88 (m, 2H), 3.00-3.19 (m, 2H), 3.24-3.38 (m, 1H), 7.24-7.39 (m, 7H), 7.50 (td, 1H, *J* = 7.5, 1.2 Hz), 8.08 (dd, 1H, *J* = 7.5, 0.9 Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 27.54, 37.66, 41.08, 45.93, 126.66, 126.92, 126.96, 127.18, 128.77, 128.83, 132.06, 133.78, 143.40, 197.81; mass spectrum, *m/z* (% rel intensity), 222 M⁺ (100), 118 (90), 104 (42), 90 (68), 89 (56), 78 (32), 63 (20), 51(27).

For more conditions, see **Table 2.9, Chapter two**.

7.2.1.3 The standard procedures to prepare **16a** by dehydrogenation of **20**.



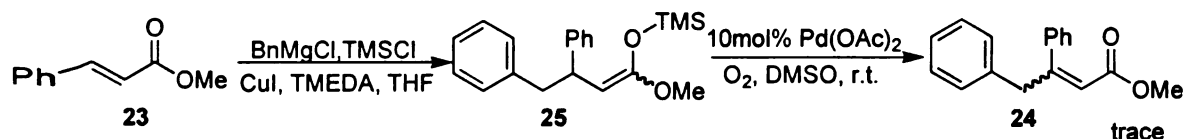
Tetralone **20** (92 g, 0.41 mol) was dissolved in 1 L mesitylene in a 2 L flask charged with a stirrer bar and bubbled with argon for 30 min. Pd/C (6.1 g, 10% wt, 1.4 mmol% of Pd) was added and the flask was connected to a condenser. The mixture was refluxed with a gentle flow of N₂ on top of the condenser. The reaction was tracked *via* TLC; after 113 h the flask was cooled down to rt (it was incomplete) and filtered off Pd/C through Celite, which was washed thoroughly by mesitylene (300 mL). The solution was extracted by 0.9 M aq. KOH (500 mL×3), TLC shows that ArOK was in water layer with a little bit of impurities. Water layer was washed with 200 mL hexanes, and subsequently acidified with 6 N HCl to pH~0. Solid was filtered and dried in *vacuo* to give 61.3 g **16a** (0.28 mol, 67%) as grey solid. Mesitylene could be recovered by vacuum distillation (56-60 °C / 10 mmHg) and a red residue was produced. Attempts to isolate **16a** from this material by column chromatography (hexanes: ethyl acetate = 6:1) failed to produce any pure **16a**. Further purification of obtained **16a** could be completed by crystallization in hexanes/ CH₂Cl₂, cooled to -20 °C to get 43.1 g (195.7 mmol, 70% recovery) of **16a** white crystal.

Spectral data for **16a**: white solid; mp = 96.0-97.5 °C (lit. value:^{17b} 96-97.5 °C);

$R_f = 0.48$ (1:3 EtOAc/hexane). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 5.32 (s, 1H), 7.06 (s, 1H), 7.34 (t, 1H), 7.41-7.50 (m, 4H), 7.62-7.64 (m, 3H), 7.82 (d, 1H, $J = 10$ Hz), 8.13 (d, 1H, $J = 9$ Hz); $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 108.41, 118.73, 121.39, 123.47, 125.34, 126.86, 127.20, 127.37, 127.99, 128.75, 134.85, 138.73, 140.67, 151.47, two carbons not located; mass spectrum, m/z (% rel intensity), 220 M^+ (100), 191.0 (45), 189.0 (30), 165.0 (23), 95 (23), 55 (21), 43 (25).

For more conditions, see **Table 2.10, Chapter two**.

7.2.1.4 Preparation of **24** via dehydrosilylation reaction of intermediary **25**.⁶⁴

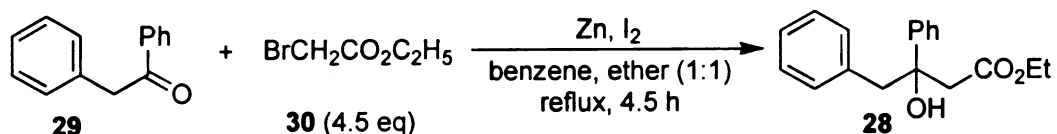


Intermediate **25** was made *via* the optimized procedures in **section 7.2.1.1** from 0.815 g (5.0 mmol) of **23**. Upon completion, the volatiles of the crude reaction mixture of the Michael reaction was removed by evaporator and the residue was put on high vacuum (2 mmHg) for 15 min. Hexanes (30 mL) was added and stirred for 30 min, solid was removed *via* filtration and washed by 150 mL hexanes three times. After removal of hexanes, residue (2.15 g) was combined with $\text{Pd}(\text{OAc})_2$ (0.1268 g, 10 mol%) and 100 mL dry DMSO in a 250 mL flask charged with a stirrer bar. The flask was flushed with O_2 for 15 min and the contents were stirred at 25 °C for 72 h. DMSO was removed by vacuum distillation, the residue was put on silica gel column, eluted by hexane: ethyl acetate=20:1. Trace amount of **24** (< 5 mg) was isolated and detected on $^1\text{H-NMR}$

spectrum.

7.2.2 Preparation of 16a via Reformatsky reaction pathway (Section 2.3)

7.2.2.1 Preparation of 28 by Reformatsky reaction:



Literature procedures.⁵⁰ Activation of Zinc: Zinc dust (10 g, 40 mesh) was stirred with 2% HCl (100 mL) at 25 °C for 15 min. After filtration, Zn was washed by 100 mL 2% HCl, followed by 100 mL water, 100 mL ethanol and then 100 mL ether three times. Zn dust was dried under high vacuum (1 mmHg) overnight.

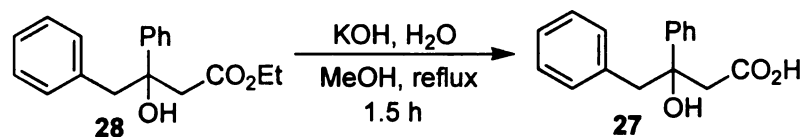
A flame-dried 100 mL 3-neck flask was charged by a stirrer bar and fitted with a condenser. To the flask was added with 9.25 g Zn (142 mmol) and the solution of 29 (1.96 g, 10 mmol) in 20 mL benzene-ether (1:1), followed by three small I₂ crystals. The solution of 30 (5 mL, 45 mmol) in 5 mL benzene was slowly added to the flask *via* syringe pump in 75 min under mild reflux. The reaction mixture was refluxed for another 4.5 h. Zn was removed by filtration and washed with 100 mL ether three times. The organic solution was combined with 100 mL 2 M HCl, the aqueous layer was extracted with 50 mL ether for three times, dried with MgSO₄ and filtered. Ether was removed by evaporator. The residue was dissolved by minimum of CH₂Cl₂ and loaded onto a silica gel column, which was eluted by a mixture of ethyl acetate with hexane (1: 10) to get 2.522 g (8.87 mmol, 88.0% yield) of 28.

Spectral data for **28**: Wax-like white solid. mp = 58.5–60.0 °C (lit. value:⁵⁰ 57–8 °C); R_f = 0.36 (1:5 EtOAc/hexane). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 1.05 (t, 3 H, J = 6.9 Hz), 2.82 (d, 1H, J = 15.9), 2.95–3.09 (m, 3H), 3.95 (q, 2H, J = 7.2 Hz), 4.20 (s, br, 1H); 6.97–7.34 (m, 10H); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 13.57, 43.32, 49.60, 60.37, 74.94, 124.91, 126.20, 126.62, 127.44, 127.68, 130.48, 136.01, 145.09, 172.50; Anal. calcd for $\text{C}_{18}\text{H}_{20}\text{O}_3$: C, 76.03; H, 7.09. Found: C, 75.91; H, 6.99.

Revised procedure.^{66b} 50 mL 3-neck flask was charged by a stirrer bar and fitted with a condenser. To the flask was added with 2.5 g Zn (38.5 mmol), **29** (0.9873 g, 5 mmol), and 3 small I_2 crystals. Then the system was flushed with N_2 gas, followed by 10 mL benzene-ether (1:1) solvent. The solution of **30** (2.5 mL, 22.5 mmol) in 2.5 mL benzene was slowly added to the flask *via* syringe pump in 75 min under mild reflux. The reaction mixture was refluxed for 4.5 h. The workup and purification procedure were the same as the original procedures. The product **28** (1.3810 g, 4.86 mmol, 97.2%) can be obtained as white solid.

For more conditions, see **Table 2.11, Chapter two**.

7.2.2.2 Synthesis of acid **27** by hydrolysis of ester **28**.

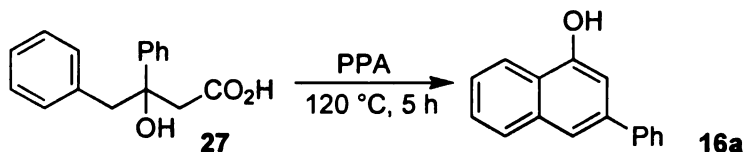


Ester **28** (2.52 g, 8.8 mmol) was refluxed with aqueous KOH (5.6 g, 100 mmol in 75 mL water) in MeOH (20 mL) in a 250 mL flask for 2 h and cooled the solution to rt. After washing by 50 mL hexane, water layer was acidified by 6 N HCl to

pH~0, followed by extraction with 50 mL ether three times. Ether layer was dried over MgSO₄, and the solvent was subsequently removed to get 2.06 g (8.0 mmol, 91.5 % yield) product **27** was obtained as white solid.

Spectral data for **27**: Wax-like white solid; mp = 118-119.5 °C (lit value⁵⁰ 120 °C); *R_f* = 0.11 (1:5 EtOAc/hexane) ¹H-NMR (CDCl₃, 300 MHz) δ 2.90 (dd, 2H, *J* = 16.5, 75 Hz), 2.93-3.09 (m, 3H), 6.95 (s, 1H), 7.06-7.50 (m, 9H); ¹³C NMR (CDCl₃, 75 MHz) δ 43.04, 49.54, 74.88, 124.78, 126.39, 126.88, 127.56, 127.87, 130.41, 135.53, 144.53, 177.42.

7.2.2.3 Synthesis of **16a** through Friedel-Crafts cyclization of **27**.



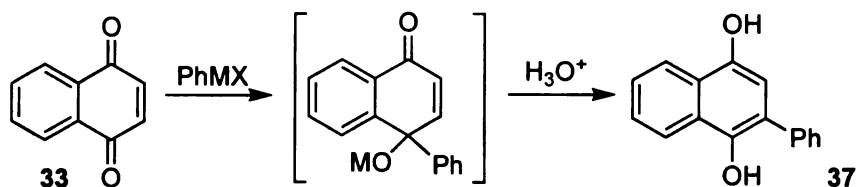
Cyclization of **27 using PPA.** Acid **27** (2.06 g, 8.05 mmol) was heated with 20 g PPA at 120 °C (oil bath temperature) for 5 h under stirring in a 100 mL flask. The crude mixture was cooled down and 30 mL water was added to quench the reaction, extracted by 30 mL CH₂Cl₂ 3 times. Organic layer was washed by 50 mL water, and dried by MgSO₄ and filtered, upon removal of solvent, residue was dissolved in minimum amount of CH₂Cl₂ and loaded onto a silica gel column and eluted by hexanes: ethyl acetate= 7:1. Pure **16a** could be isolated (0.383 g, 1.74 mmol, 21.6%).

for one hour. The residue was used directly for the following reactions without further purification.

The crude acid chloride was dissolved in 40 mL benzene under argon and cooled to 0 °C. Anhydrous SnCl₄ 2.5 mL (21.8 mmol) was injected to the stirred solution, which turned red immediately. The reaction mixture was stirred at 0 °C for 3 h before quenching with an ice-cold solution of 5 mL of concentrated HCl in 50 mL water and the solution refluxed for 30 min. After extraction with 30 mL ether three times, the organic layer was dried over MgSO₄, filtered and the solvent was stripped off over vacuum. The residue was dissolved in minimum amount of CH₂Cl₂ and loaded onto a silica gel column, which was eluted with hexane-ethyl acetate (6:1) and 0.5288 g (2.40 mmol, 51.2%) of **16a** can be afforded as white flakes.

For more conditions, see **Table 2.13** of **Chapter two**.

7.2.3 Attempted preparation of **16a** via dienone-phenol rearrangement - pathway



Addition of PhMgBr to 33 (MX= MgBr). In a 500 mL round-bottom flask were placed **33** (1.58 g, 10 mmol) and THF (200 mL) under nitrogen. The solution was cooled to -78 °C and maintained throughout the reaction. Added to the **33**

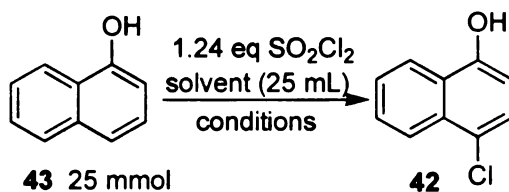
solution was a dry THF (10 mL) solution of the PhMgBr (10 mmol, from Sigma-Aldrich). The resulting mixture was stirred for 30 min. The reaction mixture was then poured through 5% aqueous NH₄Cl (150 mL) to quench the reaction and extracted with dichloromethane (2×40 mL). The organic phase was washed with water (3×60 mL) and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure to get a reddish black tarry product.

Addition of Ph₂Cd reagents to 33 (MX= CdPh).^{80d} In a two-neck, 250 mL roundbottom flask equipped with a condenser and a stir bar were placed anhydrous CdCl₂ (0.740 g, 4.2 mmol) and THF (60 mL). The CdCl₂ suspension was cooled below -10 °C and purged with nitrogen. PhMgBr solution (8.0 mmol) was then introduced *via* syringe and the resulting solution was allowed to warm to rt. Heat was then applied, and the mixture was refluxed for 1 h. The solution was then returned to -10 °C. To this solution the solution of **33** (0.6562 g, 4.15 mmol of quinone in 10 mL of THF) was then added. The resulting solution was stirred for 1 h at -10 °C, after which time the reaction mixture was raised to rt. TLC showed the conversion was not complete, and it was warmed in a 50 °C oil bath for 1 h. The reaction mixture was then poured into water (200 mL) and extracted with dichloromethane (2×40 mL). The organic phase was washed with water (3×60 mL) and dried over anhydrous MgSO₄ and filtered. The solvent was removed and a dark-green solid was obtained.

For more conditions, see **Table 2.14, Chapter two.**

7.2.4 Preparation of 16a via condensation reaction of 42

7.2.4.1 Preparation of 4-chloro-1-naphthol (42) by chlorination of 43



Literature procedures.^{88a} 1-naphthol (**43**, 3.61 g, 25.5 mmol) was dissolved in 20 mL chloroform in a 100 mL 3-neck flask equipped with stirrer bar, a condenser and an additional funnel under N₂. SO₂Cl₂ (2.5 mL, 31.1 mmol) in 5 mL chloroform was added to the solution *via* an additional funnel slowly over a period of 3 h at 25 °C. The reaction was stirred overnight, and then refluxed for 30 min. To the crude reaction mixture was added 50 mL hexanes, and the volatiles were removed by evaporator. Residue was crystallized in boiling CH₂Cl₂ and saturated by hexanes to get 1.24 g (6.96 mmol, 27.3%) needle-like crystal. The solvent in the mother liquor was removed in *vacuo* and crystallized in CH₂Cl₂ and hexanes in the same manner, additional 0.671 g (3.75 mmol, 14.7%) product obtained. The yield of **42** is 42.0%.

Spectral data for **42**: Needle-like gray solid; mp = 119-120.5 °C (lit. value.^{88a} 120-1 °C); *R_f* = 0.41 (1:3 EtOAc/ hexane). ¹H-NMR (CDCl₃, 300 MHz) δ 5.10 (br s, 1H), 6.71 (d, 1H, *J* = 9.0 Hz), 7.36 (d, 1H, *J* = 9 Hz), 7.51-7.63 (m, 2H), 8.20 (d, 2H, *J* = 9 Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 108.04, 121.95, 123.25, 124.16, 125.30, 125.54, 125.76, 127.44, 131.28, 150.45.

The final optimized procedures to prepare 42 in DCE at 0 °C before scaleup. 1-naphthol (**43**, 3.60 g, 25.0 mmol) was heated to dissolve in 20 mL DCE in a 100 mL flask equipped with stirrer bar and a bubbler under N₂. It was then cooled to 0 °C for 30 min. Crystal formed at this temperature. SO₂Cl₂ (2.5 mL, 29.9 mmol) in 5 mL DCE was slowly added to the solution *via* a syringe pump over a period of 3 h. The ice-water bath was then removed and the reaction was stirred for 30 min. To the crude mixture was added 100 mL hexanes to quench the reaction, and the solvents were removed under vacuum. The crude mixture was crystallized in boiling CH₂Cl₂ and saturated by hexanes, cooled to –20 °C to get 3.12 g (17.5 mmol, 70.0%) **42** as needle-like crystal.

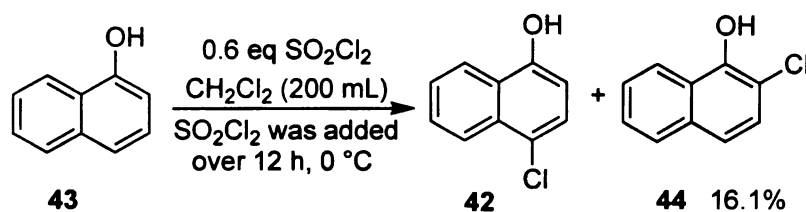
For more conditions, see **Section 2.63, Chapter two**.

Preparation of 42 by chlorination of 43 in DCE on large scale. 1-Naphthol (**43**, 120 g, 832.3 mmol) was combined with 900 mL 1,2-dichloroethane (DCE) in a 2 L 3-necked round-bottom flask, which was warmed gently with a heat gun to dissolve the solid. The flask was equipped with a 48x18 mm oval magnetic stir bar, a pressure compensating addition funnel and the other two necks were sealed with glass stoppers. The top of the addition funnel is vented to a bubbler and then into a beaker filled with aqueous NaOH to trap acidic gases (HCl and SO₂). The flask and its contents were cooled to 0 °C and SO₂Cl₂ (90 mL, 149.9 g, 97%, 1076.9 mmol) was added over 3.5 h from the addition funnel while stirring. The mixture was stirred for 0.5 h at 0 °C, and the ice-water bath was removed and

the temperature was increased to room temperature over 2.5 h. Upon completion of the reaction, the contents of the flask are purged for 30 min with N₂ introduced *via* a glass tube below the surface of the solution to remove excess gasses prior to workup. The solvent was removed *via* rotary evaporator and the crude product was crystallized from a minimum amount of boiling DCE (about 200 mL). After allowing to slowly cool to rt, filtration gave 83.62 g (468.1 mmol, 56.2%) of **42** as light steel-green needle-like crystals (mp 118-119.5 °C, literature value:^{88a} 119-120 °C). The filtrate was poured into 500 mL of hexanes and additional product (20.00 g, mp 113.0-114.0 °C) could be isolated after cooling down to -20 °C and filtration. This material was crystallized from a minimum of boiling DCE (about 30 mL) to give 13.75 g (76.98 mmol, 9.2%, mp 117.1-118.1 °C) of **42** as needle-like crystals that had essentially the same coloration as the first crop. The combined filtrates were dried and the residue (about 50 g) was dissolved in 200 mL CH₂Cl₂ and then combined with 80 g (about 200 mL) of dry silica gel in a single-necked flask. The solvent was removed from the silica gel by purging with a nitrogen stream that was vented to a bubbler. A chromatography column (6 cm diameter) was prepared by filling the column with a 1:50 mixture of ethyl acetate and hexanes and then the addition of silica gel such that after settling a depth of *ca.* 35 cm had been reached. The dried silica gel with the pre-adsorbed product was added to the solvent above the prepared bed and allowed to settle. The solvent level was lowered to the top of the column

and then a layer of sand was applied. The silica gel column was first eluted with a 50:1 mixture of hexanes to ethyl acetate under gravity for at least 1 h, then switched to 10:1 mixture of hexanes to ethyl acetate under pressure. The byproducts (**44** and **45**) were first eluted, followed by **42** (11.37 g, 63.65 mmol, 7.6%, mp 116.8-117.8 °C). The combined yield is 108.7 g (608.7 mmol, 73.0%).

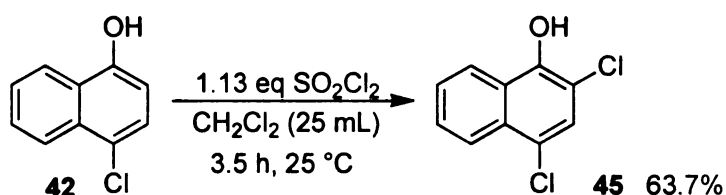
7.2.4.2 Preparation of **44** by chlorination of **43**.



1-naphthol (**43**, 7.2 g, 50 mmol) was dissolved in 195 mL CH_2Cl_2 in a 500 mL 3-neck flask equipped with stirrer bar under N_2 , which was cooled down to 0 °C. SO_2Cl_2 (2.5 mL, 30 mmol) was combined with 5 mL CH_2Cl_2 in a syringe and added to the solution *via* syringe pump slowly over 12.5 h at 0 °C. The reaction was stirred 30 min at rt. The mixture was poured onto 100 mL hexanes and the solvent was completely removed by evaporator. Crude solid (7.85 g, $^1\text{H-NMR}$ ratio of **43**: **42**: **44** = 1: 0.5: 0.4) was dissolved in minimum amount of CH_2Cl_2 and poured into 100 mL hexane, cooled down to -20 °C. The precipitation (mainly **43** and **42**) was filtered off, and the solvents in the mother liquor were evaporated. The residue was dissolved in minimum of CH_2Cl_2 , loaded onto a column and eluted by 10:1 mixture of hexanes to ethyl acetate under pressure to afford 1.4346 g (8.0 mmol, 16.1%) of **44**.

Spectrum data for **44**: white solid; mp 64 - 65 °C (lit. value^{88e} 65 °C). R_f = 0.53 (1:3 hexanes/EtOAc). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 5.98 (s, 1H), 7.34 (s, 2H), 7.48-7.58 (m, 2H), 7.74-7.89 (m, 1H), 8.19-8.28 (m, 1H); ^{13}C (CDCl_3 , 75 MHz) δ 113.20, 120.58, 121.72, 124.07, 125.53, 125.73, 126.32, 127.26, 132.89, 146.70;

7.2.4.3 Preparation of **45** by chlorination of **42**.

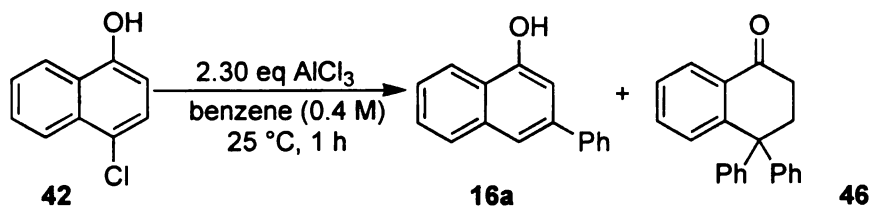


42 (1.887 g, 10 mmol) was dissolved in 20 mL CH_2Cl_2 in a 100 mL flask equipped with stirrer bar and condenser under N_2 at 25 °C. SO_2Cl_2 (1 mL, 12.6 mmol) was combined with 5 mL CH_2Cl_2 in a syringe and added to the solution *via* syringe pump slowly over 13 h at rt and continued to stir for 30 min. The mixture was poured onto 100 mL hexanes and the solvent was completely removed by evaporator. Crude solid was dissolved in CH_2Cl_2 and then 100 mL hexane was added. All solvents were evaporated once again to make sure all the unreacted SO_2Cl_2 and produced HCl and SO_2 had been got rid of. The crude mixture was dissolved in minimum of CH_2Cl_2 , put on the column and eluted by 10:1 mixture of hexanes to ethyl acetate under pressure to afford 1.44 g (6.75 mmol, 63.7%) of **45** as white needle-like crystal.

Spectrum data for **45**: white solid; mp 101 - 102 °C (lit. value:^{88e} 107-8 °C). R_f = 0.52 (1:3 hexanes/ EtOAc), $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 5.93 (s, 1H), 7.47 (s,

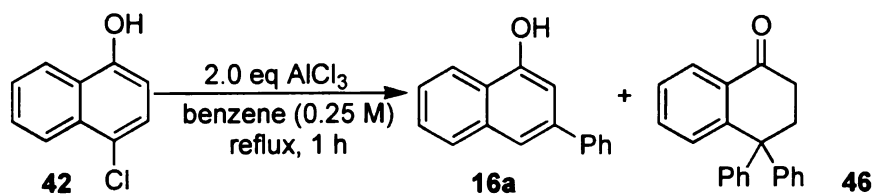
1H), 7.57-7.70 (m, 2H), 8.16 (dd, 2H, $J = 24.9, 3.9$ Hz); ^{13}C (CDCl_3 , 75 MHz) δ 112.35, 122.17, 123.10, 124.10, 124.63, 125.13, 126.54, 127.35, 129.94, 146.05;

7.2.4.4 Preparation of 16a via the condensation of 42 with benzene.



Modified procedures from literature.^{88e} A 25 mL flask was charged with stirrer bar, AlCl_3 (1.3100 g, 9.8 mmol) and argon. The solution of **42** (0.7089 g, 4.0 mmol) in 10 mL benzene was injected to the flask while stirring and the solution changed to red immediately. The reaction was stirred for 1 h before it was poured to ice, which was extracted with ether for 3 times and dried over MgSO_4 and filtered. Most of ether was removed under vacuum, the residue was absorbed on silica gel and dried over N_2 , then loaded to column, eluted by a mixture of hexane: ethyl acetate (6:1). A byproduct **46** was first eluted, followed by **16a** (0.4996 g, 2.27 mmol, 57.2%) as white flurry solid.

The isolated byproduct (0.5417g, 1.82 mmol, 45.4%) was **46**. Spectral data for **46**: white solid; mp = 179.0-185.0 °C (lit value:⁸⁵ 190-2 °C from acetone); R_f = 0.64 (1:3 EtOAc/hexane). ^1H -NMR (CDCl_3 , 300 MHz) δ 2.51 (t, 2H, $J = 6.3$ Hz), 2.95 (t, 2H, $J = 6.3$ Hz), 6.73 (d, 1H, $J = 9$ Hz), 7.02 (t, 4H), 7.25 (t, 6H), 7.29-7.40 (m, 2H), 8.12 (d, 1H, $J = 6.9$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 35.35, 36.61, 52.95, 126.45, 126.86, 127.24, 127.87, 128.88, 130.58, 132.53, 132.81, 145.43, 149.30, 197.53.



Final optimized procedures in refluxing benzene before scaleup. A

3-neck 100 mL flask equipped with a condenser was charged with stirrer bar, AlCl_3 (1.3776 g, 10.3 mmol) and argon, sealed with rubber septums. To this flask was injected 10 mL dry benzene and then heated to reflux.

The solution of **42** (0.9118 g, 5.1 mmol) in 7 mL benzene was sucked into a syringe, and then 3 mL benzene was used to rinse the flask and was sucked into the same syringe. This solution was injected to the mixture of AlCl_3 and benzene while refluxing and the solution changed to red immediately with white smoke formed. The reaction was refluxed for 1 h before it was poured to 50 g ice/ HCl (6 N, 50 mL), which was extracted with 100 mL ether for 3 times and dried over MgSO_4 and filtered. The ether was removed under vacuum; the residue was dissolved in minimum CH_2Cl_2 and was loaded onto silica gel column, which was eluted by hexane/ethyl acetate (6:1) to afford 1.0114 g (4.6 mmol, 90.1% yield) of **16a** as white flurry solid. Tetralone **46** was not detected.

For more conditions, see **Table 2.15, Chapter two**.

Condensation of 42 with benzene to prepare 16a on large scale. To a 5 L 3-necked round bottom flask equipped with a mechanical stirrer, condenser and an addition funnel was added AlCl_3 (130.0 g, 975.0 mmol) and then the flask was

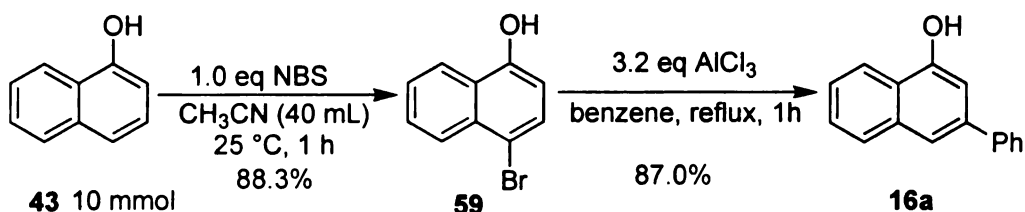
flushed with N₂ for about 0.5 h. Benzene (800 mL, reagent grade) was added to the flask and the slurry was heated to reflux while stirring. **42** (100.1 g, 560.5 mmol) was combined with 1000 mL benzene (reagent grade) in a 2 L flask and the mixture was gently heated with a heat gun to dissolve the solid. This solution was transferred to an addition funnel and was added to the reaction mixture over 1.5 h. Both the 2 L flask and the addition funnel were rinsed with 100 mL benzene twice which was added to the 5 L flask as well. The benzene solution was refluxed for 1 h before it was cooled to room temperature and then 1.0 L of 6 N HCl that had been pre-chilled in an ice-bath was introduced all at once. The resulting mixture was stirred for 30 min. The benzene layer was separated and the water layer was extracted with ether (3 x 600 mL). The combined organic layer was washed with 400 mL water, 400 mL saturated aq NaHCO₃ solution and finally with 400 mL water. The organic layer was dried over MgSO₄ and filtered; all of the solvents were removed by rotary evaporator. The residue (126.7 g) was crystallized by dissolving in boiling CH₂Cl₂ (about 200 mL) and then hexane (about 500 mL) is added with heating such that constant boiling is maintained. The solution was allowed to cool to room temperature and then allowed to cool in a refrigerator overnight. The mixture was filtered to give 103.7 g (471.4 mmol, 84.1%) of **16a** as a fluffy beige amorphous solid (mp 96-97.5 °C, literature value:^{17b} 96-97.5 °C). The solvent of the mother liquor was removed *via* rotary evaporator and the residue (21.75 g) was dissolved in 200 mL toluene, which was

extracted 3 times by aq KOH (50 g in 1 L water, 400 mL + 300 mL +300 mL). The combined aqueous layer was cooled in an ice bath and acidified by 6 N HCl (~200 mL) to pH~1 which was extracted by ether (3 x 400 mL). The combined ether layer was washed with 400 mL water and then dried over MgSO₄. The ether was removed by rotary evaporator and the brownish oily residue was fairly pure 3-phenyl-1-naphthol. Further purification of this material was achieved by column chromatography. The material was dissolved in 100 mL CH₂Cl₂ and combined with 50 g (about 100 mL) of silica gel. The solvent was removed from the silica gel by purging with a nitrogen stream that was vented to a bubbler. A chromatography column (6 cm diameter) was prepared by filling the column with a 1:50 mixture of ethyl acetate and hexanes and then the addition of silica gel such that after settling a depth of 30 to 50 cm had been reached. The dried silica gel with the pre-adsorbed product was added to the solvent above the prepared bed and allowed to settle. The solvent level was lowered to the top of the column and then a layer of sand was applied. Elution with a 1:10 mixture of ethyl acetate:hexanes afford 11.31 g (51.41 mmol, 9.2%, mp 92.5-94.5 °C) **16a** as a light yellow oil. This could be rendered to solid form by dissolving in 50 mL of CH₂Cl₂, addition of 200 mL of hexane and then removal of the solvent by rotary evaporator to provide a fluffy light yellow solid. The total yield is 115.03 g (522.9 mmol, 93.3%).

Note: The procedures of the condensation reaction **42** with benzene to

prepare **16a** on large scale can be applied to the condensation reaction by using **44**, or the mixture of **42** and **44**, or the crude product of the chlorination reaction in **section 7.2.4.1** as the starting materials. See **Table 2.22** of **Chapter two** for details.

7.2.4.5 Preparation of **16a** via the condensation of **59** with benzene.



To a solution of **43** (1.4576 g, 10 mmol) in 40 mL of CH₃CN was added NBS all at once (1.8630 g, 10.5 mmol) at 25 °C while stirring. The color changed to light yellow after 1 h. The solvent was removed in *vacuo*, the residue was dissolved in 30 mL ether and washed with 10 mL water three times, and dried with MgSO₄. The residue was purified by a silica gel column using hexanes:CH₂Cl₂:EtOAc = 20:2:1 to afford 2.06 g **59** (8.92 mmol, 88.3%) as off-white solid.

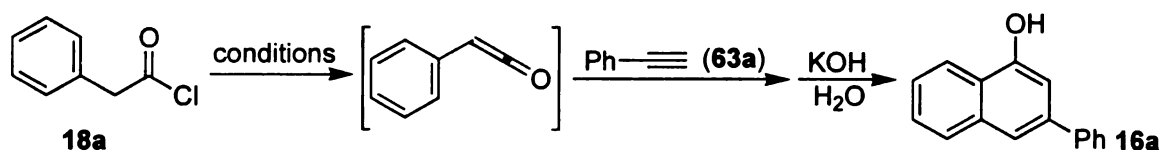
Spectral data for **59**: mp 126-127 °C, decomposed (lit. value:^{88e} 129 °C). *R*_f = 0.40 (1:4 EtOAc/hexane). ¹H-NMR (CDCl₃, 300 MHz) δ 5.24 (br, s, 1H), 6.67 (d, 1H, *J* = 8.1 Hz), 7.50-7.62 (m, 3H), 8.14-8.19 (m, 2H); ¹³C-NMR (CDCl₃, 75 MHz) δ 109.43, 113.72, 122.40, 125.85, 126.29, 127.32, 128.12, 129.63, 132.97, 151.46;

Note: 1) The reaction can be scaled up to 50 g of **43** in the same manner. However, it was found the reaction was incomplete (94% conversion based on

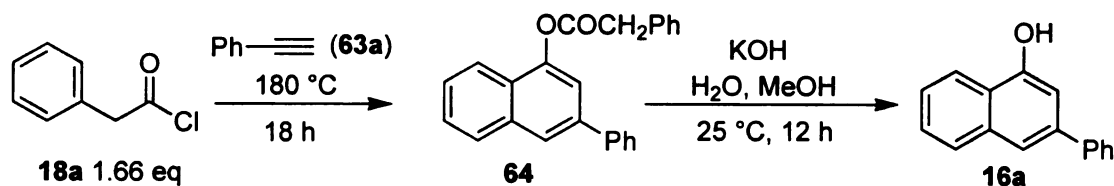
^1H -NMR spectrum, and **59** could be isolated by crystallization in 150 mL DCE with 52% yield) with 2-bromo-1-naphthol as the only detectable byproduct (23.7% isolated yield). It was found NBS was not very soluble in CH_3CN , which made it hard to perform to add NBS slowly to **43**. It was reasoned other solvents could be used to dissolve NBS, and then added slowly to the solution of **43** in CH_3CN . This might be useful to improve the yield of **59**.

2) The procedures of the condensation reaction **59** (490 mg, 2.2 mmol) with benzene (20 mL) and AlCl_3 (936 mg, 7.0 mmol) to prepare **16a** (421 mg, 1.91 mmol, 87%) are the same as the optimized procedures on small scale in section 7.2.4.3.

7.2.5 Preparation of **16a** via the CAEC cascade reaction pathway



7.2.5.1 Thermally induced reaction of **18a** with **63a** under neat conditions

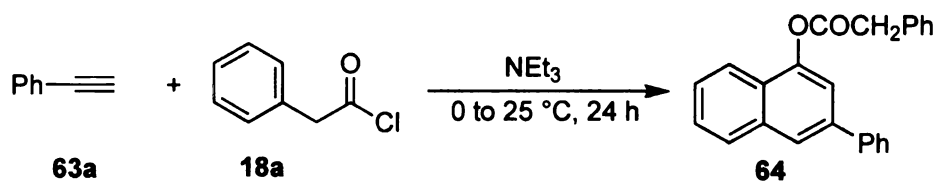


A 50 mL flask equipped with a condenser was charged with stirrer bar and flushed with argon for 5 min. Phenylacetic chloride **18a** (10 mL, 75.5 mmol) and phenylacetylene **63a** (5 mL, 45.5 mmol) was mixed in the flask and heated in a 180 °C oil bath for 16 h.

The crude reaction mixture was cooled to 25 °C and transferred the black tar to a 250 mL flask and stirred with 5 g KOH (89.3 mmol) in a mixture of 10 mL water and 200 mL methanol for 12 h. Most of the MeOH was removed by evaporator. The residue was stirred with 250 mL ether for 30 min and filtered through Celite. Ether layer was washed in turn with 100 mL 6 N HCl, 100 mL brine and dried over MgSO₄ and filtered. This material was refluxed with charcoal for 20 min but the color did not change. Removed the charcoal by filtration, and the solvent was removed in *vacuo*, the residue was dissolved in minimum amount of CH₂Cl₂ and loaded onto a silica gel column, eluted with ether: CH₂Cl₂: hexane = 1:1:8 to get **16a** (6.025 g, 27.4 mmol, 30.0%) as brown solid.

For more conditions, see **Table 2.25, Chapter two**.

7.2.5.2 Base induced reaction of **18a** with **63a** under neat conditions.



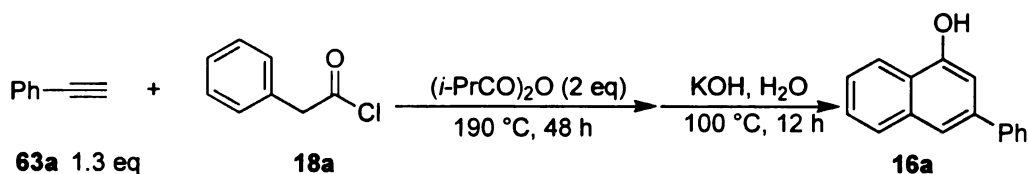
A 25 mL flame-dried flask was charged with a stirrer bar and argon. **18a** (4 mL, 30 mmol) and **63a** (3.3 mL, 30 mmol) was added and cooled to 0 °C. Triethylamine (i.e. TEA, 5 mL, 35.9 mmol) was added in 45 min by a syringe pump, and a lot of yellow precipitation formed immediately. The temperature of the viscous mixture was allowed to rise to 25 °C for 24 h. The reaction was diluted by 100 mL ether and the insoluble solid (TEA·HCl) was filtered off and discarded.

Residue was dissolved in a minimum amount of CH₂Cl₂ and loaded onto a silica gel column, eluted by hexane: EtOAc= 8:1 to get an unknown compound as yellow solid (1.23 g).

Spectral data for this unknown compound: White wax-like solid; *R_f*= 0.22 (1:5 EtOAc/hexane). ¹H-NMR (CDCl₃, 300 MHz) δ 3.13 (s, 1H), 3.74 (s, 1H), 6.67 (dd, 1H, *J* = 1.8, 7.8 Hz), 7.15-7.43 (m, 9H); ¹³C-NMR (CDCl₃, 75 MHz) δ 37.30, 39.89, 116.42, 117.18, 126.83, 126.91, 127.97, 128.20, 128.38, 128.44, 128.62, 128.82, 129.29, 129.82, 130.40, 130.64, 131.52, 135.39, 157.93, 160.13, 162.31, 167.19; IR (neat) 3030 w, 1770 s, 1728 vs, 1562 s, 1495 m, 1132 m, 1099 s cm⁻¹; mass spectrum, *m/z* (relative intensity) 472 (2), 354 (20), 326 (5), 263 (7), 207 (8), 178 (10), 154 (12), 118 (28), 91 (100), 65 (13).

For more conditions, see **Table 2.26** and **2.27** of **Chapter two**.

7.2.5.3 Thermally induced reaction using (*i*-PrCO)₂O as a trapping agent



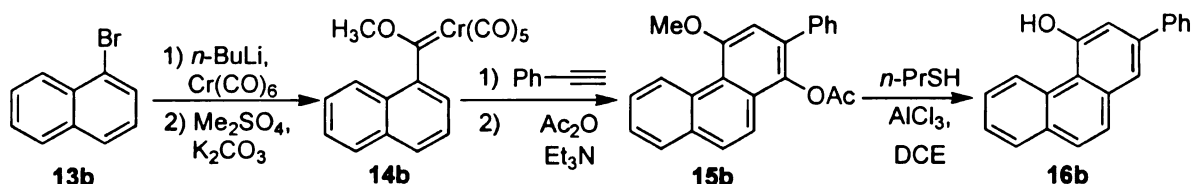
A single-neck 250 mL round bottom flask equipped with a 48x18 mm oval magnetic stir bar was charged with argon, **18a** (10.1 mL, 74.71 mmol), **63a** (11 mL, 100.2 mmol) and isobutyric anhydride (25 mL, 146.2 mmol). A condenser was flushed with N₂, and then connected to the flask. The resulting mixture was heated and stirred in a 190 °C oil bath for 48 h with gentle nitrogen flow across top

of the condenser. The oil bath was cooled to below 100 °C (ca. 60 °C), and then aq. KOH (25 g, 445.6 mmol in 100 mL H₂O) was added. It was stirred and heated in a 100 °C oil bath overnight (12 to 15 h), the orange solution was cooled to 0 °C. It was cautiously acidified by HCl (6 N) until pH~6, and the color of the aqueous layer changed to orange then disappeared. It was then extracted with ether (3×100 mL). The combined organic layer was washed with brine (100 mL) and dried over MgSO₄ and filtered. Most of the solvent in this dark-colored solution was removed on rotary evaporator; the residue was then distilled under vacuum (80 mmHg/ 81-2 °C) to remove *i*PrCO₂H. Residue was dissolved in CH₂Cl₂ and combined with silica gel (ca. 100 mL). After inserting a piece of cotton into the neck of the trap of the rotary evaporator and removing the solvents, both the flask and trap was put on high vacuum (0.5 mmHg) for 30 min. A chromatography column (6 cm diameter) was prepared by filling the column with hexanes and then the addition of silica gel such that after settling a depth of 15 to 20 cm (about 350 mL silica gel) had been reached. The dried silica gel with the pre-adsorbed product was added to the solvent above the prepared bed and allowed to settle. The solvent level was lowered to the top of the column and then a layer of sand was applied immediately. The column was then eluted with a 1:2 mixture of CH₂Cl₂: hexanes under gravity (ca.1 h). When TLC indicated that the product began to elute, elution was continued under N₂ pressure to collect the desired product, which was stripped of solvent by rotary evaporator and then dried at 0.5

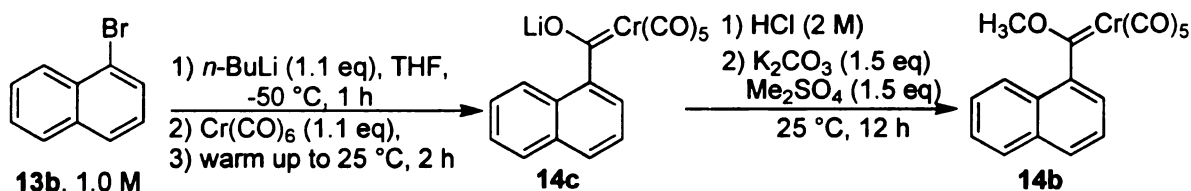
mmHg vacuum overnight to afford 11.5 g (52.2 mmol, 69.9%, mp 95-96 °C, lit. value:^{17b} 96-97.5 °C) of **16a** as baige-colored cotton-like solid.

7.3 Experiments for Chapter three

7.3.1 Preparation of **16b** via Wulff-Dötz benzannulation reaction

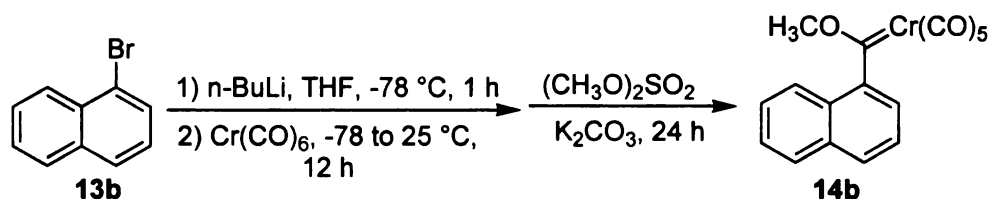


7.3.1.1 Preparation of pentacarbonyl[1-naphthyl(methoxy)chromium] carbene **14b**.



Following literature procedures.^{119,17b,c} To an oven-dried 2 L, 3-necked flask equipped with a stirrer bar and flushed with N₂, was added 60 mL (418.5 mmol) of 1-bromonaphthalene. One liter of dry THF was added to the flask and the resulting solution was cooled to -50 °C (dry ice/ ethanol) for 30 min. *n*-butyllithium (190 mL, 475 mmol, 2.5 M) was added *via* cannula over a 15 min period. The mixture was stirred for 1 h at -50 °C to afford a bright yellow slurry. To this slurry was added 105 g (477 mmol) of Cr(CO)₆ *via* a powder funnel followed by a brief N₂ flush. The reaction mixture was allowed to warm to ambient temperature over 2 h. The dark brown reaction mixture was suction filtered through a 3 cm bed of packed Celite in a 12 cm diameter Büchner funnel. The filtrate was poured into a

2 L separatory funnel, diluted with 200 mL of diethyl ether, and washed twice with 400 mL of HCl (2 M). The resulting red organic layer was quickly added to a 2 L, 3-necked flask containing 90 g (651 mmol) of K_2CO_3 and was allowed to stir for 10 min or until bubbling ceased. The orange solution was treated with 62 mL (636 mmol) of $(\text{CH}_3)_2\text{SO}_4$ and was allowed to stir for 12 h at 25 °C. The red solution was decanted from the solid residue by pouring into a 3 cm bed of packed Celite in a 12 cm diameter Büchner funnel under water aspirator vacuum. The solid residue was rinsed twice with 50 mL of CH_2Cl_2 and the solution decanted into the Büchner funnel. The filtrate was diluted with 400 mL of hexanes, and washed with 400 mL of brine. The organic layer was dried over MgSO_4 . The solvent was removed under reduced pressure to afford red oil. Crystallization was achieved by dissolving the solid in 40 mL of CH_2Cl_2 and addition of 170 mL of pentane, followed by cooling to -20 °C for 12 h. The red crystals were harvested by suction filtration, washed by 50 mL pentane twice to afford 99.8 g (275.5 mmol) of **14b**. A second crop of 3.06 g (8.45 mmol) of **14b** was obtained after removal of solvent and dissolving the residue in 25 mL of CH_2Cl_2 , and addition of 40 mL of pentane and cooling to -20 °C for 12 h. The combined yield was 68.5%.



Optimized procedures. To a dry 2 L 3-necked round-bottom flask equipped

with a stirrer bar and an addition funnel was flushed with N₂ overnight, and 1-bromonaphthalene (60 mL, 418.5 mmol) was added followed by 400 mL of freshly distilled tetrahydrofuran under positive pressure of N₂. As the solution was cooled to -78 °C in dry ice/ acetone bath and the temperature was equilibrated for 30min while stirring, *n*-butyllithium (190 mL, 2.5 M in hexane, 475.0 mmol) was transferred to the addition funnel *via* cannula, and then it was added to 1-bromonaphthalene over 15min. The mixture was stirred for 1h at -78 °C to form a milk-like yellow slurry. Chromium hexacarbonyl (105 g, 477.0 mmol) was added through a powder funnel to this slurry, and the reaction mixture was allowed to warm to room temperature overnight under positive N₂. To this dark brown reaction mixture was added K₂CO₃ (90 g, 651.2 mmol) and (CH₃O)₂SO₂ (62 mL, 635.9 mmol) and the resulting red suspension was stirred for 24 h before it was suction filtered through a 2.5 cm bed of packed Celite in a 13.5 cm diameter Büchner funnel. Both the flask and the funnel were rinsed with 400 mL of CH₂Cl₂ till the filtrate was light yellow. The organic solvent was removed by rotary evaporator and the resulting red oil was combined with 150 mL hexanes, which was cooled down to -20 °C overnight. The red crystal was collected by suction filtration to give 118.66 g (327.6 mmol, 78.3%, mp 86-7 °C, lit. value:^{17b} 89-90 °C) of **14b** after vacuum for at least 24 h. The filtrate was dried and the residue was mixed with minimum amount of hexanes and loaded onto silica gel (about 45 cm long after settling down) column (4.5 cm diameter) prepared by hexanes, and

eluted by hexanes to get 11.83 g (32.7 mmol, 7.8%) red solid (mp 89.0-90.5 °C).

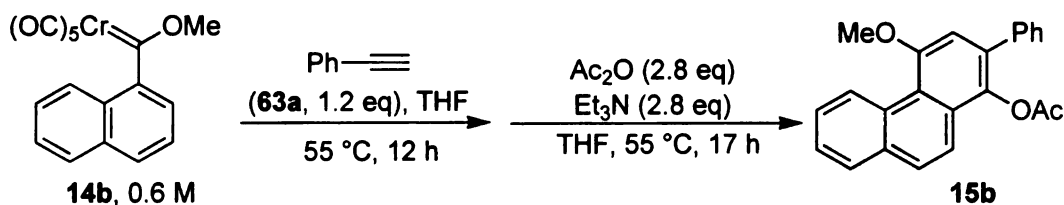
The total yield of **14b** is 130.5 g (360.3 mmol, 86.1%).¹¹⁹

Spectral data for **14b**: red crystal. R_f = 0.23 (hexanes: ethyl acetate = 9:1).

$^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 4.16 (br s, 3H), 7.03 (d, 1H, J = 4.8 Hz), 7.51 (s, 4H), 7.77-7.86 (d, 2H, J = 25.5 Hz); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 66.00, 118.77, 123.70, 124.24, 124.90, 125.13, 126.79, 127.40, 128.70, 128.95, 133.34, 216.12, 225.00, one carbon not located.

For more conditions, see Table 3.1 and 3.2, Chapter three.

7.3.1.2 Preparation of 1-acetoxy-4-methoxy-2-Phenylphenanthrene **15b**.



A dry 2 L 3-necked round-bottom flask equipped with a reflux condenser was purged with nitrogen overnight, and then naphthyl carbene complex **14b** (110.0 g, 303.6 mmol) was added followed by 500 mL of dry THF under positive pressure of nitrogen. The solution was heated at 55 °C with gentle N_2 flow blowing through the top of the condenser. Phenylacetylene (**63a**, 40 mL, 356.9 mmol) in 5 mL THF was added slowly by means of a syringe pump over 3 h, and then the temperature was maintained for 12 h. Upon examination by TLC to confirm that consumption of the carbene complex was complete, triethylamine (120 mL, 865.7 mmol) and acetic anhydride (80 mL, 846.3 mmol) were added and the resulting solution was

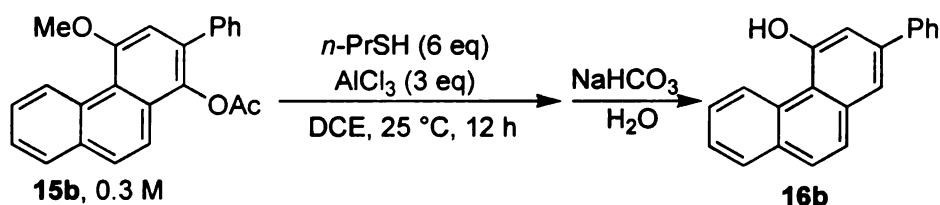
heated at 55 °C for 17 h under nitrogen. The solvent was removed by rotary evaporator upon cooling, the residue was dissolved in 500 mL CH₂Cl₂ which was washed with water (400 mL) twice and dried over MgSO₄ followed by filtered through Celite. The filtrate was stripped of solvents to give a brown crude product (110 g). Minimum amount of boiling ethyl acetate (350 mL to 400 mL) was used to crystallize this crude product, cooled down to room temperature for 12 h then to -20 °C overnight to give a greenish yellow crystal **15b** (67.5 g, 197.1 mmol, 64.9%, mp 158.5-159.5 °C). Residue from the dried mother liquor was crystallized in 50 mL ethyl acetate to afford additional **15b** (5.2 g, 15.2 mmol, 5.0%, mp 155.5-156.5 °C, lit. value:^{17b} 160-1 °C). More of compound **15b** (7.2 g, 21.0 mmol, 6.9%, mp 147.5-148.5 °C) was obtained from the mother liquor *via* flash chromatography as follow: mother liquor was combined with 30 g silica gel and dried under gentle N₂ flow. This material was put on a column prepared by EtOAc:CH₂Cl₂:hexane =1:2:20 with silica gel (ca. 700 mL, which made a 40 cm long silica gel in a 5 cm diameter column). It was eluted by EtOAc:CH₂Cl₂:hexane =1:2:20 to get the product with some impurities, which was further purified by boiling with 20 mL EtOAc and then saturated by 100 mL hexanes and cooling to -20 °C. The total isolated yield of **15b** is 79.9 g (233.4 mmol, 76.7%).

Spectral data for **15b**: white solid, *R*_f = 0.23 (1:9 EtOAc: hexane). ¹H-NMR (CDCl₃ 300 MHz) δ 2.19 (s, 3H), 4.14 (s, 3H), 7.13 (s, 1H), 7.36 (t, 1H, *J* = 7.3 Hz), 7.43 (t, 2H, *J* = 7.6 Hz), 7.53-7.63 (m, 4H), 7.70 (d, 1H, *J* = 8.9 Hz), 7.78 (d, 1H, *J*

= 9.0 Hz), 7.85 (d, 1H, J = 7.8 Hz), 9.62 (d, 1H, J = 8.8 Hz); ^{13}C NMR (CDCl_3 75 MHz) δ 20.74, 55.98, 109.56, 119.50, 120.95, 126.30, 126.89, 127.52, 127.63, 128.35, 128.43, 128.56, 129.06, 129.30, 130.09, 131.93, 132.47, 137.34, 138.02, 156.65, 169.70.

For more conditions, see **Table 3.3 of Chapter three**.

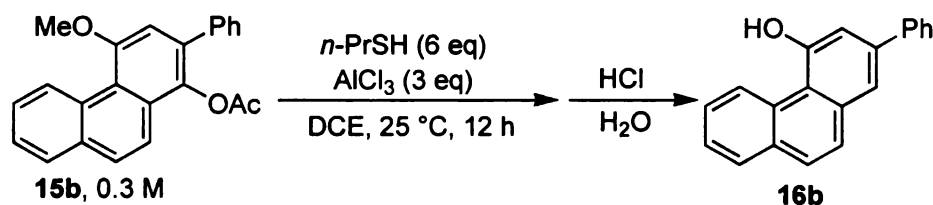
7.3.1.3 Preparation of 3-phenylphenanthrol **16b**:



Literature procedures: workup with base.^{119,17b,c} A dry 500 mL 3-necked round-bottom flask equipped with a stirrer bar was purged with N_2 . AlCl_3 (23 g, 174.3 mmol) was added followed by 200 mL of DCE, and $n\text{-PrSH}$ (32 mL, 353 mmol). The resulting mixture was stirred for 15 min to give a yellow solution before **15b** (20.0 g, 58.4 mmol) was added in four portions over 30 min. The resulting red slurry was stirred at 25 °C for 12 h. The crude reaction mixture was concentrated to about 100 mL by heating the flask to 50 °C by connecting it to an aspirator with volatiles collected in a trap consisting of a 2 L 3-necked flask which was cooled to -78 °C in a dry ice/ acetone bath. The remaining contents were cooled in ice bath for at least 30min, and then poured into a 500 mL separatory funnel, diluted with 100 mL of CH_2Cl_2 , and carefully treated with 20 mL aliquots of saturated aq. NaHCO_3 until bubbling ceased. The resulting dark orange organic

layer was suction filtered through a 3 cm bed of wet packed silica gel in a Büchner funnel, washed three times with CH₂Cl₂ (50 mL). It was concentrated under reduced pressure to a volume of 50 mL and cooled to -20 °C overnight, the precipitate was collected by filtration and washed with pentane to get 7.58 g of **16b** (28.1 mmol). The filtrate was dissolved in a minimum amount of CH₂Cl₂ and loaded onto silica gel, eluted with a mixture of hexanes and CH₂Cl₂ (1:1) to afford the 2nd crop (1.80 g, 6.67 mmol) The two crops were combined to give 59.5% yield of **16b** as an off-white solid.

Spectral data for **16b**: R_f = 0.33 (1:5 EtOAc:hexane); ¹H-NMR (CDCl₃, 500 MHz) δ 5.71 (s, 1H), 7.18 (s, 1H), 7.35 (t, 1H, J = 7.5 Hz), 7.45 (t, 2H, J = 7.6 Hz), 7.55 (t, 1H, J = 7.2 Hz), 7.72 (t, 1H, J = 7.4 Hz), 7.64-7.70 (m, 5H), 7.84 (d, 1H, J = 7.8 Hz), 9.58 (d, 1H, J = 8.5 Hz); ¹³C NMR (CDCl₃ 75 MHz) δ 112.20, 118.52, 119.86, 125.99, 126.65, 127.21, 127.62, 128.25, 128.42, 128.89, 130.13, 132.57, 135.27, 139.17, 140.09, 154.61 (two carbons not located).



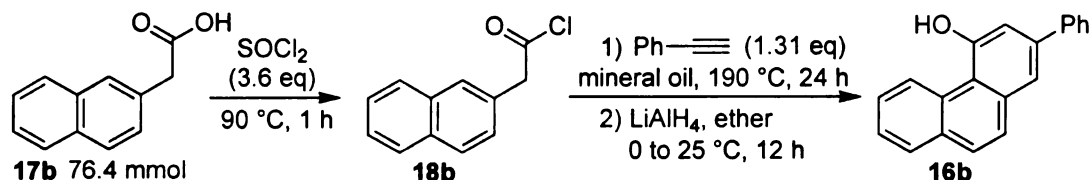
Optimized procedures: workup with HCl. A dry 2 L 3-necked round-bottom flask equipped with a stirrer bar was purged with nitrogen overnight, and AlCl₃ (93 g, 645.1 mmol) was added followed by 900 mL of dichloroethane (*i.e.* DCE), and *n*-PrSH (125 mL, 1.38 mol). The resulting mixture was stirred for 20 min to give a

yellow solution before **15b** (79.9 g, 233.4 mmol), to which was added in three portions over 30 min (10 g; 35 g after 15 min and 35 g after 30 min). The resulting red slurry was stirred at 25 °C for 12 h under an N₂ atmosphere. The crude reaction mixture was concentrated to about 500 mL by heating the flask to 50 °C by connecting it to an aspirator with volatiles collected in a trap consisting of a 2 L 3-necked flask which was cooled to -78 °C in a dry ice/ acetone bath. The remaining contents were cooled in ice bath for at least 30 min, quenched slowly with chilled aq. HCl (6 N, 400 mL). The organic layer was separated from a 1 L reparatory funnel and the aqueous layer was extracted by 400 mL CH₂Cl₂ twice, the combined organic layer was washed with 200 mL water, 200 mL saturated NaHCO₃ solution and another 200 mL water, dried with anhydrous MgSO₄. After filtration through Celite and removal of solvent over vacuum, the residue (83.4 g) was combined with 150 mL CH₂Cl₂, cooled down to -20 °C for 12 h, the formed light pink crystal was filtered to get 47.42 g (175.5 mmol, 75.3%, mp 157.5-158.0 °C, lit. value:^{17b} 154-5 °C) VAPOL monomer **16b**. Residue from dried mother liquor was crystallized by boiling with 50 mL CH₂Cl₂ and then saturating with 100 mL hexanes and cooled to rt then to -20 °C to get 2nd crop product 5.01 g (18.55 mmol, 7.95%, mp 153.9-154.5 °C). The total isolated yield of **16b** is 52.43 g (194.1 mmol, 83.2%).

For more conditions, see Table 3.4 of Chapter three.

7.3.2 Preparation of 16b via the CAEC cascade reaction of 18b with 63a

7.3.2.1 In mineral oil as solvent with a LiAlH₄ workup



General procedures to prepare acid chloride 18b: A single-neck 250 mL round bottom flask equipped with a large 48x18 mm oval magnetic stir bar and a condenser was charged with 14.23 g (76.42 mmol, from Milestone Pharm Tech USA Inc., Lot #: T1161) of **17b** and SOCl₂ (20 mL, 274 mmol). The top of the condenser is vented to a bubbler and then into a beaker filled with aq. NaOH to trap acidic gases (HCl and SO₂). The mixture was heated to reflux for 1 h in a 90 °C oil bath, and then all of the volatiles were carefully removed by swirling it under high vacuum (1 mmHg) for 1 h with 2nd liquid N₂ trap to protect the pump. Crude **18b** (ca. 16.7 g) could be obtained as a yellow solid (color was different when **17b** were from other vendors).

Spectral data for **18b**: white wax-like solid; ¹H-NMR (CDCl₃, 300 MHz) δ 4.28 (s, 2H), 7.34-7.37 (dd, 1H, *J* = 4.5, 1.5 Hz), 7.47-7.52 (m, 2H), 7.35 (s, 1H), 7.98-7.86 (m, 3H).

Note: **18b** can also be prepared using (COCl)₂. Typical procedures:

Acid **17b** 14.23 g (76.42 mmol) was dissolved in CH₂Cl₂ (25 mL) in a 250 mL flask, to which was added (COCl)₂ (10 mL, 118 mmol, 1.5 eq). DMF (1 mL, 12.9

mmol) was injected and a violent reaction occurred to release a lot of gaseous byproducts. The color changed to yellow when the reaction settled down after *ca.* 10 min. It was then stirred at 25 °C for 1 h. The volatile was removed in *vacuo* to get the crude **18b**. This material was used for the CAEC cascade reaction as described above with phenylacetylene (**63a**, 11 mL, 100 mmol) using (*i*-PrCO)₂O (**93**, 25 mL, 146.2 mmol) as trapping agent, which gave **16b** (13.74 g, 50.5 mmol, 66.5%, mp 151-2 °C).

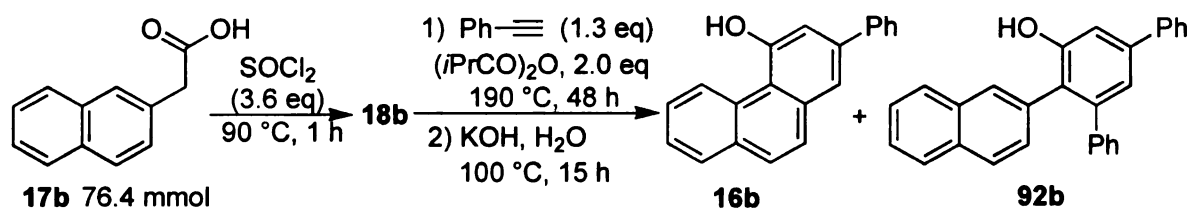
For more conditions, see **Table 3.11** of **Chapter three**.

To the flask containing the resulted yellow solid was filled with argon, charged with phenylacetylene (**63a**, 11 mL, 100 mmol) and mineral oil (9 mL). The condenser was flushed with N₂, and then connected to the flask. The resulting mixture was heated and stirred at 190 °C for 24 h with gentle N₂ flow across the top of the condenser. The brown reaction mixture was cooled to 25 °C, ether (100 mL) was added and then cooled to 0 °C for 30 min. LiAlH₄ (5.0 g, 132 mmol) was added cautiously in small portions. After stirring at 25 °C overnight, pre-cooled 6 N HCl (100 mL) was added carefully after the mixture was chilled to 0 °C again. The orange water layer was extracted with ether (100 mL×3) and the combined organic layer was washed with brine (100 mL) and dried over MgSO₄ and filtered. The solvent was removed in *vacuo*, the residue was dissolved in the minimum amount of CH₂Cl₂, and loaded onto a chromatography column (6 cm diameter) prepared by hexanes and silica gel (15 to 20 cm long, about 350 mL silica gel).

The column was first eluted with hexanes. A void volume of about 500 mL was collected and discarded (containing mineral oil). The column was then eluted with a 1:2 mixture of CH₂Cl₂: hexanes. A dark-colored band was followed by a byproduct; elution was continued when TLC indicated **16b** started to elute. It was combined together; solvents were removed in *vacuo* to get **16b** (8.54 g, 31.6 mmol, 41.4%, mp 140-1 °C, lit. value:^{17b} 154-5 °C) as a greenish brown solid.

For more conditions, see **Table 3.5** and **3.6** of **Chapter three**.

7.3.2.2 In (*i*-PrCO)₂O as a trapping agent (workup with KOH).



Acid **17b** (14.23 g, 76.42 mmol) was from Milestone Pharm Tech USA Inc. (Lot #: T1161), which was used to prepare **18b** with SOCl₂ (20 mL, 274 mmol) in the same manner as illustrated in **Section 7.3.2.1**. To the flask containing the resulted **18b** (ca 16.7 g) was filled with argon, charged with phenylacetylene (**63a**, 11 mL, 100.2 mmol) and (*i*-PrCO)₂O (**93**, 25 mL, 146.2 mmol). The condenser used for the reaction was first flushed with N₂ and then connected to the flask, which was heated and stirred in a 190 °C oil bath for 24 h with a gentle nitrogen flow across the top of the condenser. The brown reaction mixture was cooled down to below 100 °C (ca. 60 °C, oil bath temperature), and then aqueous KOH (25 g, 445.6 mmol in 100 mL H₂O) was slowly added. This two-phase mixture was

stirred in a 100 °C oil bath overnight (15 h), and the color changed to orange. It was cooled to rt and ether (100 mL) was added and stirred for 10 min before the organic layer was isolated in a separatory funnel. The water layer was extracted twice with ether (100 mL×2) and the combined organic layer was washed with brine (100 mL) and dried over MgSO₄ and filtered.

General procedures to isolate and purify 16b via silica gel chromatography column: The dark-colored solution was combined with silica gel (about 100 mL). After inserting a piece of cotton into the neck of the trap of the rotary evaporator and removing the solvents, both the flask and trap was put on high vacuum (2 mmHg) for 30 min. A chromatography column (6 cm diameter) was prepared by filling the column with hexanes and then the addition of silica gel such that after settling a depth of 15 to 20 cm (about 350 mL silica gel) had been reached. The dried silica gel with the pre-adsorbed product was added to the solvent above the prepared bed and allowed to settle. The solvent level was lowered to the top of the column and then a layer of sand was applied immediately. The column was then eluted with a 1:2 mixture of CH₂Cl₂: hexanes under gravity (about 1 h). A void volume of about 700 mL was collected and discarded. This was followed by a dark colored (dark brown to black) fast-moving mixture of impurities, which smells strongly like phenylacetylene (about 2 g from 1.5 to 2 L of solution after the solvents were removed). When TLC indicated that the byproduct (**92b**) began to elute, a second fraction was collected that contained **92b** (about

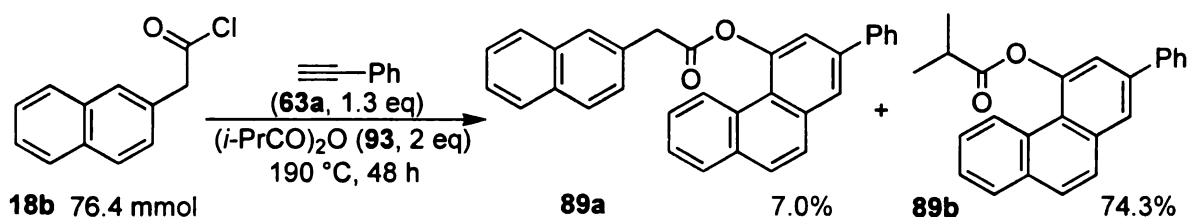
700 mL, containing 2.0 g, $R_f = 0.50$ using 1:3 EtOAc: hexane). When **92b** had finished eluting, elution was continued under N_2 pressure to collect the desired product (totally 4-5 L), which was stripped of solvent by rotary evaporator and then dried in *vacuo* overnight to afford 15.5 g (57.4 mmol, 75.1%, mp 152-153 °C, lit. value:^{17b} 154-5 °C) of **16b** as a yellow solid.

A byproduct 1-(2-naphthyl)-2,4-diphenylphenol (**92b**) was isolated (2.24 g, 6.04 mmol, 7.9%) as a white crystal. Spectral data for **92b**: mp 207-208 °C; $R_f = 0.22$ (1:1 CH_2Cl_2 :hexane); 1H -NMR ($CDCl_3$, 500 MHz) δ 5.37 (s, 1H), 7.13-7.16 (m, 3H), 7.17-7.20 (m, 3H), 7.35 (dd, 2H, $J = 7.5, 2.0$ Hz), 7.41 (t, 1H, $J = 8.0$ Hz), 7.48 (s, 1H), 7.50 (s, 1H), 7.51-7.55 (m, 2H), 7.72-7.74 (m, 2H), 7.71 (d, 1H, $J = 8.5$ Hz), 7.71 (q, 2H), 7.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 113.32, 121.72, 125.75, 126.74, 126.88, 127.37, 127.91, 128.07, 128.20, 129.08, 129.16, 129.21, 129.79, 129.95, 132.76, 132.82, 133.67, 140.70, 141.25, 142.29, 142.96, 153.70, two carbons not located; ^{13}C NMR (d^6 -acetone, 75 MHz) δ 113.50, 120.14, 126.03, 126.11, 126.76, 126.90, 127.20, 127.87, 127.99, 128.13, 128.22, 129.42, 130.12, 130.29, 130.42, 132.26, 133.36, 135.29, 140.84, 141.11, 142.17, 143.53, 156.30, one carbon not located; ; IR (thin film) 3522 br vs, 1701 w, 1684 w, 1653 m, 1558 m, 1506 w, 761 w, 700 m cm^{-1} ; mass spectrum, m/z (% rel intensity) 373.8 (30), 372.5 M^+ (100), 371.3 (15), 352.2 (13), 326.3 (8), 265.3 (10), 252.2 (8), 175.1 (10), 91.1 (5). HRMS calcd for $C_{28}H_{19}O$ m/z 371.1436, meas 371.1430.

General procedures to isolate and purify 16b via crystallization and silica gel chromatography column: the reaction and workup step was the same and the brown crude reaction mixture (22 g) was crystallized under N₂ protection as follows: To a 100 mL round bottom flask was added stirrer bar and 10 mL CH₂Cl₂. It was equipped with condenser (flushed with N₂ in advance) and heated to reflux while stirring. CH₂Cl₂ (10 mL×5) was added slowly *via* syringe till a clear dark brown solution formed, which was cooled to down to 25 °C then to –20 °C overnight. The yellow crystal (7.57 g, 28.05 mmol, 36.7%, mp 155-6 °C) was collected by filtration and washed with 15 mL CH₂Cl₂/hexanes (1:2). The dark-colored mother liquor was combined with silica gel (about 100 mL), which was dried under a gentle N₂ flow. A chromatography column (6 cm diameter) was prepared by filling the column with hexanes and then the addition of silica gel such that after settling a depth of 15 to 20 cm (about 350 mL silica gel) had been reached. The dried silica gel with the pre-adsorbed product was added to the solvent above the prepared bed and allowed to settle. The flask was rinsed with small amount of CH₂Cl₂ from washing bottle and the added to the column. The solvent level was lowered to the top of the column and then a layer of sand was applied immediately. The column was then eluted with a 1:2 mixture of CH₂Cl₂:hexanes under gravity. A void volume of about 500 mL was collected and discarded. This was followed by a yellow fast-moving mixture of impurities (1.7 g tarry material from 1.6 to 1.7 L). When TLC indicated that the byproduct (**92b**)

began to elute, a second fraction was collected that contained this byproduct (about 500-600 mL, containing 1.9 g, 5.16 mmol), followed by a part of overlapped mixture of these two products (350-400 mL, from which 1.51 g solid could be isolated after removal of solvents. This material contained 1.2 g **16b** base on ^1H -NMR spectrum, and could be further purified by either crystallization in CH_2Cl_2 or column under the same conditions). When **92b** had finished eluting, elution was continued under N_2 pressure to collect the desired product (totally 3-3.5 L), which was stripped of solvent by rotary evaporator and then dried in *vacuo* overnight to afford 4.22 g (15.6 mmol, 20.4%, mp 150-1 °C) of **16b** as orange solid. The combined yield was 57.1%.

7.3.2.3 Isolation of ester intermediates of **89a** and **89b** without KOH workup.



Two intermediates are isolated without basic hydrolysis, they are **89a** and **89b**. The procedures: The reaction was performed under the same conditions in **Section 7.3.2.2**. After heating in a 190 °C oil bath for 48 h, it was cooled down to 25 °C, volatiles were removed under high vacuum (1 mmHg). Residue (27 g) was dissolved in minimum amount of CH_2Cl_2 and loaded onto silica gel prepared by hexanes. It was eluted by a mixture of CH_2Cl_2 and hexanes (1:2) to afford the first component (**89b** was the major product in this portion) and then the second

component (**89a** was the major product in this portion). Both portions were crystallized in boiling CH₂Cl₂ and saturated by hexanes, cooled to 25 °C then –20 °C to get pure **89a** (2.34 g, 5.34 mmol, 7.0%) as white cotton-like crystal and **89b** (19.3 g, 56.8 mmol, 74.3%) as yellow leaf-like crystal. The byproduct **92b** was not located.

Spectral data for **89a**: mp 177-8 °C; *R_f* = 0.22 (1:1 CH₂Cl₂: hexane); ¹H-NMR (CDCl₃, 500 MHz) δ 4.32 (s, 2H), 7.07 (t, 1H, *J* = 7.0 Hz), 7.40 (t, 1H, *J* = 7.0 Hz), 7.45-7.51 (m, 3H), 7.52-7.56 (m, 2H), 7.57 (d, 1H, *J* = 1.5 Hz), 7.66 (dd, 1H, *J* = 8.5 Hz, *J* = 2.0 Hz), 7.72-7.78 (m, 4H), 7.83-7.84 (d, 1H, *J* = 7.5 Hz), 7.88-7.90 (m, 2H), 7.93 (d, 1H, *J* = 7.5 Hz), 8.00 (s, 1H), 8.01 (d, 1H, *J* = 2.0 Hz), 8.78 (d, 1H, *J* = 8.5 Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 42.73, 121.07, 122.45, 125.17, 126.41, 126.68, 126.75, 126.82, 126.89, 127.43, 127.60, 127.84, 128.02, 128.07, 128.58, 128.93, 129.18, 130.55, 133.02, 133.16, 133.88, 135.28, 139.35, 139.77, 149.17, 170.05, four carbons not located; ¹³C NMR (*d*⁶-acetone/ *d*⁶-DMSO 75 MHz) δ 41.86, 121.23, 122.41, 124.82, 126.37, 126.68, 126.74, 127.12, 127.37, 127.65, 128.03, 128.04, 128.38, 128.46, 128.58, 128.61, 128.74, 129.04, 129.16, 129.44, 131.66, 133.00, 133.22, 133.93, 135.37, 139.13, 139.27, 149.64, 170.40, one carbon not located; ; IR (salt plate) 1745 vs, 1622 w, 1454 m, 1385 m, 1235 m, 1116 m, 812 m, 753 m cm⁻¹; mass spectrum, *m/z* (% rel intensity) 438.1 M⁺ (8), 271.2 (18), 270.0 (100), 238.9 (15), 168.0 (10), 140.9 (44), 114.9 (12); HRMS calcd for C₃₂H₂₃O₂ *m/z* 439.1698, meas 439.1702.

Spectral data for **89b**: yellow crystal; mp 121-2 °C; R_f = 0.50 (1:3 EtOAc: hexane); $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ 1.54 (d, 6H, J = 7.0 Hz), 3.14-3.2 (m, 1H), 7.44 (t, 1H, J = 7.5 Hz), 7.54 (t, 2H, J = 7.5 Hz), 7.58 (d, 1H, J = 2.0 Hz), 7.62-7.68 (m, 2H), 7.77-7.82 (m, 4H), 7.92-7.94 (m, 1H), 8.04 (s, 1H), 9.18 (d, 1H, J = 8.0 Hz); $^1\text{H-NMR}$ (d^6 -acetone, 500 MHz) δ 1.48 (d, 6H, J = 7.0 Hz), 3.21 (octet, 1H, J = 7.0 Hz), 7.43 (t, 1H, J = 7.5 Hz), 7.53 (t, 2H, J = 7.5 Hz), 7.65 (td, 1H, J = 7.0 Hz, J = 1.0 Hz), 7.69-7.73 (m, 1H), 7.75 (d, 1H, J = 1.5 Hz), 7.81-7.90 (m, 4H), 7.97 (d, 1H, J = 8.0 Hz), 8.18 (d, 1H, J = 2.0 Hz), 9.22 (d, 1H, J = 8.5 Hz); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 19.33, 35.13, 121.11, 122.67, 125.00, 126.84, 126.88, 127.58, 127.65, 128.06, 128.52, 129.09, 129.14, 129.19, 130.09, 133.27, 135.29, 139.46, 139.94, 149.42, 175.83; $^{13}\text{C NMR}$ (d^6 -acetone, 75 MHz) δ 19.33, 34.77, 121.09, 122.70, 124.66, 126.74, 127.10, 127.16, 127.26, 127.37, 127.63, 128.07, 128.19, 128.47, 129.06, 129.16, 129.30, 133.32, 135.38, 139.30, 139.50, 149.82, 175.45; IR (salt plate) 2973 w, 1754 s, 1453 m, 1386 m, 1176 m, 1107 vs, 882 m, 749 m, 695 m cm^{-1} ; mass spectrum, m/z (% rel intensity) 341.3 (6), 340.1 M^+ (30), 270.3 (35), 270.1 (100), 239.0 (60), 165 (10), 138.8 (10), 119.6 (17), 70.9 (22), 43.0 (58).
 Anal. calcd for $\text{C}_{24}\text{H}_{20}\text{O}_2$: C, 84.68; H, 5.92. Found: C, 84.34; H, 5.86.

For more conditions, see **Section 3.4 and 3.5 of Chapter three**.

7.3.2.4 Preparation of **16b** by using **17b** from Ochem Inc.

Compound **17b** was first purified by crystallization in EtOH/ H_2O as follows:

To a 250 mL round bottom flask was added **17b** (15 g, Ochem Inc., Lot #:

0712053B), stirrer bar and 60 mL EtOH. It was equipped with condenser and heated to reflux. A yellow solution formed and was hot filtered *via* filter paper, insoluble impurities (about 0.04 g) was discarded. The solvent of filtrate was completely removed in *vacuo*, and the residue was combined with 50 mL H₂O and heated to boil. EtOH (25 mL) was added slowly *via* syringe till a clear solution formed, which was cooled to down to 25 °C overnight. The crystal (13.24 g, 88% recovery) was collected by filtration and washed with 15 mL EtOH/H₂O (3:1) and dried under high vacuum. This material was used for the following reaction.

Crystallized acid **17b** (14.23 g, 76.42 mmol) was used to prepare **18b** with SOCl₂ (20 mL, 274 mmol) in the same manner as illustrated in **Section 7.3.2.1**. To the flask containing the resulted light yellow solid (the color was dark greenish brown if **17b** was not purified) was added **63a** (11 mL, 100.2 mmol) and (*i*-PrCO)₂O (25 mL, 146.2 mmol) under argon. The condenser used for the reaction was flushed with N₂ before it was connected to the flask, which was heated and stirred in a 190 °C oil bath for 48 h with gentle nitrogen flow across top of the condenser. The black reaction mixture was cooled to below 100 °C (about 60 °C, oil bath temperature), and then aq. KOH (25 g, 445.6 mmol in 100 mL H₂O) was added. After stirring in a 100 °C oil bath overnight (15 h), the brown solution was cooled to 25 °C and ether (150 mL) was added and stirred for 10 min before the organic layer was isolated in a separatory funnel. The black tarry material on the bottom of the funnel was kept in water layer and eventually discarded. The

water layer was extracted twice with ether (150 mL×2) and the combined organic layer was washed with brine (100 mL) and dried over MgSO_4 and filtered. The dark-colored solution was combined with silica gel (about 100 mL). The following procedures for the isolation and purification of **16b** are the same as in **Section 7.3.2.2.**, from which 12.63 g (46.78 mmol, 61.2%, mp 154-5 °C) of **16b** was afforded as orange solid. This is to be compared to 75.1% yield obtained with the same procedure on small scale as from 2-naphthylacetic acid obtained from Milestone Pharm Tech USA Inc. (See **Section 7.3.2.2**).

7.3.2.5 Preparation of 16b by using 17b from Sigma-Aldrich Inc..

Acid **17b** (14.23 g, 76.42 mmol from Sigma-Aldrich Inc., Lot #: 03824CE) was used to prepare **18b** with SOCl_2 (20 mL, 274 mmol) in the same manner as illustrated in **Section 7.3.2.1**. To the flask containing the resulted white solid was filled with argon and charged with phenylacetylene (**63a**, 11 mL, 100.2 mmol) and $(i\text{-PrCO})_2\text{O}$ (25 mL, 146.2 mmol). The condenser used for the reaction was flushed with N_2 before it was connected to the flask, which was heated and stirred in a 190 °C oil bath for 48 h with gentle nitrogen flow across top of the condenser. The orange reaction mixture was cooled to below 100 °C (ca. 60 °C, oil bath temperature), and then aq. KOH (25 g, 445.6 mmol in 100 mL H_2O) was added. After stirring in a 100 °C oil bath overnight (15 h), the orange solution was cooled to 25 °C and ether (150 mL) was added and stirred for 10 min before the organic layer was isolated in a separatory funnel. The water layer was extracted twice with

ether (150 mL×2) and the combined organic layer was washed with brine (100 mL) and dried over MgSO_4 , filtered. The solvent was completely removed in *vacuo* and the brown solid (22 g) was crystallized under N_2 protection as follows: To a 250 mL round bottom flask was added stirrer bar and 50 mL CH_2Cl_2 . It was equipped with condenser (flushed with N_2 in advance) and heated to reflux. CH_2Cl_2 (60 mL) was added slowly *via* syringe till a clear dark brown solution formed, which was cooled to down to 25 °C then to –20 °C overnight. The crystal (11.92 g, 44.15 mmol, 57.8%, mp 156-7 °C) was collected by filtration and washed with 15 mL CH_2Cl_2 /hexanes (1:2).

The dark-colored mother liquor was combined with silica gel (about 100 mL). After inserting a piece of cotton into the neck of the trap of the rotary evaporator and removing the solvents, both the flask and trap was put on high vacuum (0.5 mmHg) for 30 min. A chromatography column (6 cm diameter) was prepared by filling the column with hexanes and then the addition of silica gel such that after settling a depth of 15 to 20 cm (about 350 mL silica gel) had been reached. The dried silica gel with the pre-adsorbed product was added to the solvent above the prepared bed and allowed to settle. The solvent level was lowered to the top of the column and then a layer of sand was applied immediately. The column was then eluted with a 1:2 mixture of CH_2Cl_2 : hexanes under gravity (about 1 h). A void volume of about 700 mL was collected and discarded. This was followed by a yellow fast-moving mixture of impurities (1.7 to 1.8 L). When TLC indicated that

the byproduct (**92b**) began to elute, a second fraction was collected that contained this byproduct (about 700-800 mL, containing 2.3 g), followed by a part of overlapped mixture of these two products (300-400 mL, from which 1.1 g solid could be isolated after removal of solvents. This material contained 0.71 g **16b** base on ^1H -NMR spectrum, and could be further purified by either crystallization in CH_2Cl_2 or column under the same conditions). When **92b** had finished eluting, elution was continued under N_2 pressure to collect the desired product (totally 3-3.5 L), which was stripped of solvent by rotary evaporator and then dried in *vacuo* overnight to afford 3.45 g (12.7 mmol, 16.6%, mp 151-3 °C) of **16b** as orange solid. The combined yield was 74.4%.

7.3.2.6 Preparation of **16b** using (*i*-PrCO) $_2$ O on large scale.

A single-neck 1 L round bottom flask equipped with a large 48x18 mm oval magnetic stir bar and a condenser was charged with 57 g (306 mmol from Milestone Pharm Tech USA Inc., Lot #: T1161) of **17b** and SOCl_2 (45 mL, 618 mmol). The top of the condenser is vented to a bubbler and then into a beaker filled with aqueous NaOH to trap acidic gases (HCl and SO_2). The mixture was heated to reflux for 1 h in a 90 °C oil bath, and then all of the volatiles were distilled off. It was then put on high vacuum (2 mmHg) and swirled until the residue solidified with 2nd liquid N_2 trap to protect the pump. The extra liquid N_2 trap was then removed and the residue was kept under vacuum for 1 h. After filling with argon, the flask containing the yellow crude **18b** was added with

phenylacetylene (45 mL, 410 mmol) and (*i*-PrCO)₂O (100 mL, 603 mmol). The condenser was flushed with N₂ and then connected to the flask. The above mixture was heated and stirred in a 190 °C oil bath for 48 h with gentle nitrogen flow across top of the condenser. The brown reaction mixture was cooled to about 60 °C (oil bath temperature), aq. KOH (100 g, 1.8 mol in 400 mL H₂O) was slowly added. After stirring in a 100 °C oil bath overnight (15 h), the orange solution was cooled to rt and ether (400 mL) was added and stirred for 30 min before the organic layer was isolated in a 2 L separatory funnel. The water layer was extracted twice with ether (400 mL×2) and the combined organic layer was washed with brine (400 mL), dried over MgSO₄ and filtered. The dark-colored solution was combined together (5 drops were collected for ¹H-NMR analysis) and the solvents were removed in *vacuo*. The residue was collected in a 500 mL flask and dried under high vacuum (1 mmHg) overnight to get (ca. 80 g) dark brown crude product. The crude ¹H-NMR spectrum indicated it was a mixture of **16b** and **92b** with a 1: 0.15 ratio.

The crude mixture in the flask was combined with a stirrer bar and 100 mL CH₂Cl₂ and boiled under protection of N₂. More CH₂Cl₂ was then added in 50 mL aliquot until dissolve (totally 200 mL). The solution was allowed to cool to rt and then to -20 °C in a refrigerator overnight. The mixture was filtered and washed with a mixture of CH₂Cl₂: hexanes (1:2, 15 mL×2) to give 34.4 g (127.2 mmol, 41.5%) of **16b** as a beige crystal (mp 156-7 °C, lit. value:^{17b} 154-5 °C). The

dark-colored mother liquor was collected in a 500 mL flask and combined with silica gel (ca. 150 mL). After inserting a piece of cotton into the neck of the trap of the rotary evaporator and removing the solvents, both the flask and trap was put on high vacuum (0.5 mmHg) for 1 h. It was filtered through a short column of additional silica gel as follows. To a sintered glass funnel (OD 10 cm, 18 cm long) a short pad of Celite (30 g) was prepared, then silica gel (400 mL) was added followed by the crude mixture absorbed on silica gel, and finally a thin layer of sand (2-3 cm). It was then eluted with hexanes: CH_2Cl_2 = 1:1 with a vacuum produced by water aspirator. The first eluate of ca. 1 L was discarded. This eluant by TLC contains fast running impurities (ca. 10 g, black) and a small amount of double-inserted byproduct **92b**. An additional of 2.5 L of hexanes: CH_2Cl_2 = 1:1 was pass through and collected, and this product-containing fraction was concentrated on a rotary evaporator to afford a mixture of **16b** and **92b** (25 g) as an orange solid.

This solid was refluxed with 10 mL *i*PrOH under N_2 to dissolve, cooled to 25 °C then to -20 °C overnight. The solid was filtered, washed with *i*PrOH (3×10 mL) to get pure **92b** (5.93 g, 15.9 mmol) as white solid. The mother liquor was stripped of solvent in *vacuo*, the orange residue (22 g, mp 146-7 °C) was boiled with 100 mL hexanes: DCE = 2:1 under N_2 , and more of this mixture of solvents was added (in 50 mL aliquots, totally about 350 mL) till dissolved. It was cooled down to 25 °C then -20 °C to get 2nd crop of **16b** (12.4 g, 45.9 mmol, 15%, mp 157-8 °C). The

total yield was 56.5%.

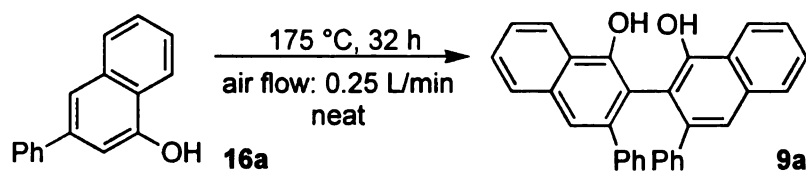
SOCl_2 (50 mL) could be recovered from this process. Acid **18b** could be recovered from aqueous KOH as follow: It was acidified with HCl (6 N) to pH~1 and extracted with ether (3×100 mL), the combined organic layer was washed with brine (100 mL), dried over MgSO_4 and filtered. Ether was removed *via* rotary evaporator, the leftover orange solution (**18b** in ca. 90 mL of isobutyric acid) was distilled under vacuum produced by a water aspirator (80 mmHg/ 81-2 °C) to get 7.20 g crude **18b** as orange solid. This material was crystallized in EtOH/ H_2O in the same way in **Section 7.3.2.4** to get 5.15 g (27.5 mmol, 9%) yellow leaf-like crystal.

For more conditions, see **Section 3.6 of Chapter three**.

7.4 Experiments for Chapter four

7.4.1 Preparation of VANOL 9a by oxidation coupling of monomer 16a.

7.4.1.1 Small scale under neat conditions.

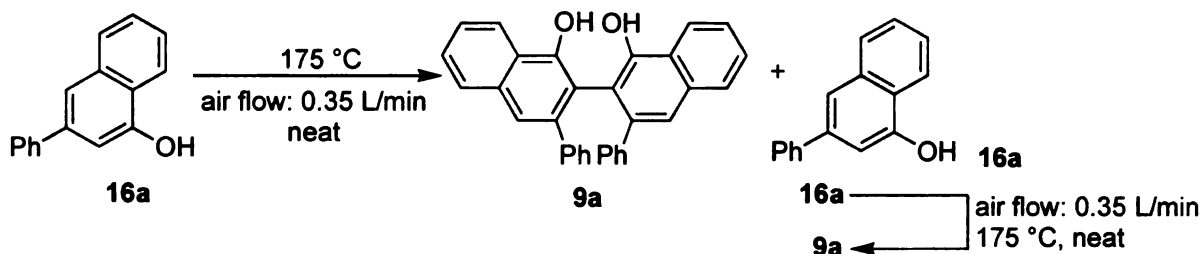


Monomer **16a** (4 g, 18.2 mmol) was loaded into a 250 mL 3-neck round bottom flask equipped with large 48x18 mm oval magnetic stir bar and condenser, stirred in a 175 °C oil bath, with neat air (0.25 mL/min) blown gently into the flask *via* needle to the surface of the reaction mixture from one of the neck. The sublimed

monomer in the condenser was washed down using a ethyl acetate washing bottle after 12 h. The reaction was stirred for another 20 h till the stirrer stopped. The flask was thoroughly cooled down in ice bath, the crude mixture was broken into pieces by stirring with small amount of CH₂Cl₂ (5 mL) at 0 °C till no big chunks visible. The suspension was filtered and light brown powder was collected, washed with cold CH₂Cl₂ (5 mL) to get 2.387 g **9a** (5.45 mmol, 60%). The solvent in the filtrate was removed, residue was loaded onto silica gel and was eluted with CH₂Cl₂: hexanes = 2:3, the 2nd part of **9a** (0.3275 g, 0.75 mmol, 8.2%) can be recovered. Overall yield: 65.8%

The spectrum of **9a**: R_f = 0.36 (1:9 EtOAc/hexane). ¹H-NMR (CDCl₃) δ 5.83 (s, 2H), 6.61 (d, 4H, J = 7.2 Hz), 6.93 (t, 4H, J = 7.7 Hz), 7.03 (t, 2H, J = 7.3 Hz), 7.29 (s, 2H), 7.50-7.54 (m, 4H), 7.73-7.75 (m, 2H), 8.30-8.32 (m, 2H); ¹³C NMR (CDCl₃ 75 MHz) δ 112.64, 122.00, 122.78, 122.86, 125.66, 126.59, 127.43, 127.51, 127.67, 128.86, 134.56, 140.12, 140.65, 150.33.

7.4.1.2 Large scale under neat conditions.



Monomer **16a** (104.6 g, 474.5 mmol) was introduced into a 2 L 3-necked round bottom flask equipped with a 60x18 mm oval magnetic stir bar and a 400

mm Allihn water cooled condenser. A glass tube (6 mm id) was introduced into the flask *via* the second neck to about 5 cm above the surface of naphthol and was used to provide a stream of house air which is maintained at a flow rate of 0.35 L/min. The third neck was sealed with a rubber septum. The flask was heated in an oil bath in a 175 °C oil bath while at the same time the molten **16a** is stirred as fast as possible. The sublimed starting material that collects in the condenser was washed down by ethyl acetate every 2 h at which time the condenser, glass tube and rubber septum were then removed to allow the ethyl acetate to distill off which took a few minutes. The condenser, glass tube and rubber septum were replaced and the reaction continued. This process was repeated until the stirrer bar stopped. The flask was removed from the oil bath and briefly allowed to cool (~100 °C, less than 5 min) and then CH₂Cl₂ (200 mL) was added to the flask and the mixture stirred until uniform black slurry was produced and all the large chunks had been broken up (a few hours). The suspension was cooled in a freezer (-20 °C) and then filtered through a Buchner funnel. The light brown powder was washed with chilled CH₂Cl₂ (50 mL, -20 °C) into the 2 L 3-neck round bottom flask. The light brown powder was washed with chilled (0 °C, 50 mL) CH₂Cl₂ and dried under high vacuum for 12 h. This yielded 52.40 g (119.5 mmol) of racemic **9a** as a yellow powder.

The solvent of the filtrate was removed by distillation; the long condenser was re-installed, the residue was heated to 175 °C again and stirred as quickly as

possible under the same airflow. The sublimed monomer in the condenser was washed down by ethyl acetate every 6 h, and the flask was opened to distill off the ethyl acetate for a while (about 5 min). The flask was closed and let the reaction continue. This process was repeated till the stirrer bar stopped (about 20 h). The flask was removed from oil bath and briefly cooled down before it solidified (about 5 min); CH_2Cl_2 (200 mL) was added to the flask and stirred till no big chunks visible. The suspension was cooled down to 0 °C and filtered into the 2 L 3-neck flask. The solid was washed with chilled (0 °C) 50 mL CH_2Cl_2 , collected and dried over vacuum to afford 12.14 g (27.7 mmol) **9a**.

The filtrate was dried *via* a simple distillation and the long condenser was re-installed, the residue was heated to 175 °C again and stirred as quickly as possible under the same airflow. The sublimed monomer in the condenser was washed down by ethyl acetate every 6 h, and the flask was opened to distill off the ethyl acetate for a while (about 5 min). The flask was closed and let the reaction continue. This process was repeated till the stirrer bar stopped (about 18 h). The flask was removed from oil bath and briefly cooled down before it solidified (about 5 min); CH_2Cl_2 (30 mL) was added to the flask and stirred till no big chunks visible. The suspension was cooled down to 0 °C and filtered into the 2 L 3-neck flask. The powder was washed with chilled (0 °C) 20 mL CH_2Cl_2 , collected and dried over vacuum to afford 9.26 g (21.12 mmol) **9a**.

The filtrate was combined with 30 g silica gel and dried over N_2 gas and it was

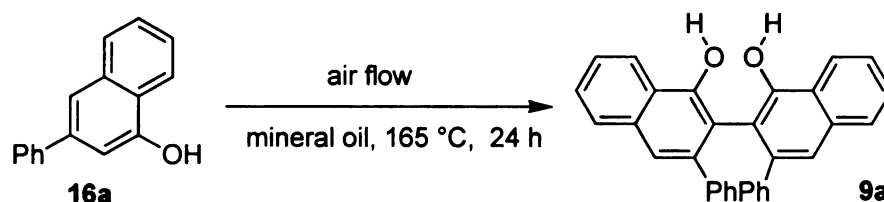
put onto a column (6 cm diameter) prepared with 50 cm of silica gel and about 1000 mL solvent with ethyl acetate: hexanes= 50:1. The column was eluted with ethyl acetate: hexanes= 10:1 to afford **16a** as yellow to brown solid, which was heated to 175 °C again in the 500 mL 3-neck flask equipped with the long condenser and stirred as quickly as possible under the same airflow as above. The sublimed monomer in the condenser was washed down by ethyl acetate every 6 h, and the flask was opened to distill off the ethyl acetate for a while (about 5 min). The flask was closed and let the reaction continue. This process was repeated till the stirrer bar stopped (about 15 h). The flask was removed from oil bath and briefly cooled down before it solidified (about 5 min); CH₂Cl₂ (15 mL) was added to the flask and stirred till no big chunks visible. The suspension was cooled down to 0 °C and filtered into the 500 mL 3-necked flask. The powder was washed with 5 mL-chilled CH₂Cl₂, dried over *vacuo* to afford 4.40 g (10.03 mmol) **9a**.

The filtrate was dried *via* a simple distillation and the long condenser was re-installed, the residue was heated to 175 °C again and stirred as quickly as possible under the same airflow. The sublimed monomer in the condenser was washed down by ethyl acetate every 6 h, and the flask was opened to distill off the ethyl acetate for a while (about 5 min). The flask was closed and let the reaction continue. This process was repeated till the stirrer bar stopped (about 8 h). The flask was removed from oil bath and briefly cooled down before it solidified (about

5 min); CH₂Cl₂ (10 mL) was added to the flask and stirred till no big chunks visible. The suspension was cooled down to 0 °C and filtered into the 500 mL 3-necked flask. The powder was washed with 2 mL-chilled CH₂Cl₂, collected and dried over vacuum to afford 1.22 g (2.78 mmol) **9a**.

The filtrate was dried *via* a simple distillation and the long condenser was re-installed, the residue was heated to 175 °C again and stirred as quickly as possible under the same airflow. The sublimed monomer in the condenser was washed down by ethyl acetate every 6 h, and the flask was opened to distill off the ethyl acetate for a while (about 5 min). The flask was closed and let the reaction continue. This process was repeated till the stirrer bar stopped (about 8 h). The flask was removed from oil bath and cooled down; CH₂Cl₂ (50 mL) was added to the flask to dissolve all the residue, which was combined with 10 g silica gel and dried over N₂ gas and it was put on a column (4 cm diameter) prepared with 50 cm of silica gel and about 750 mL solvent with ethyl acetate: hexanes = 50:1. The column was eluted with ethyl acetate: hexanes = 15:1 to afford 0.91 g (2.08 mmol) VANOL **9a**. The total yield: 80.33 g (80.6%).

7.4.1.3 Small scale in mineral oil.



VANOL monomer **16a** (5.04 g, 22.9 mmol) was introduced by a funnel into a

500 mL 3-necked round bottom flask equipped with a 48x18 mm oval magnetic stir bar and a 400 mm Allihn water cooled condenser, followed by 25 mL light mineral oil through the same funnel. A glass tube (6 mm id) was introduced into the flask *via* the second neck to about 5 cm above the surface of naphthol and was used to provide a stream of house air which is maintained at a flow rate of 0.12-0.15 L/min. The third neck was sealed with a rubber septum. The flask was put into an oil bath and heated to 165 °C without disturbance until solid melted. Airflow was allowed to blow into the flask while the molten **16a** was stirred as fast as possible. The reaction was stopped after 24 h by switching the airflow to N₂ while the flask was removed from the oil bath and cooled down to ambient temperature (**Note**: The reaction was tracked by TLC, which showed that it was complete after about 17 h). Hexanes (50 mL) was added to the flask, and the mixture was stirred for 30 min and then it was cooled down to -20 °C overnight (12 h) before the solid was collected by suction filtration. The orange powder (about 4.58 g, pure **9a** on ¹H-NMR spectrum, 214-216 °C softened and 224-229 °C melted) was dried on high vacuum (1 mmHg) and crystallized in CH₂Cl₂ (ca. 60 mL), the dark-colored solution was cooled to 25 °C then to -20 °C overnight (12 h). The brown crystal was collected *via* suction filtration, washed by hexanes (50 mL) three times and dried over vacuum to get **9a** (4.45 g, 10.16 mmol, 88.7%, mp 231-232 °C, lit. value:^{17b} 231-233 °C) as yellow crystal.

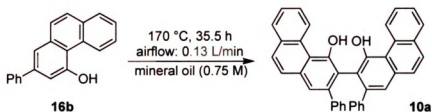
7.4.1.4 Standard procedure to prepare VANOL by oxidative coupling of 16a.

Oil bath (19 cm id with about 1.5 L oil in it) was heated to 165 °C while stirring with a magnetic stir. **16a** (50.05 g, 227.5 mmol) was introduced by a funnel into a 2 L 3-necked round bottom flask equipped with a 60x18 mm oval magnetic stir bar and a 400 mm Allihn water cooled condenser, followed by 250 mL light mineral oil through the same funnel. A glass tube (6 mm id) was introduced into the flask via the second neck to about 5 cm above the surface of naphthol and was used to provide a stream of house air which is maintained at a flow rate of 0.15 – 0.20 L/min. The third neck was sealed with a rubber septum. The stirrer bar in the oil bath was removed before the flask was put into it to warm up for about 15 min till solid melted. Airflow was allowed to blow into the flask while the molten **16a** was stirred as fast as possible. The airflow was switched to N₂ after the reaction was kept at same temperature for 24 h, the flask was removed from the oil bath and cooled down to ambient temperature before hexanes (500 mL) was added to the flask. The mixture was stirred for 30 min and then it was cooled down to –20 °C overnight (12 h) before the solid was collected by suction filtration. The crude product (about 46 g, brown powder, 216-219 °C softened and 224-227°C melted) was dried on high vacuum and crystallized in 600 mL CH₂Cl₂, the dark-colored solution was cooled down to room temperature then to –20 °C overnight (12 h). The brown crystal was collected via suction filtration, washed by hexanes (50 mL) 3 times and dried over vacuum to get first crop product (37.4 g, 85.3 mmol, 74.7%,

mp 231-232 °C, literature value:^{17b} 231-233 °C). The mother liquor was dried and the residue was crystallized in 60 mL CH₂Cl₂ and cooled down to -20 °C overnight to get 5.04 g brown crystal (11.5 mmol, 10.1%, mp 230-231 °C). The combined yield was 42.4 g (96.8 mmol, 85.2%).

7.4.2 Preparation of VAPOL 10a by oxidative coupling of 16b in mineral oil

7.4.2.1 On small scale



VAPOL monomer **16b** (5.09 g, 18.8 mmol) was introduced by a funnel into a 500 mL 3-necked round bottom flask equipped with a 48x18 mm oval magnetic stir bar and a 400 mm Allihn water cooled condenser, followed by 25 mL light mineral oil through the same funnel. A glass tube (6 mm id) was introduced into the flask *via* the second neck to about 5 cm above the surface of **16b** and was used to provide a stream of house air, which was maintained at a flow rate of 0.12 – 0.15 L/min. The third neck was sealed with a rubber septum. The flask was put into an oil bath and heated to 170 °C without disturbance until solid melted (ca. 30 min). Airflow was allowed to blow into the flask while the molten **16b** was stirred as fast as possible. Solid formed after 4 h, and the reaction was tracked by TLC till the reaction was complete (ca. 35.5 h), and the airflow was switched to N₂ while the flask was removed from the oil bath and cooled to ambient temperature.

Hexanes (50 mL) was added to the flask. The mixture was stirred for 30 min and then it was cooled down to -20 °C overnight before the solid was collected by suction filtration. The beige powder (**10a**, pure on ¹H-NMR spectrum, 4.8 g) was dried on high vacuum (1 mmHg) and crystallized in minimum boiling EtOAc (ca. 150 mL), the dark-colored solution was cooled to room temperature then to -20 °C overnight. The solid was filtered to collect the brown crystal *via* suction filtration and washed by hexanes (10 mL) twice, dried over vacuum to get first crop of racemic VAPOL (**10a**, 2.99 g, 5.56 mmol, 59.1%). The mother liquor was concentrated on rotary evaporator to saturation, heated briefly by heat gun to dissolve the solid, and cooled to -20 °C overnight to get 1.25 g VAPOL (2.32 mmol, 24.7%). The combined yield was 83.8%.

The spectrum of **10a**: white solid; mp 310-311 °C; R_f = 0.29 (1:9 EtOAc:hexane). ¹H-NMR (CDCl₃, 300 MHz) δ 6.59 (s, 2H), 6.66 (d, 4H, J = 7.7 Hz), 6.93 (t, 4H, J = 7.5 Hz), 7.04 (t, 2H, J = 7.4 Hz), 7.42 (s, 2H), 7.61 (t, 2H, J = 7.3 Hz), 7.64-7.67 (m, 4H), 7.79 (d, 2H, J = 8.8 Hz), 7.91 (d, 2H, J = 7.7 Hz), 9.71 (d, 2H, J = 8.4 Hz); ¹³C-NMR (CDCl₃ 75 MHz) δ 115.77, 118.09, 123.23, 126.36, 126.81, 126.99, 127.03, 127.53, 128.44, 128.82, 129.29, 130.28, 132.80, 135.27, 139.70, 141.56, 153.41 (one carbon not located).

7.4.2.2 On large scale

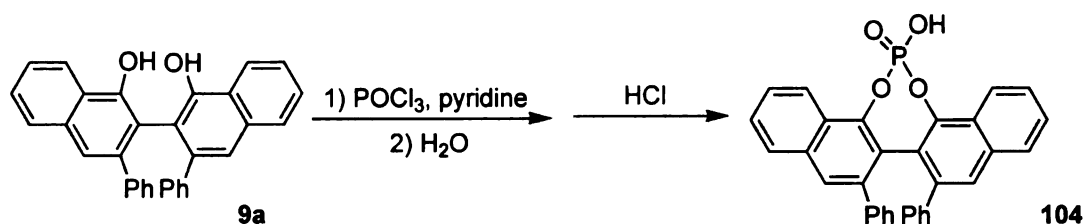
Oil bath (19 cm id with about 1.5L oil in it) was heated to 170 °C while stirring with a magnetic stir. **16b** (50.0 g, 185.2 mmol) was introduced by a funnel into a 2

L 3-necked round bottom flask equipped with a 60x18 mm oval magnetic stir bar and a 400 mm Allihn water cooled condenser, followed by 250 mL light mineral oil through the same funnel. A glass tube (6 mm id) was introduced into the flask *via* the second neck to about 5 cm above the surface of **16b** and was used to provide a stream of house air, which was maintained at a flow rate of 0.15 – 0.20 L/min. The third neck was sealed with a rubber septum. The stirrer bar in the oil bath was removed before the flask was put into it to warm up for about 30 min till solid melted without disturbance of the mixture. Airflow was allowed to blow into the flask while the molten **16b** was stirred as fast as possible. The airflow was switched to N₂ gas after the reaction was kept at same temperature for 36 h, the flask was removed from the oil bath and cooled down to ambient temperature before hexanes (500 mL) was added to the flask. The mixture was stirred for 30 min and then it was cooled down to –20 °C overnight (12 h) before the solid was collected by suction filtration. The crude product (45.1 g, brown powder, 286-287 °C softened and 293-295 °C melted) was dried on high vacuum and crystallized in minimum boiling toluene (about 1 L), the dark-colored solution was cooled down to room temperature then to –20 °C overnight. The top solution was filtered without disturbing the precipitate over vacuum, then a piece of new filter paper was used to collect the brown crystal *via* suction filtration which was washed by hexanes (50 mL) twice and dried over vacuum to get first crop product (33.3 g, 61.9 mmol, 66.8%, mp 310-311 °C, lit. value:^{17b} > 250 °C). The mother liquor was

dried and the residue was crystallized in 150 mL toluene and cooled down to room temperature for 12 h followed by $-20\text{ }^{\circ}\text{C}$ overnight to get 7.0 g VAPOL (13.0 mmol, 14.0%, mp $298\text{--}299\text{ }^{\circ}\text{C}$). The combined yield was 40.3 g (74.9 mmol, 80.9%).

7.5 Experiments for Chapter five

7.5.1 The preparation of 104 from VANOL 9a



Original procedures. To a 2 L RBF charged with N_2 was added 100.0 g (228.04 mmol) VANOL and 800 mL pyridine while stirring. POCl_3 (26 mL, 278.94 mmol) was added dropwisely in a period of 10 min and kept stirring for 2 h at room temperature. The solution was heated in oil bath to $90\text{ }^{\circ}\text{C}$ (oil bath temperature) for 1 h. Upon cooling 100 mL H_2O was added and it was heated to reflux for 1.5 h. Pyridine was removed by rotary evaporator and 6 N HCl (1 L) was added. The mixture was heated to reflux for 2.5 h and cooled down to room temperature, which was allowed to stand overnight. The solid was filtered and washed by totally 5 L water to remove the pyridine salt. The white solid was collected and dissolved in 2 L ethyl acetate. Small amount of water was removed in a separatory funnel; organic layer was dried over MgSO_4 , and the solvent was removed by evaporator. The residue was dried on vacuum for 36 h. The yield: 112.83 g (225.4 mmol,

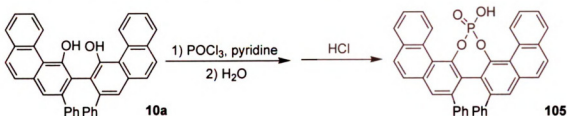
98.8%; white solid).

The spectrum of **104**: white solid. mp = 245-250 °C dec. $^1\text{H-NMR}$ (CDCl_3 300 MHz) δ 5.80 (br s, 1H), 6.45 (d, 4H, $J = 7.5$ Hz), 6.88 (t, 4H, $J = 7.4$ Hz), 7.06 (t, 2H, $J = 7.2$ Hz), 7.47 (s, 2H), 7.49-7.51 (m, 4H), 7.77 (d, 2H, $J = 7.4$ Hz), 8.46 (d, 2H, $J = 7.3$ Hz).

Revised procedures. To a 1-necked 500 mL round bottom flask flushed with N_2 was added 40.0 g (91.3 mmol) of racemic VANOL *via* a powder funnel. As the contents of the flask were stirred with a 48x18 mm oval magnetic stir bar, 150 mL of pyridine was added and used to rinse the funnel. The flask was fitted with a rubber septum and a nitrogen balloon. To the transparent brown solution was added phosphorus oxychloride (17.0 mL, 182.4 mmol) dropwise over a period of 10 min *via* a plastic syringe. Upon addition of POCl_3 the flask becomes hot and a beige precipitate forms but does not stop the stirrer. The resulting suspension was stirred for 6 hours at room temperature. Water (120 mL) was added slowly in 3 to 4 portions and the addition of each subsequent portion was delayed until boiling had subsided. The resulting biphasic suspension was stirred at room temperature for 2 h. The pyridine was removed by rotary evaporator and the residue was dissolved in 250 mL CH_2Cl_2 to give a brown solution which was washed twice with 500 mL 1 N HCl. The solution was dried over MgSO_4 and filtered; the solvent was removed to give the crude product, which was dried overnight under high vacuum. This left the crude product as a yellow amorphous

solid which was used directly in the resolution without further purification. The yield: 44.0 g (87.9 mmol, 96.4%).

7.5.2 The preparation of **105** from VAPOL **10a**.



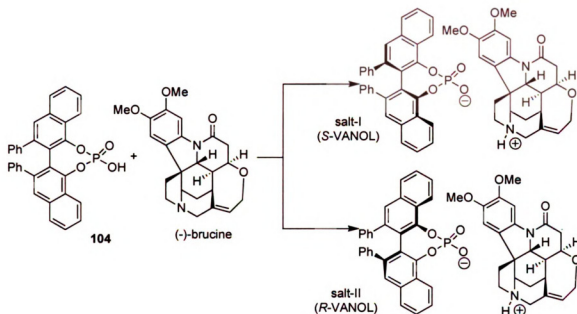
Original procedures. The original procedures to prepare 41.6 g of **105** (69.3 mmol, 93.2%) from VAPOL **10a** (40.0 g, 74.3 mmol) are the same as the original procedures to prepare **104** in the **section 7.5.1**.

The spectrum of **105**: white solid, $\text{Mp} > 350^\circ\text{C}$. $^1\text{H-NMR}$ (CDCl_3 300 MHz) δ 6.51 (d, 4H, $J = 7.2$ Hz), 6.60 (br, s, 1H), 6.93 (t, 4H, $J = 7.3$ Hz), 7.09 (t, 2H, $J = 7.5$ Hz), 7.23 (s, 2H), 7.52-7.55 (m, 4H), 7.66 (d, 2H, $J = 8.8$ Hz), 7.76 (d, 2H, $J = 9$ Hz), 7.87 (d, 2H, $J = 7.5\text{Hz}$), 9.87 (d, 2H, $J = 8.5$ Hz).

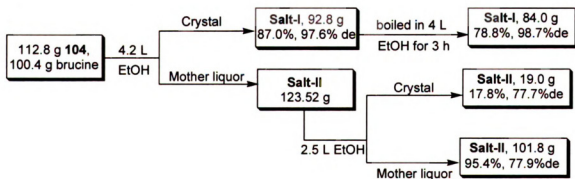
Revised procedures. To a 500 mL RBF charged with N_2 was added 30.91 g (57.4 mmol) VAPOL and pyridine (170 mL) while stirring. Phosphorous oxychloride (10.7 mL, 114.8 mmol) was added dropwisely in a period of 10min after all solid dissolved and the resulting solution was stirred for 6 hours at room temperature. A lot of solid formed after about 45 min. Water (75 mL) was added slowly and the resulting biphasic suspension was stirred at room temperature for 2 hours. Pyridine was removed by rotary evaporator and the residue was combined with 250 mL 1 N HCl, which was filtered and washed with 500 mL 1 N

HCl. It was dried over high *vacuo* overnight and used directly for resolution without further purification. The yield of **105** was 34.3 g (54.4 mmol, 100%).

7.5.3 The resolution of **104** by using (-)-brucine.



7.5.3.1 The resolution of **104** in EtOH to isolate the salt-I first.



The phosphoric acid **104** (112.8 g, 225.4 mmol), (-)-brucine dihydrate (100.4 g, 233.3 mmol, technical grade) and a stirrer bar was placed in a 6 L Erlenmeyer flask. EtOH (4.2 L) was introduced to the flask and heated to gently boil for 3 h while it was stirred with a large 60x18 mm oval magnetic stir bar. The heat was

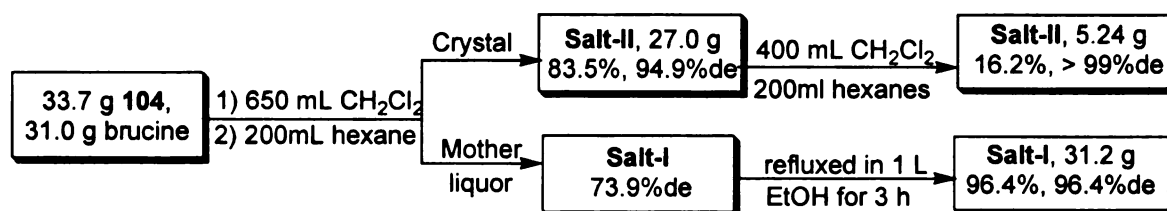
stopped to cool the solution down. When the boiling stopped, the stirrer was shut down and the solution was allowed to cool down overnight. The solid was collected by filtration and dried over high vacuum for 12 h to afford 92.8 g (103.7 mmol, 87.0%) salt-I. It was revealed that the 2,2'-binaphthol chiral axis in this salt has an S-configuration by reduction of a small sample (For the procedures, see **Note** below) with 97.6% de.

The solvent in the mother liquor was completely removed by rotary evaporator and the residue (123.5 g) was gently boiled with 1 L EtOH in the same 6 L Erlenmeyer flask. More EtOH was added (500 mL each) till solid dissolved (totally 2.5 L EtOH used). It was boiled for 10 min before it was cooled down to room temperature overnight. The solid was isolated and dried over high vacuum for 12 h to afford 19.1 g salt-II (21.3 mmol, 17.8%, 77.7% de). The solvent in the mother liquor was completely removed by rotary evaporator and 101.8 g solid was salt-II with 77.9% de.

Note: The procedures for the reduction of the 104-brucine salt to test the ee. From a thoroughly mixed salt-II was removed a small sample (0.2 to 0.5 g) which was placed in a 25 mL flask equipped with a stir bar. The flask was sealed with a rubber septum, filled with argon, and fitted with a N₂ balloon. Toluene (2 mL) was injected and the flask was cooled in an ice bath for at least 30 min. Red-Al (1 mL, 65 wt % in toluene, 3.28 mmol) was added dropwise with stirring. The ice bath was removed and the solution was stirred for 30 min. The flask was

cooled to 0 °C and pre-chilled 6 N HCl (3 mL) was added dropwise to quench the reaction. To the biphasic mixture was added ether (3 mL) and the resulting mixture was stirred for 5 min to make sure extraction was complete. The organic layer was collected by pipette and dried over MgSO₄, filtered and evaporated to dryness with vacuum. The residue was taken up in 1 mL CH₂Cl₂ and the resulting solution was passed through a short silica gel column prepared in a Pasteur pipette by packing with (from bottom to top) cotton, a thin layer of sand, 5 cm silica gel and another thin layer sand. The flask was rinsed with 3 mL CH₂Cl₂, and this also flushed through the column with the assistance of a rubber bulb on the top of the pipette. The filtrate was dried under vacuum and the residue was dissolved in 0.5 mL ethyl acetate and 3 mL hexanes. This solution (3–4 µL) was used in the determination of the optical purity of the VANOL by HPLC with the following conditions: Pirkle D-Phenylglycine column with a 98:2 mixture of hexane/isopropanol (254 nm, flow rate: 1 mL/min to 2 mL/min over 30 min). Under these conditions, the retention time of (*R*)-VANOL was 17.4 min and that of (*S*)-VANOL was 19.8 min.

7.5.3.2 The resolution of **104** in CH₂Cl₂/ hexanes to isolate salt-II first.

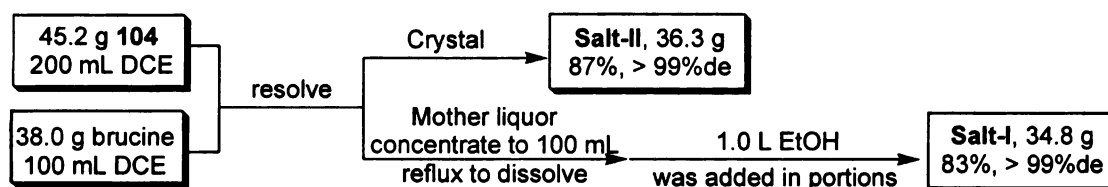


The phosphoric acid **104** (33.7 g, 67.3 mmol) was placed in a 2 L round bottom

flask equipped with condenser and a 48x18 mm oval magnetic stir bar. CH_2Cl_2 (650 mL) was introduced to the flask and heated to reflux to dissolve the solid. Brucine dihydrate (31.10g, 72.24 mmol, technical grade) was added to the solution and stirred to dissolve. Hexanes (200 mL) was slowly added through the condenser in a period of 30 minutes while refluxing. After a while some white solid crashed out of solution and the heat was stopped to cool the solution down. When the boiling stopped, the stirrer was shut down and the solution was allowed to cool down overnight. The solid was collected by filtration and dried over high vacuum for 12 h to afford 27.0 g (30.17 mmol, 83.5%) salt-II with 94.9% de.

The mother liquor was dried by rotary evaporator and combined with 100 mL CH_2Cl_2 , which was heated to reflux to dissolve the solid. Ethanol (500 mL) was slowly added while refluxing over 30 min, solid should precipitate; Another 500 mL ethanol was added to the mixture and it was refluxed for 10 min before it was cooled down to room temperature overnight. The solid was isolated and dried over high vacuum for 12 h to afford 31.2 g (34.7 mmol, 96.4%) salt-I. It was revealed that the 2,2'-binaphthol chiral axis in this salt has an S-configuration by reduction of a small amount of the sample with 96.4% de.

7.5.3.3 The resolution of 104 in 1,2-dichloroethane (DCE).

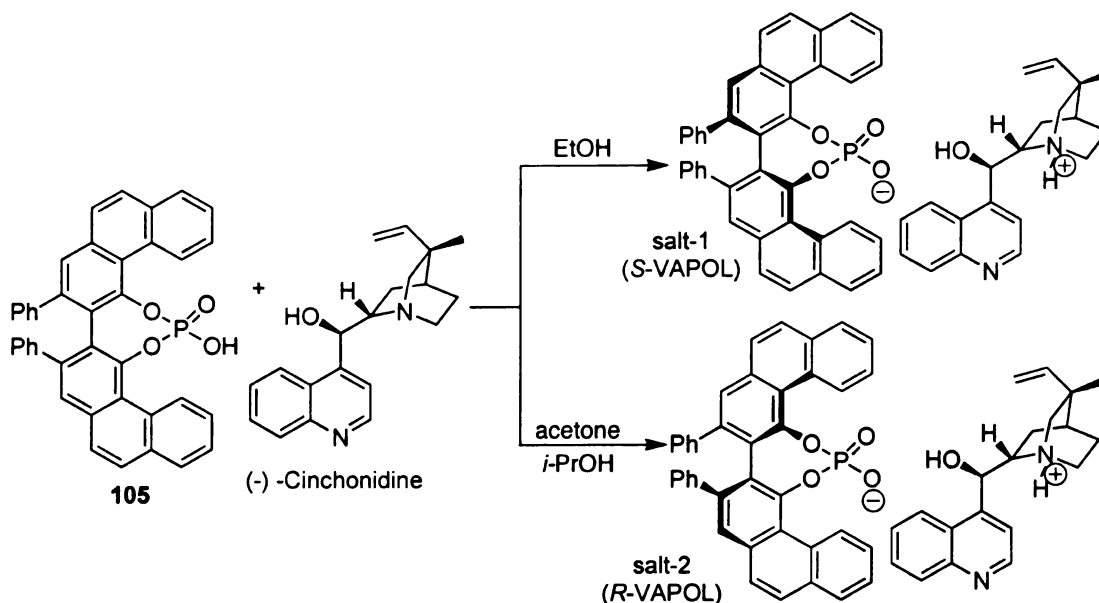


The phosphoric acid **104** (45.2 g, 90.3 mmol) was placed in a 500 mL 3-neck round bottom flask that was equipped with condenser and stirrer bar 48x18 mm and which had been flushed with a N₂ stream that was introduced *via* a needle in a septum on one of the necks of the monitored by a bubbler attached to the condenser. To the flask was added DCE (200 mL) and the contents of the flask were stirred and brought to a boil by heating the flask with a heating mantel. To a separate 250 mL pear-shaped flask was added brucine dihydrate (38.0 g, 88.6 mmol, technical grade, 92.6%) and 90 mL of DCE. The contents of the flask was purged with N₂ for about 2 min, and then sealed with rubber septum which was fitted with a nitrogen balloon. This flask was heated by swirling in hot flowing water (50 °C) until a clear colorless solution (volume about 110 mL) resulted which had a small amount of a grey insoluble impurities floating on top. The resulting solution was placed in a hot water bath (50 °C) and 60 mL of the brucine solution was removed by a syringe equipped with a 12 gauge needle and added to **104** solution over a period of about 1 minute to give a brownish clear solution. The remainder of the brucine solution (about 50 mL) was loaded into the syringe leaving the insoluble material in the flask. The brucine solution was slowly added to the solution of **104** *via* syringe pump (addition rate: 100 mL/h). Solid began to form when about 22 mL of the solution was left in the syringe. The addition was paused while the suspension was refluxed for 15 min, and then the addition was resumed to complete the addition to the suspension. An

additional portion of DCE (10 mL) was used to rinse the pear flask leaving the insoluble material in the flask. The final washing was added over a period of one minute. The resulting suspension was cooled down slowly to room temperature and let it settle for 48 h without disturbance. The white solid was collected by filtration through a Buchner funnel and washed three times with DCE (25 mL) and then dried over high vacuum for 12 h to afford 36.3 g (40.5 mmol, 87%, >99%de) of the salt-II.

The dark yellow mother liquor was stripped of volatiles by rotary evaporator and combined with 100 mL DCE in a 2 L 1-neck round bottom flask fitted with a condenser. The resulting mixture was stirred and brought to a boil to dissolve the solid residue. A total of 1000 mL of ethanol was added in portions as follows: First 300 mL of ethanol was added and the resulting solution was returned to a boil and then an additional ethanol (200 mL) was added and again returned to a boil. At this point another 200 mL portion of ethanol was added and the mixture was refluxed for 15 min until it appeared that no further accumulation of precipitate was occurring. Finally, an additional 300 mL portion of ethanol was then added and the mixture was refluxed for 10 min before being allowed to cool to room temperature overnight undisturbed. The beige solid was isolated by filtration in a Buchner funnel and dried over high vacuum for 12 h to afford 34.8 g (38.9 mmol, 83%, >99%de) of the salt-I. The filtrate was stripped of volatiles to give 10.50 g of a light brown solid (salt-I, 32%de).

7.5.4 The resolution of **105** by using (-)-cinchonidine.



To a boiling suspension of the **105** (40.0 g, 65.9 mmol) in 2 L absolute ethanol in a 4 L Erlenmeyer flask was added (-)-cinchonidine (20.0 g, 65.2 mmol) while stirring on hot plate (Corning) with a 60x18 mm oval magnetic stir bar. Ethanol (500 mL) was used to rinse all (-)-cinchonidine into the suspension, which was gently boiled for 30min before it was cooled down to room temperature overnight. The solution was filtered without disturbing the solid till most of the liquid went through the Buchner funnel, and then the filter paper was replaced by a new one and the left solid was broken, filtered and washed with ethanol (50 mL). This solid (17.6 g, 19.3 mmol, 58%) was showed by $^1\text{H-NMR}$ spectrum to be salt-1. The mother liquor was dried by rotary evaporator and combined with 2 L 2-propanol, which was heated to boil in a 4 L Erlenmeyer flask and acetone was added slowly till solid dissolved (about 500 mL) while stirring. This solution was cooled down to

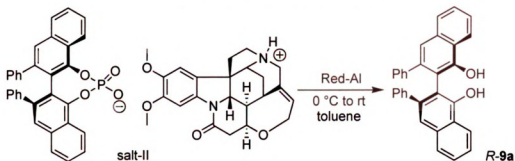
room temperature overnight and then to $-20\text{ }^{\circ}\text{C}$, crystal (26.1 g, 28.7 mmol, 87%) was collected and ^1H -NMR showed it was pure salt-2. The filtrate was dried and dissolved in minimum boiling CH_2Cl_2 (about 50 mL), to which ethanol (100 mL) was added in two portions and heated for 15 min till solid crashed out. More ethanol was then introduced (400 mL in two portions) and heated to boil then to room temperature overnight. Solid was filtered and washed with 25 mL ethanol twice, which was confirmed to be pure salt-1 by ^1H -NMR (9.24 g, 10.1 mmol, 31%). The mother liquor was dried by rotary evaporator and combined with 500 mL 2-propanol, which was heated to boil and acetone was added slowly till solid dissolved (about 50 mL) while stirring. This solution was cooled down to room temperature overnight and then to $-20\text{ }^{\circ}\text{C}$, crystal (5.20 g, 5.7 mmol, 12%) was collected and ^1H -NMR showed it was pure salt-2. The filtrate (the ratio of salt-1 to salt-2 was proved to be 3:1 by ^1H -NMR spectrum, totally 8.6 g) was dried and dissolved in minimum boiling CH_2Cl_2 (15 mL), to which ethanol (25 mL $\times$ 2+50 mL) was added, each time it was heated to boil for 10 min. Solid crashed out, and more ethanol (150 mL, which made the total volume of ethanol of 250 mL) was introduced and heated to boil then cooled to rt overnight. Solid was filtered and washed with 25 mL ethanol, which was confirmed to be pure salt-1 by ^1H NMR (3.06 g, 3.36 mmol, 10%). Further crystallization by 2-propanol (150 mL) and acetone as described above was not as reliable. Total amount of salt-1 and salt-2: 30.0 g (99%) and 31.3 g, (99%) respectively.

The spectrum of the salt-1: white solid; $^1\text{H-NMR}$ (CDCl_3 500 MHz) δ 0.75-0.85 (m, 1H), 1.50-1.80 (m, 6H), 2.28 (s, 1H), 2.38 (s, 1H), 2.62-2.81 (m, 2H), 4.10 (s, br, 1H), 4.70 (d, 1H, $J = 17.1$ Hz), 4.83 (d, 1H, $J = 10$ Hz), 5.08-5.12 (m, 1H), 5.92 (s, 1H), 6.49 (d, 4H, $J = 7.8$ Hz), 6.60 (br s, 2H), 6.77 (t, 1H, $J = 7.7$ Hz), 6.85 (t, 4H, $J = 7.6$ Hz), 7.01 (t, 2H, $J = 7.3$ Hz), 7.15 (m, 3H), 7.19-7.27 (m, 4 H), 7.43 (s, 2H), 7.55-7.61 (m, 6H), 7.75 (d, 1H, $J = 8.4$ Hz), 8.67 (d, 1H, $J = 4.4$ Hz), 10.08 (d, 2H, $J = 8.6$ Hz), 11.79 (s, br, 1H).

The spectrum of the salt-2: light yellow crystal; $^1\text{H-NMR}$ (CDCl_3 500 MHz) δ 0.97-1.05 (m, 1H), 1.20-1.29 (m, 1H), 1.50-1.58 (m, 1H), 1.62-1.73 (m, 2H), 1.98-2.07 (m, 1H), 2.18-2.19 (m, 1H), 2.40-2.50 (m, 3H), 3.10-3.15 (m, 1H), 4.05-4.15 (m, 1H), 4.75 (d, 1H, $J = 17.2$ Hz), 4.81 (d, 1H, $J = 10.4$ Hz), 5.22-5.32 (m, 1H), 6.39 (s, 1H), 6.55 (d, 4H, $J = 7.4$ Hz), 6.61 (br s, 1H), 6.89 (t, 4H, $J = 7.6$ Hz), 6.98 (t, 2H, $J = 7.8$ Hz), 7.04 (t, 2H, $J = 7.3$ Hz), 7.36-7.31 (m, 4H), 7.50 (s, 2H), 7.59-7.68 (m, 6H), 7.75 (d, 2H, $J = 7.8$ Hz), 8.16 (d, 1H, $J = 7.7$ Hz), 8.40 (d, 1H, $J = 7.9$ Hz), 8.69 (d, 1H, $J = 5.0$ Hz), 9.94 (d, 2H, $J = 8.6$ Hz), 11.85 (s, 1H).

7.5.5 The liberation of the optically pure VANOL and VAPOL ligands by reductive cleavage of the salts using Red-Al.

7.5.5.1 The liberation of *R*-VANOL by reductive cleavage of salt-II.

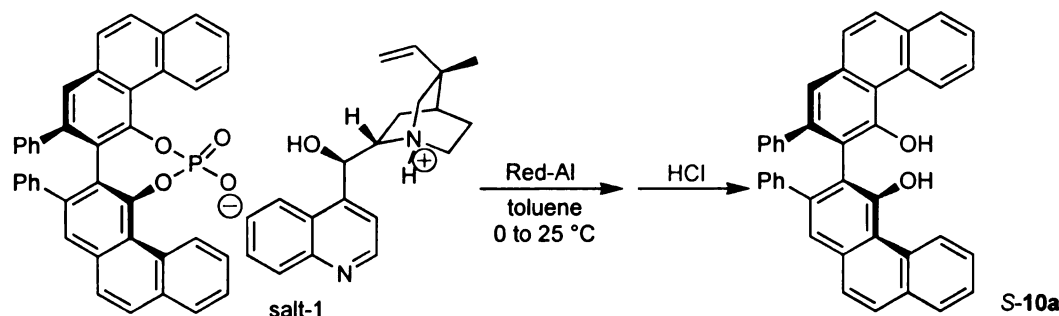


To an oven-dried 1 L RBF was added the salt-II (52.7 g, 58.8 mmol), 250 mL reagent-grade toluene and a 48x18 mm oval magnetic stir bar. The flask was equipped with and a 1 L pressure compensating addition funnel which was sealed with a rubber septum. It was flushed with N₂ for at least 30 min, and the mixture was cooled to 0 °C. A nitrogen balloon was used to balance the pressure. Red-Al (75 mL, 65% wt in toluene, 246 mmol) was added to the funnel and then slowly added to the flask over 3 h while stirring, and then it was warmed up to room temperature for 4.5 h. The flask was cooled down to 0 °C and chilled (0 °C) HCl (6 N, 500 mL) was added slowly to quench the reaction as follows: The first 20 mL of HCl was added a pipette full at a time down inside wall of the flask, and the remainder was added in 3 - 5 portions over 10 min. The mixture was put into a 2-L separatory funnel and organic layer was collected. The water layer was extracted by 500 mL ethyl acetate 3 times. The combined organic layer was washed with 400 mL brine, dried over MgSO₄ and filtered. Upon removal of the solvent the

residue (ca. 25 g) was dissolved in minimum amount of CH_2Cl_2 (ca. 50 mL) and loaded onto a silica gel column (4.5 cm OD, silica gel was filled to a depth of 40 cm) and eluted by hexanes: CH_2Cl_2 = 1:2. When TLC indicated that VANOL began to elute, a 2 L round bottomed flask was used to collect all of the VANOL. When the elution was complete (ca. 2 L), 5 drops of this solution was saved for HPLC analysis. The rest of solution was stripped of solvents to give a foam-like solid. This solid was dissolved in a minimum (ca. 50 mL) of CH_2Cl_2 and then 300 mL hexanes was added. The solution was slowly evaporated by a rotary evaporator to dryness. The residue was again taken up in a minimum of (ca. 50 mL) of CH_2Cl_2 and then 300 mL of hexanes was added. The resulting mixture was shaken vigorously under a strong N_2 flow until a solid crashed out. This mixture was then slowly evaporated to dryness. This process gave *R*-VANOL as a white powder-like solid that was more stable to long term storage. Yield: 22.7 g (51.9 mmol, 88.1%). The optical purity of (*R*)-VANOL was determined as follow: 5 drops of saved (*R*)-VANOL solution was diluted with 2 mL of hexanes, from which ca. 4 μL was injected into an HPLC with a Pirkle D-Phenylglycine column and eluted with a 98:2 mixture of hexane/isopropanol (254nm, flow rate: 2 mL/min over 30 min). Under these conditions, the retention time of (*R*)-VANOL was 18.3 min and that of (*S*)-VANOL was 20.6 min. The ee of this sample was >99 %.

The *S*-VANOL can be obtained in the same way. Solid might crash out upon acidification of the crude mixture with HCl, which can be removed *via* filtration.

7.5.5.2 The standard procedure to liberate S-VAPOL by reductive cleavage.



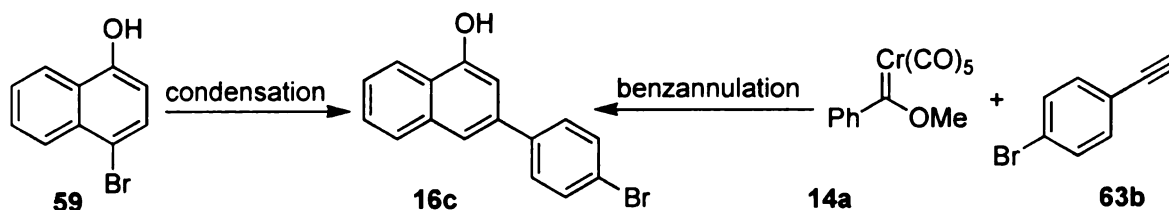
A 500 mL 3-neck round bottom flask equipped with stirrer bar was sealed with one rubber septum and two adapters; one of them was connected to bubbler. N₂ was introduced from another adapter for 1 hr. The salt-1 (36.3 g, 40.6 mmol) was put into the flask and the adapters were switched to two rubber septums with a N₂ balloon on it. Toluene (200 mL) was added followed by a 48x18 mm oval magnetic stir bar. The mixture was cooled down in ice-water bath for 1 h, and then Red-Al (54 mL, 177.0 mmol as a 65 wt% solution in toluene) was added *via* syringe pump over 3 h by using a 12-gauge needle while stirring. The suspension was allowed to stir at room temperature overnight and then was chilled in ice-water bath for 1 h, and then pre-cooled HCl (6 N, 150 mL, 0 °C) was added and the mixture was stirred at room temperature for 5 min before it was poured into a 1 L separatory funnel. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (100 mL) three times. The combined organic layer was washed with brine (100 mL) and then dried by MgSO₄. After filtration through Celite, the solvent was removed in *vacuo*. The residue (*ca.* 20 g) was dissolved in minimum amount of CH₂Cl₂ (about 110 mL, a little bit heat from

heating gun may help to dissolve) and was loaded onto a chromatography column (6 cm diameter) prepared by filling the column with a mixture of 1:20 CH₂Cl₂ and hexanes and then the addition of silica gel such that after settling a depth of ca. 15 cm had been reached. When the solvent level was lowered to the top of the column, the column was eluted with a 1:1 mixture of hexanes to CH₂Cl₂ and tracked with TLC and till product came down the column. All solution (about 1.5 L) was combined together, from which 5 drops was collected by pipette which was later used for optical purity determination, the rest was dried slowly on rotary evaporator to give shining yellow crystal. To remove the color, the crystal was combined with 30 mL CH₂Cl₂, swirled for about 1 min and then 100 mL hexane was added; this mixture was filtered and rinsed by hexanes (25 mL, twice). The solid (19.8 g, 36.8 mmol 90.6% as light yellow crystal) was collected and dried overnight. The optical purity of S-VAPOL (**S-10a**) was determined to be > 99% by HPLC using a Pirkle D-phenylglycine column as described below: the collected 5-drop solution was diluted by 5 mL hexanes, from which 4 µL was injected to HPLC with the following conditions: 260 nm, 2 mL/min, 25: 75 mixture of 2-propanol and hexanes, and the *t_R* = 14.0 min for S-VAPOL and *t_R* = 23.9 min for R-VAPOL.

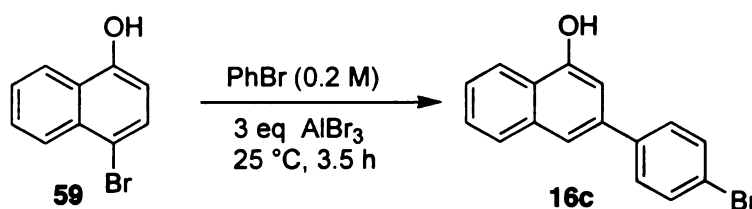
The R-VAPOL (**R-10a**) can be obtained in the same way.

7.6 Experiments for Chapter six

7.6.1 Preparation of 3-(*p*-bromophenyl)-1-naphthol (**16c**).



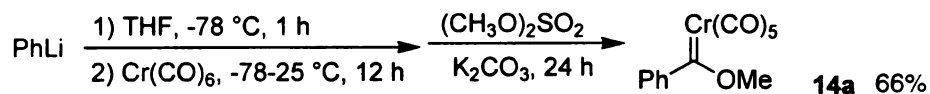
7.6.1.1 Preparation of **16m** by condensing **59** with PhBr using AlBr₃



A 50 mL 3-neck flask equipped with a stirrer bar was charged with AlBr₃ (2.231 g, 8.36 mmol) and then filled with argon. Bromobenzene (5 mL) was injected and stirred to dissolve. The color changed to red. A solution of **59** (0.6617 g, 3.0 mmol) in 12 mL bromobenzene was injected to the flask over a period of 10 min. The color changed to dark brown then dark green. The reaction was stirred for 3.5 h before it was poured to 50 mL 6 N HCl at 0 °C, which was extracted with 50 mL ether twice. The organic layer was dried over MgSO₄ and filtered. All solvents from the filtrate were removed in *vacuo* to get a black tarry mixture. This material was dissolved in minimum amount of CH₂Cl₂ and loaded onto column, eluted by a mixture of hexanes with EtOAc (10:1) to get a yellow solid (0.575 g). ¹H-NMR spectrum showed it was a mixture. It was crystallized either in boiling CH₂Cl₂/hexanes, or in boiling minimum amount of acetic acid, or toluene, the formed

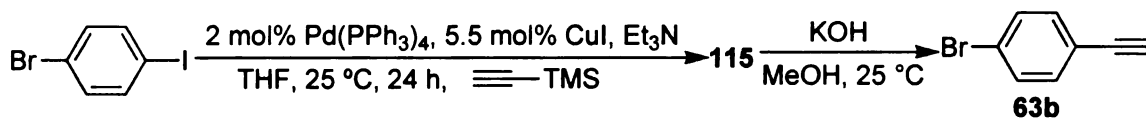
white crystal was still a mixture.

7.6.1.2 Preparation of 16m via Wulff-Dötz benzannulation reaction



Preparation of pentacarbonyl[1-phenyl(methoxy)chromium] carbene **14a**.

To a flame-dried 500 mL 3-necked round-bottom flask equipped with a stirrer bar and an addition funnel was filled with argon, and PhLi (16 mL, 1.8 M, 28.8 mmol) was injected followed by 200 mL of freshly distilled THF under positive pressure of N₂. As the solution was cooled to -78 °C in dry ice/ acetone bath and the temperature was equilibrated for 1 h while stirring, Cr(CO)₆ (6.03 g, 27.4 mmol) was added through a powder funnel and the reaction mixture was allowed to warm to room temperature overnight under positive N₂. To this dark brown reaction mixture was added K₂CO₃ (6.2 g, 45 mmol) and (CH₃O)₂SO₂ (42 mL, 45 mmol) and the resulting red suspension was stirred for 24 h before it was suction filtered through a 2.5 cm bed of packed Celite by a Büchner funnel. Both the flask and the funnel were rinsed with 100 mL of CH₂Cl₂ till the filtrate was light yellow. The organic solvent was removed in *vacuo*, the resulting red oil was loaded on a silica gel column, eluted with hexanes to get 5.64 g (18.05 mmol, 66%) **14a** as red solid.

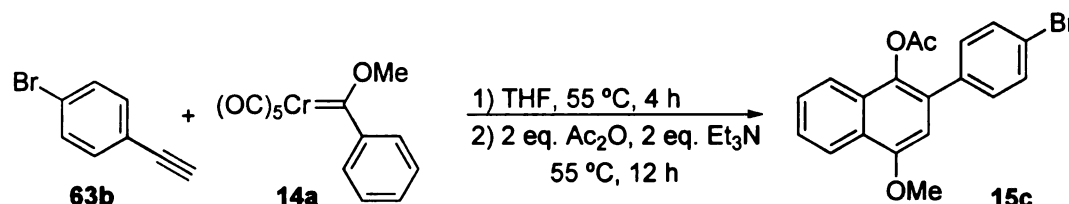


Preparation of 4-bromophenylacetylene 63b. To a 250 mL flame-dried flask filled with argon was added the CuI (0.232 g, 1.2 mmol), Pd(PPh₃)₂Cl₂ (0.315 g, 0.45 mmol) and 4-iodobromobenzene (6.24 g, 22 mmol). The flask was then connected to vacuum and then filled with argon with an argon balloon on it. Following the addition of THF (40 mL) and TEA (12 mL, 86.6 mmol), it was cooled down to 0 °C and stirred for 1 h. Then trimethylsilyl acetylene (3.1 mL, 22 mmol) was added slowly over 30 min. The reaction mixture was stirred for 24 h. The crude mixture was filtered *via* Celite which was washed with EtOAc (300 mL). After removal of most of the solvent by rotary evaporation, the residue was put on column made by silica gel with hexanes, which was eluted by hexanes to get 5.345 g (21.1 mmol, 95.7%) of **115** as a white solid.

115 (7.125 g, 28.1 mmol) was taken up in 130 mL MeOH and treated with KOH (3.72 g, 66.3 mmol) in a 250 mL flask. The reaction mixture was stirred at room temperature for 24 h to give complete conversion as monitored by TLC. To the reaction mixture was added 200 mL H₂O and this was followed by extraction with Et₂O. The organic layer was dried over MgSO₄ and concentrated under reduced pressure to give the crude **63b** as off-white solid. Purification by silica gel chromatography (hexanes as eluent) afforded **63b** (3.70 g, 20.4 mmol) as white solid in 72.6% yield.

Spectral data for **115**: white solid, mp 60 - 61 °C,¹⁵⁵ R_f = 0.50 (hexane).
¹H-NMR (CDCl₃, 300 MHz) δ 0.25 (s, 9H), 7.31 (d, 2H, J = 8.6 Hz), 7.42 (d, 2H, J = 8.6 Hz); ¹³C NMR (CDCl₃ 75 MHz) δ -0.15, 95.53, 103.81, 122.00, 122.72, 131.42, 133.35;

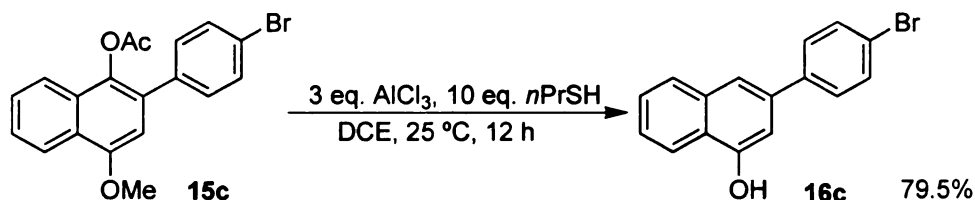
Spectral data for **63b**: white solid, mp 64-65 °C, R_f = 0.50 (hexane). ¹H-NMR (CDCl₃, 300 MHz) δ 3.07 (s, 1H), 7.30 (d, 2H, J = 8.5 Hz), 7.42 (d, 2H, J = 8.6 Hz).



Preparation of 2-(4-bromophenyl)-4-methoxynaphthalenyl acetate 15c.

To a 250 mL flame-dried flask filled with argon was added carbene complex **14a** (4.53 g, 14.5 mmol) and 40 mL dry THF. The flask was put into a 55 °C oil bath. Acetylene **63b** (3.70 g, 20.4 mmol) in dry THF (60 mL) was injected over 3 h under positive pressure of N₂. The contents were stirred for another hour. Ac₂O (5 mL, 64.6 mmol) and Et₃N (7.5 mL, 54 mmol) were added, the reaction mixture was stirred at 55 °C for 12 h. The flask was then cooled to room temperature. The precipitate was removed by Celite filtration, washed with EtOAc (100 mL). The filtrate was collected brought to dryness in *vacuo*. The residue was dissolved in minimum amount of CH₂Cl₂, loaded onto a silica gel column and eluted by a mixture of 1:15 EtOAc/ hexanes to give (4.64 g, 12.5 mmol, 86.3%) as a light yellow solid.

Spectral data for **15c**: white solid, mp 137 –138 °C;^{18f} R_f = 0.33 (1: 9 EtOAc/Hexanes). ¹H NMR (CDCl₃, 300 MHz) δ 2.25 (s, 3H), 4.04 (s, 3H), 6.82 (s, 1H), 7.48 (d, 2H, J = 7.6 Hz), 7.58-7.65 (m, 4H), 7.83 (d, 1H, J = 7.8 Hz), 8.39 (d, 1H, J = 7.8 Hz).

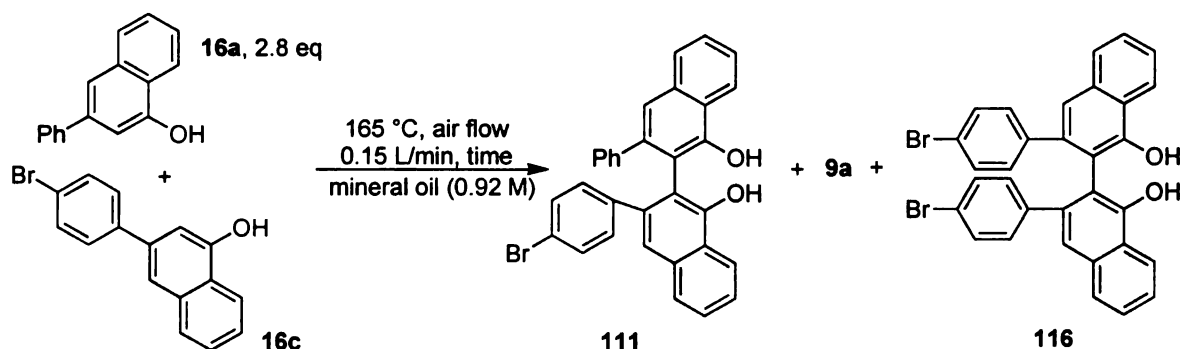


Preparation of 3-(4-bromophenyl)naphthol 16m. To a 100 mL 3-neck flask flushed with N₂ was added stirrer bar, AlCl₃ (6.0 g, 41.6 mmol), 40 mL DCE and *n*-PrSH (8 mL, 88 mmol). It was stirred for 20 min before **15c** (4.645 g, 12.5 mmol) in 15 mL DCE was added over a period of 15 min. It was stirred for 12 h at 25 °C. The reaction was quenched by slow addition of HCl (3 N, 50 mL with 100 g ice). It was stirred and 50 mL of CH₂Cl₂ was used to dilute it. The organic layer was collected, and the aqueous layer was extracted with CH₂Cl₂ (100 mL $\times$ 2). The combined organic layer was washed in turn with NaHCO₃ (aq. sat.) and brine, dried over MgSO₄ and filtered. The filtrate was concentrated under reduced pressure to give the crude product as a brown solid. Purification by dissolving it in CH₂Cl₂ and loaded it onto a silica gel column, eluted by a mixture of 1:2:20 EtOAc/CH₂Cl₂/hexanes to give the product **16c** (3.0 g, 9.95 mmol, 79.5%) as a white solid.

Spectral data for **16c**: white solid, mp 168-9 °C;^{18f} R_f = 0.43 (1:3

EtOAc/hexanes). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 5.40 (s, 1H), 7.05 (d, 1H, $J = 1.5$ Hz), 7.52-7.63 (m, 7H), 7.88 (dd, 1H, $J = 1.6, 7.9$ Hz), 8.22 (dd, 1H, $J = 1.2, 8.1$ Hz); ^{13}C (CDCl_3 , 75 MHz) δ 107.97, 118.70, 121.47, 121.73, 123.66, 125.60, 127.09, 128.02, 128.84, 131.92, 134.91, 137.63, 139.82, 151.84; IR (thin film) 3231 br vs, 1603 m, 1400 s cm^{-1} ; mass spectrum, m/z (% rel intensity) 300 M^+ (62, ^{81}Br), 298 M^+ (100, ^{79}Br), 191 (30), 189 (84), 163 (12), 109 (25), 95 (60), 82 (20), 62 (12). Anal. calcd for $\text{C}_{16}\text{H}_{11}\text{BrO}$: C, 64.24; H, 3.71. Found: C, 64.30; H, 3.33.

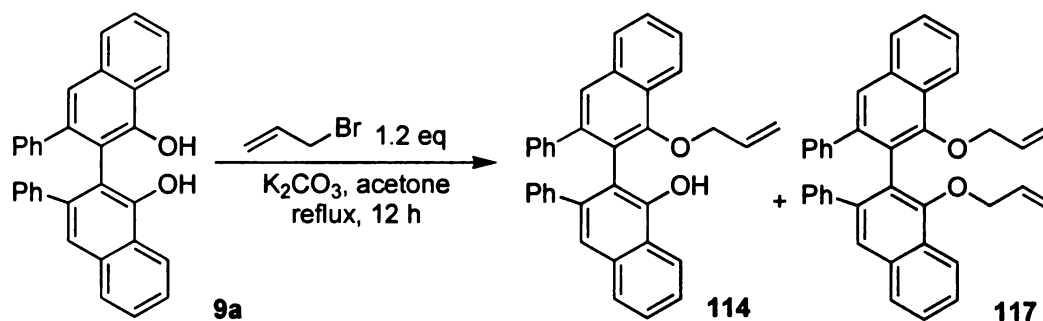
7.6.1.3 Attempted preparation of 111 by oxidative coupling of 16a with 16c



Oil bath was heated to 165 °C while stirring with a magnetic stir. **16a** (2.076 g, 9.4 mmol) and **16c** (1.007 g, 3.37 mmol) was introduced into a 100 L 3-necked round bottom flask equipped with a 60x18 mm oval magnetic stir bar and a 400 mm Allihn water cooled condenser, followed by 25 mL light mineral oil through the same funnel. A needle was introduced into the flask *via* the second neck to about 5 cm above the surface of naphthol and was used to provide a stream of house air which was maintained at a flow rate of 0.15 L/min. The third neck was sealed with a rubber septum. The stirrer bar in the oil bath was removed before

the flask was put into it to warm up for about 15 min till solid melted. Airflow was allowed to blow into the flask while the contents were stirred as fast as possible. The reaction was kept at same temperature for 24 h, and the airflow was switched to N₂. The flask was removed from the oil bath and cooled to ambient temperature before hexanes (100 mL) was added to the flask. The mixture was stirred for 30 min and then it was cooled down to -20 °C overnight before the solid was collected by suction filtration. The crude product was dried on high vacuum. The crystallization in CH₂Cl₂, or silica gel columns (EtOAc/CH₂Cl₂/hexanes = 1:2:20 as eluent), or preparative TLC using the same eluent all failed to separate this mixture.

7.6.1.4 Attempted preparation of 114 by alkylation of 9a with allyl bromide

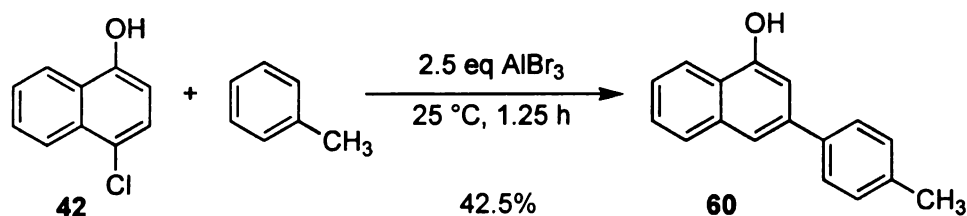


In a 100 mL round bottom flask fitted with a reflux condenser are placed of **S-9a** (4.38 g, 10 mmol) and 20 mL of acetone. The mixture is warmed on a steam bath to dissolve the entire solid. The solution is cooled to room temperature, and 2.07 g K₂CO₃ (15 mmol) is added followed by 1.04 mL (12 mmol) of allyl bromide. The mixture is stirred at refluxing temperature for 20 hours. TLC showed all **S-9a** was consumed with two new products formed with $R_f = 0.62$ for one of them and

$R_f = 0.68$ for another (1:3 EtOAc /hexanes).

After filtration, as much of the acetone as possible is removed in *vacuo*. The residual is dissolved in minimum amount of CH_2Cl_2 and loaded on to a column. It is rinsed with EtOAc/ CH_2Cl_2 /hexanes=1:2:20 to get 1.25 g yellow solid, which was dissolved in CDCl_3 and the ^1H -NMR spectrum showed it was a mixture. TLC showed two new components ($R_f = 0.34$ and $R_f = 0.56$ (1:3 EtOAc /hexanes)) formed.

7.6.1.5 Preparation of 60 with toluene as the solvent



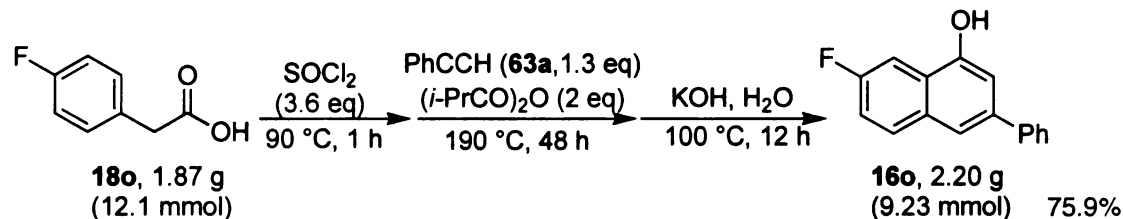
Compound **60** (317 mg, 1.35 mmol, 42.5%) was prepared with the procedure used for the preparation of **16b** described in **Section 7.6.1.1**. The reaction was carried out with 568 mg (3.18 mmol) of **42** and 2.16 g AlBr_3 (8.13 mmol) in 10 mL toluene.

Spectral data for **60**: off-white solid, mp $135 - 136^\circ\text{C}$, $R_f = 0.24$ (1:5 EtOAc/hexane). ^1H -NMR (CDCl_3 , 300 MHz) δ 2.46 (s, 3H), 5.33 (s, 1H), 7.12 (d, 1H, $J = 1.46$ Hz), 7.31 (s, 1H), 7.33 (s, 1H), 7.48-7.58 (m, 2H), 7.61 (s, 1H), 7.64 (s, 1H), 7.68 (s, 1H), 7.89-7.91 (m, 1H), 8.18-8.22 (m, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 31.37, 108.60, 118.68, 121.66, 123.66, 125.42, 127.09, 127.36, 128.21, 129.80, 135.24, 137.54, 138.24, 139.08, 151.89; IR (thin film) 3441 br vs, 1684 m,

1653 s, 1616 m, 1558 m, 1541 w, 1506 w, 812 m cm^{-1} ; mass spectrum, m/z (% rel intensity) 235.1 (72), 234.0 M^+ (100), 232.8 (60), 201.9 (61), 188.9 (85), 164.8 (40), 138.9 (20), 115.0 (35), 107.2 (65), 88.5 (35), 63.5 (25), 51.0 (20), 40.9 (45). HRMS calcd for $\text{C}_{17}\text{H}_{13}\text{O}$ m/z 233.0966, meas 233.0968.

7.6.2 Preparation of 16o-w via the CAEC cascade reaction with the procedure given for 16a in section 7.2.5.3

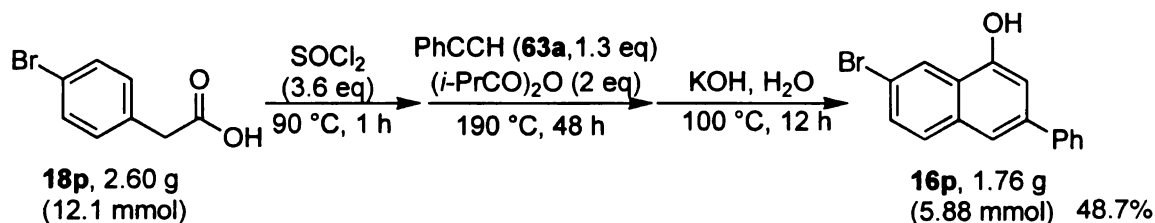
7.6.2.1 Preparation of 16o via the CAEC cascade reaction of 18o



Spectral data for **16o**: yellow cotton-like solid; mp 85-87 $^\circ\text{C}$, R_f = 0.22 (1:5 EtOAc/hexanes); $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ 5.30 (s, 1H), 7.12 (s, 1H), 7.30 (td, 1H, $^3J_{\text{HF}}$ = 8.6, $^3J_{\text{HH}}$ = 8.6, $^4J_{\text{HH}}$ = 2.7 Hz), 7.41 (t, 1H, J = 7.5 Hz), 7.49 (t, 2H, J = 7.7 Hz), 7.65-7.70 (m, 3H), 7.82 (dd, 1H, $^3J_{\text{HF}}$ = 10, $^4J_{\text{HH}}$ = 2.5 Hz), 7.86 (dd, 1H, $^3J_{\text{HH}}$ = 9.0, $^3J_{\text{FH}}$ = 5.6 Hz); ^{13}C (CDCl_3 , 75 MHz) δ 105.87 ($^2J_{\text{CF}}$ = 22.8), 109.39, 117.53 ($^2J_{\text{CF}}$ = 25.4), 118.90, 124.52 ($^3J_{\text{CF}}$ = 9.3), 127.49, 127.78, 129.14, 130.62 ($^3J_{\text{CF}}$ = 8.8), 132.20, 138.40, 138.42, 140.88, 151.48 ($^4J_{\text{CF}}$ = 5.2), 159.72, 160.69 ($^1J_{\text{CF}}$ = 245.4); IR (thin film) 3308 br w, 1608 s, 1501 vs, 1414 m, 1242 w, 1173 s, 873 m, 761 m cm^{-1} ; mass spectrum, m/z (% rel intensity) 238.5 M^+ (73), 237.6 (100), 209.3 (30), 208.5 (28), 207.3 (14), 206.5, (15), 182.5 (10), 103.4 (11), 40.3 (10), 39.5 (26). HRMS calcd for $\text{C}_{16}\text{H}_{10}\text{OF}$ m/z 237.0716, meas 237.0719. Anal.

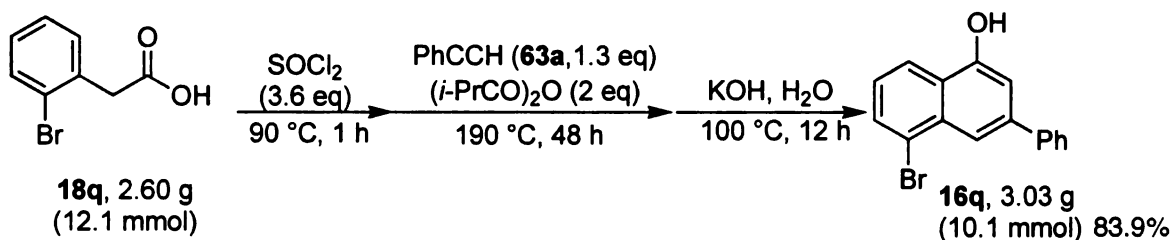
calcd for C₁₆H₁₁FO: C, 80.66; H, 4.65. Found: C, 80.13; H, 4.74.

7.6.2.2 Preparation of 16p via the CAEC cascade reaction of 18p



Spectral data for **16p**: needle-like yellow crystal; mp 97-98 °C; R_f = 0.24 (1:5 EtOAc/hexanes); ¹H-NMR (CDCl₃, 500 MHz) δ 5.30 (s, 1H), 7.07 (s, 1H), 7.40 (t, 1H, J = 7.0 Hz), 7.41 (t, 2H, J = 7.0 Hz), 7.58 (dd, 1H, J = 8.5, 2.0 Hz), 7.61 (s, 1H), 7.53 (d, 2H, J = 8.0 Hz), 7.71 (d, 1H, J = 9.0 Hz), 8.38 (s, 1H); ¹³C (CDCl₃, 75 MHz) δ 109.53, 118.87, 119.57, 124.53, 124.88, 127.50, 127.97, 129.18, 129.87, 130.57, 133.59, 139.61, 140.71, 151.07. IR (thin film) 3520 br w, 1588 s, 1493 m, 1407 m, 1377 w, 1089 m, 865 m cm⁻¹; mass spectrum, m/z (% rel intensity) 300.9 (13), 299.8 M⁺ (⁸¹Br, 98), 297.8 M⁺ (⁷⁹Br, 100), 191.3 (⁸¹Br, 27), 190.5 (⁸¹Br, 40), 189.3, (⁷⁹Br, 41), 188.5 (⁷⁹Br, 40), 150.0 (13), 149.1 (14), 94.9 (34), 93.9 (40), 39.5 (37). HRMS calcd for C₁₆H₁₀O⁷⁹Br m/z 296.9915, meas 296.9913.

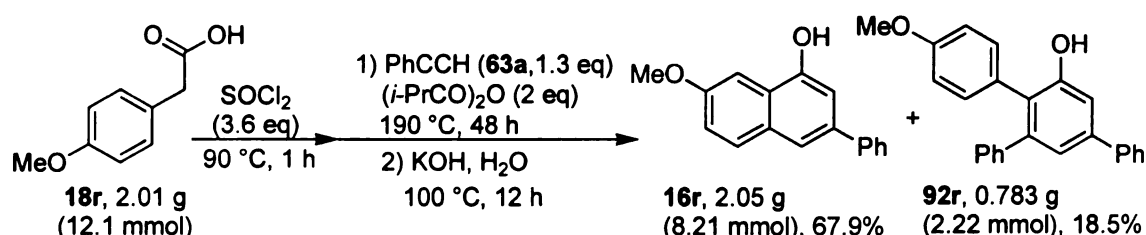
7.6.2.3 Preparation of 16q via the CAEC cascade reaction of 18q



Spectral data for **16q**: cotton-like white solid; mp 130-131 °C; R_f = 0.14 (1:5 EtOAc/hexanes); ¹H-NMR (CDCl₃, 500 MHz) δ 5.46 (s, 1H), 7.15 (s, 1H), 7.32 (t,

1H, $J = 10$ Hz), 7.42 (t, 1H, $J = 7.5$ Hz), 7.49 (t, 2H, $J = 7.7$ Hz), 7.71-7.73 (m, 2H), 7.83 (d, 1H, $J = 7.5$ Hz), 8.06 (d, 1H, $J = 0.5$ Hz), 8.22 (d, 1H, $J = 8.5$ Hz); ^{13}C (CDCl_3 , 75 MHz) δ 109.40, 118.37, 121.85, 123.21, 125.08, 125.66, 127.72, 128.04, 129.15, 131.33, 133.69, 140.51, 140.89, 152.12. IR (thin film) 3485 br vs, 1653 s, 1635 s, 1558 m, 1394 w cm^{-1} ; mass spectrum, m/z (% rel intensity) 300.1 M^+ (^{81}Br , 85), 298.1 (^{79}Br , 80), 297.3 (55), 218.1 (10), 191 (38), 189 (100), 149 (15), 94.0 (40). Anal. calcd for $\text{C}_{16}\text{H}_{14}\text{BrO}$: C, 64.24; H, 3.71. Found: C, 64.56; H, 3.79.

7.6.2.4 Preparation of 16r via the CAEC cascade reaction of 18r

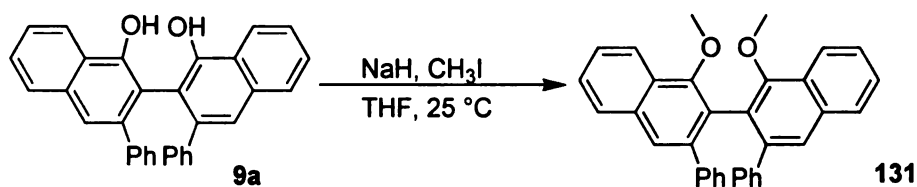


Spectral data for 16r: yellow solid; mp 78-79 $^\circ\text{C}$; $R_f = 0.13$ (1:5 EtOAc/hexanes); $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ 3.98 (s, 3H), 5.47 (br, s, 1H), 7.08 (s, 1H), 7.22 (dd, 1H, $J = 4.0, 2.5$ Hz), 7.37 (t, 1H, $J = 6.5$ Hz), 7.47 (t, 2H, $J = 7.5$ Hz), 7.50 (s, 1H), 7.62 (s, 1H), 7.66 (d, 2H, $J = 7.0$ Hz), 7.78 (d, 1H, $J = 4.0$ Hz); ^{13}C (CDCl_3 , 75 MHz) δ 55.68, 100.17, 109.11, 118.88, 119.99, 124.75, 127.38, 127.43, 129.05, 129.90, 130.74, 136.74, 141.21, 151.05, 157.73. IR (thin film) 3468 br vs, 1658 s, 1641 s, 1500 m, 1402 w, 1257 m, 1032 w, 761 m cm^{-1} ; mass spectrum, m/z (% rel intensity) 251.4 (10), 250.1 M^+ (100), 207.1 (55), 178.1 (42), 176.1 (15), 124.9 (12), 76.4 (7). Anal. calcd for $\text{C}_{17}\text{H}_{14}\text{O}_2$: C, 81.58; H, 5.72.

Found: C, 81.12; H, 5.41.

Spectral data for **92r**: yellow solid, mp 205-207 °C, R_f = 0.19 (1:5 EtOAc/hexanes); $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ 3.81 (s, 3H), 5.26 (br, s, 1H), 6.90 (d, 2H, J = 9.0 Hz), 7.13 (d, 2H, J = 9.0 Hz), 7.12-7.16 (m, 2H), 7.19-7.22 (m, 2H), 7.29 (dd, 2H, J = 9.5 Hz, J = 1.5 Hz), 7.38 (t, 2H, J = 7.5 Hz), 7.47 (t, 2H, J = 7.5 Hz), 7.70 (d, 2H, J = 7.5 Hz); ^{13}C (CDCl_3 , 75 MHz) δ 55.46, 113.06, 114.89, 121.50, 126.74, 127.33, 127.49, 127.80, 127.87, 127.99, 129.03, 129.91, 132.34, 140.74, 141.45, 141.91, 143.01, 153.77, 159.37; IR (thin film) 3429 br vs, 1653 s, 1558 m, 1456 w, 1246 w, 1178 w cm^{-1} ; mass spectrum, m/z (% rel intensity) 351.9 M^+ (100), 270.1 (90), 239.1 (30), 202.1 (18), 165.3 (15), 144.7 (25), 119.7 (16), 77.2 (15), 43.0 (22). HRMS calcd for $\text{C}_{25}\text{H}_{19}\text{O}_2$ m/z 351.1385, meas 351.1379.

7.6.3 Preparation of **131** by di-methylation of **9a** with MeI and NaH



In a 100 mL round bottom flask fitted with a reflux condenser are placed of racemic **9a** (11.0 g, 25 mmol) and 150 mL dry THF. The mixture is stirred to dissolve the solid completely. The solution is cooled to 0 °C, and 2.01 g NaH (83.7 mmol) is added and stirred for 15 min. To the mixture was added 8 mL (128.5 mmol) of MeI. The mixture is stirred at room temperature for 12 h. TLC showed **9a** was completely consumed. HCl (0.4 N, 150 mL) was cautiously added to quench

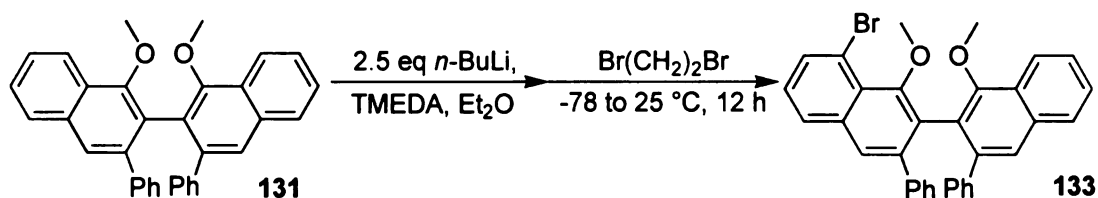
the reaction, organic layer washed with brine, dried with MgSO_4 and filtered, solvent was stripped of and the residue (11.5 g) was dissolved in minimum amount of CH_2Cl_2 and loaded onto a silica gel column, eluted with $\text{EtOAc}/\text{CH}_2\text{Cl}_2/\text{hexanes} = 1:2:20$ and yielded **131** (10.75 g, 23.0 mmol, 91.9%).

Spectral data for **131**: yellow solid, mp 158-159 °C, $R_f = 0.51$ (1:1 $\text{CH}_2\text{Cl}_2/\text{hexanes}$). $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 3.71 (s, 6H), 6.70 (d, 4H, $J = 7.2$ Hz), 6.95 (t, 4H, $J = 7.2$ Hz), 7.06 (t, 2H, $J = 6$ Hz), 7.50-7.59 (m, 6H), 7.84-7.90 (m, 2H), 8.23-8.28 (m, 2H); ^{13}C (CDCl_3 , 75 MHz) δ 60.69, 122.63, 124.92, 125.07, 125.48, 125.82, 126.10, 126.76, 127.14, 127.83, 128.70, 134.27, 139.81, 140.51, 154.46; ^{13}C (d^6 -DMSO, 75 MHz) δ 61.56, 123.00, 125.38, 126.14, 126.86, 126.97, 127.24, 127.29, 128.20, 129.08, 129.49, 134.82, 140.68, 141.24, 154.26; IR (thin film) 3449 br vs, 3057 m, 2930 m, 1653 s, 1489 m, 1358 s, 1113 m, 760 s, 704 s cm^{-1} ; mass spectrum, m/z (% rel intensity) 467.2 (31), 466.1 M^+ (100), 420 (18), 302 (11), 202 (30), 194.9 (35), 193.7 (23), 187.6 (26), 186.5 (33), 77 (10), 40.2 (29). HRMS calcd for $\text{C}_{34}\text{H}_{27}\text{O}_2$ m/z 467.2011, meas 467.2005.

Note: The conditions to make **131** using K_2CO_3 are the same as in Section 7.6.1.4.

7.6.4 Preparation of 8-substituted *O,O'*-dimethylIVANOL

7.6.4.1 Preparation of 8-bromo *O,O'*-dimethylIVANOL **133**

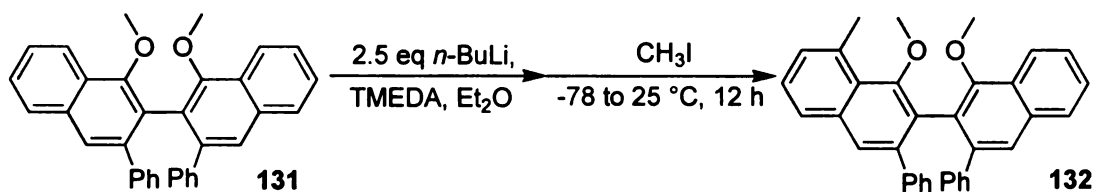


In a 100 mL flame-dried round-bottomed flask was filled with argon and then added a stirrer bar, dry Et₂O (50 mL) and TMEDA (1.0 mL, 6.86 mmol). *n*-BuLi (2.5 M in hexane, 3.6 mL, 9.0 mmol) was added and it was stirred for 15 min. **131** (1.2476 g, 2.89 mmol) was added and the mixture was stirred at rt for 3 h. The resulting light brown suspension was cooled to -78 °C, and Br(CH₂)₂Br (3.0 mL, 34.8 mmol) was added *via* syringe over a period of 10 min. The solution was allowed to warm to room temperature and was left stirring overnight. The reaction mixture was cooled to 0 °C, 1 M HCl (50 mL) was added, and the reaction mixture was stirred for 2 h. The phases were separated, and the organic phase was washed twice with 1 M HCl (50 mL) and then brine (50 mL), dried over MgSO₄ and filtered. The solvent in the filtrate was removed in *vacuo*, and the resulting white solid was dissolved in minimum amount of CH₂Cl₂ and loaded onto a column, eluted by CH₂Cl₂/hexanes = 1:10 to give **133** (0.496 g, 0.91 mmol, 31.4 %). **131** (0.469 g, 1.00 mmol, 34.8%) was recovered.

Spectral data for **133**: white crystal, mp 191-192 °C, *R_f* = 0.55 (1:1 CH₂Cl₂/hexanes). ¹H-NMR (CDCl₃, 500 MHz) δ 3.57 (s, 3H), 3.82 (s, 3H), 6.81 (d,

2H, $J = 5.0$ Hz), 6.86 (d, 2H, $J = 5.1$ Hz), 6.96-7.02 (m, 4H), 7.07-7.13 (m, 2H), 7.27-7.31 (m, 1H), 7.53-7.58 (m, 4H), 7.81 (d, 1H, $J = 7.5$ Hz), 7.82-7.90 (m, 2H), 8.24-8.26 (m, 1H); ^{13}C (CDCl_3 , 75 MHz) δ 61.57, 61.74, 116.93, 123.46, 125.50, 125.53, 125.97, 126.28, 126.51, 126.72, 127.23, 127.73, 127.78, 128.47, 128.71, 128.80, 129.15, 129.43, 133.65, 134.96, 126.95, 140.32, 140.40, 141.04, 141.10, 154.18, 154.64; three carbons not located; ^{13}C (d^6 -DMSO, 75 MHz) δ 61.77, 61.87, 116.09, 123.14, 124.95, 125.46, 125.76, 126.40, 126.86, 127.29, 126.36, 127.50, 127.76, 128.22, 128.29, 129.02, 129.16, 129.30, 129.54, 129.70, 134.18, 134.96, 137.06, 140.42, 140.56, 141.14, 141.21, 153.77, 154.28; one carbon not located; IR (thin film) 3493 w, 1599 m, 1540 m, 1356 m, 1322 m, 988 m, 702 m cm^{-1} ; mass spectrum, m/z (% rel intensity) 545.8 M^+ (^{81}Br , 50), 543.8 M^+ (^{79}Br , 50), 480.0 (12), 389.2 (17), 202.2 (^{81}Br , 52), 200.2, (^{79}Br , 62), 188 (58), 186 (51), 183.6 (100), 180 (32), 157 (31), 150 (30), 129 (24), 105 (24), 77 (24). Anal. calcd for $\text{C}_{34}\text{H}_{25}\text{BrO}_2$: C, 74.87; H, 4.62. Found: C, 74.49; H, 4.71.

7.6.4.2 Preparation of 8-methyl *O,O'*-dimethylIVANOL **132**



The procedure for the synthesis of **132** followed the same conditions in **Section 7.6.4.1** using **131** (463 mg, 1.0 mmol), $n\text{-BuLi}$ (1.5 mL, 3.75 mmol), and TMEDA (0.6 mL, 4.1 mmol) in 20 mL Et_2O , from which yielded 211 mg of **132**

(0.44 mmol 44.2%).

Spectral data for **132**: yellow solid, mp 155-156 °C, R_f = 0.33 (1:1 CH₂Cl₂/hexanes). ¹H NMR (CDCl₃, 300 MHz) δ 3.01 (s, 3H), 3.57 (s, 3H), 3.82 (s, 3H), 6.86-7.19 (m, 10H), 7.34-7.46 (m, 2H), 7.53-7.69 (m, 4H), 7.76 (d, 1H, J = 7.5 Hz), 7.90-7.96 (m, 1H), 8.29-8.35 (m, 1H); ¹H NMR (*d*⁶-DMSO, 500 MHz) δ 2.75 (s, 3H), 3.33 (s, 3H), 3.60 (s, 3H), 6.95 (d, 2H, J = 7.0 Hz), 7.01-7.12 (m, 8H), 7.29 (d, 1H, J = 7 Hz), 7.39 (t, 1H, J = 7.0 Hz), 7.54-7.56 (m, 2H), 7.67 (s, 1H), 7.69 (s, 1H), 7.80 (d, 1H, J = 8.0 Hz), 8.00-8.04 (m, 2H); ¹³C (CDCl₃, 75 MHz) δ 23.48, 60.21, 60.95, 122.86, 125.01, 125.44, 125.77, 125.85, 125.91, 126.09, 126.15, 126.33, 126.67, 126.85, 127.15, 127.20, 127.94, 128.64, 128.87, 128.96, 134.24, 134.38, 135.74, 139.50, 140.19, 140.54, 140.78, 153.95, 155.50, two carbons not located; ¹³C (*d*⁶-DMSO, 75 MHz) δ 23.67, 61.03, 61.69, 123.15, 125.37, 126.13, 126.35, 126.74, 126.84, 126.98, 127.12, 127.13, 127.23, 127.67, 128.07, 128.20, 129.11, 129.21, 129.54, 129.95, 134.02, 134.88, 136.15, 140.13, 140.92, 141.08, 141.46, 154.23, 155.68, two carbons not located; IR (thin film) 3476 br, vs, 1653 s, 1558 m, 1541 w, 1456 w cm⁻¹; mass spectrum, m/z (% rel intensity) 481.3 (36), 480.3 M⁺ (100), 434.3 (18.5), 240.3 (13), 201.2 (27), 194.2 (88), 178.2 (34), 105.0 (17), 77.2 (12), 39.8 (30); HRMS calcd for C₃₅H₂₉O₂ m/z 481.2168, meas 481.2176.

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