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DEVELOPMENT OF ONE-POT Pd-MEDIATED REACTIONS
& A SYNTHETIC APPROACH TO MONOCILLIN I

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KYOUNGSOO LEE

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Major Professor's Signature

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Date

DEVELOPMENT OF ONE-POT Pd-MEDIATED REACTIONS & A SYNTHETIC APPROACH TO MONOCILLIN I

By

Kyoungsoo Lee

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ABSTRACT

DEVELOPMENT OF ONE-POT Pd-MEDIATED REACTIONS & A SYNTHETIC APPROACH TO MONOCILLIN I

By

Kyoungsoo Lee

Our group has developed a one-pot Pd-catalyzed hydrostannation/Stille coupling catalytic tin sequence that use in situ generated tin hydride to reduce some of the toxicity, cost, and purification concerns associated with the use of organotins in Stille reactions. Previously we demonstrated that vinyl, aryl, and benzyl halides are all acceptable electrophiles for this sequence but acid chlorides. Efforts to develop a one-pot hydrostannation/Stille coupling protocol with acid chlorides as the electrophile have revealed that using Me_3SnF (better than Bu_3SnF) / PMHS as a tin hydride source and adding the acid chloride to the reaction mixture after the initial hydrostannation, allows for the formation of variety of α,β-unsaturated ketones in a single pot in excellent yields.

In case of bromo-substituted-benzoyl chloride, high chemoselectivity was observed. Despite two potential coupling sites (acid chloride and aryl bromide) this substrate chemoselectively reacted with the *in situ* generated vinyl stannane at the acid chloride site to afford the product in near quantitative yield. Then, without isolation, an additional allyl, vinyl or aryl stannane is reacted at the aryl bromide site to afford doubly coupled products in good overall yields.

During this reaction, aldehyde was formed as by-product in the one-pot hydrostannation /Stille coupling reaction. We examined how these aldehydes are

formed. Finally, studies showed that PMHS in the presence of fluoride was leading to reduction of acid chlorides to aldehydes.

Having developed several one-pot hydrostannation/Stille methods, we sought to validate their utility in the theater of target synthesis, then a total synthesis of monocillin I was attempted. The details of these studies will be described.

To My Lovely Family

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LIST OF SCHEMES

LIST OF ABBREVIATIONS

Ac	acetyl
Acac	acetylacetonate
AIBN	2,2'-azobisisobutyronitrile
$AgNO_3$	silver nitrate
aq	aqueous
BPS	*tert*-butyldiphenyl
CH_2Cl_2	dichloromethane
CI	chemical ionization
CSA	camphorsulfonic acid
Cy	cyclohexyl
DCC	dicyclohexylcarbodiimide
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
EI	electric ionization
eq	equation
FAB	fast atom bombardment

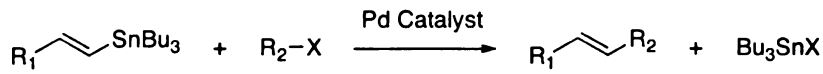
h	hour
HMPA	hexamethyl phosphoramide
HRMS	high resolution mass spectrometry
HWE	Horners-Wadsworth-Emmons reaction
IMES-H_2	4,5-dihydro-1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
KHMDS	potassium bis(trimethylsilyl)amide
LiHMDS	lithium bis(trimethylsilyl)amide
m-CPBA	m-chloroperbenzoic acid
Mes	mesityl
mL	milliliter
mmol	millimole
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	N-bromosuccinimide
NMP	N-methyl-2-pyrrolidinone
NOE	nuclear Overhauser effect
Ph	phenyl
PMB	*p*-methoxybenzyl
RCM	ring closing metathesis
r.t.	room temperature
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran

TFP	tri-2-furyl phosphine
TMS	trimethylsilyl
PTSA	*p*-toulenesulphonic acid

CHAPTER 1. Introduction

Pd-catalyzed cross-coupling reactions have provided a simple, powerful and indispensable methodology for the construction of carbon–carbon σ-bonds.[1] Among those coupling reactions, the Stille reaction is convenient and widely used.[2] It involves the Pd-catalyzed cross-coupling of organostannanes and various electrophiles, such as vinyl halides, aryl halides, benzyl halides or triflates and acid chlorides.[3] (Scheme 1)

Scheme 1. Stille Cross-Coupling Reaction of Vinylstannane



R_1 and R_2 = many possibilities

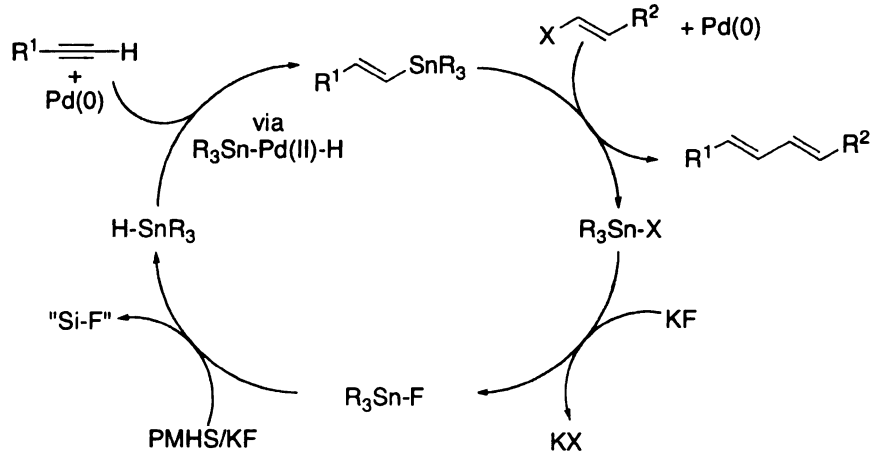
X = halogen, OTf, ONf, OAc

Despite the well-established power of the Stille reaction, there are negative issues associated with handling the often unstable and/or toxic organostannanes used in these couplings.[4] To obviate direct manipulation of the stannane coupling partners, procedures that promote the in situ generation of organotin species and their subsequent reactions have been explored.

In 1996, Pattenden described a stepwise one-pot palladium catalyzed hydrostannation/Stille coupling.[5] A one-pot hydrostannation/Stille coupling which does not require the isolation of the vinylstannane can be advantageous when dealing with stannanes. From those previous works, it was envisioned that a Stille reaction catalytic in tin could be achieved if an organotin hydride could

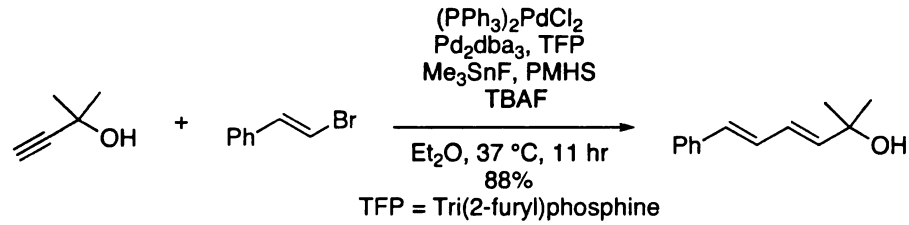
undergo an in situ chemoselective sequence of Pd(0)-catalyzed vinylstannane formation followed by cross-coupling, and then regeneration from the organotin halide byproduct. (Scheme 2) Our group has developed a one-pot Pd-catalyzed hydrostannation/Stille coupling catalytic tin sequence[6] that uses an in situ generated tin hydride to reduce some of the toxicity, cost, and purification concerns associated with the use of organotins in Stille reactions.

Scheme 2. Stille Reaction Catalytic Tin



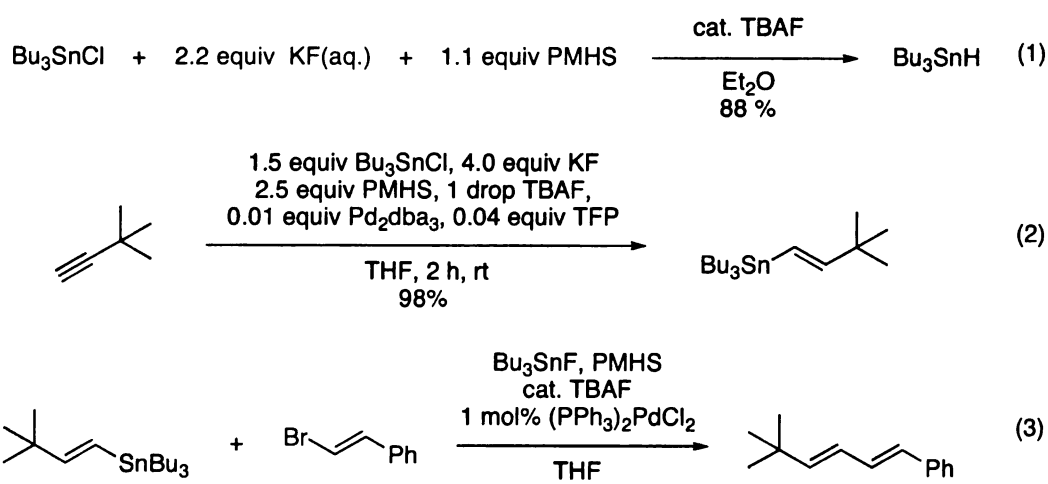
Making the Stille sequence catalytic in tin represented a significant "Greening" of the reaction. However, in practice for Stille reactions run at bench scale or with elaborate coupling partners the real advantage of the sequence is that it allows for multiple organostannane reactions to be telescoped into a single reaction vessel. With this in mind additional development of such one-pot reaction schemes is of value are they catalytic in tin or stoichiometric in tin. In the later case this would be especially true if the stoichiometric tin could be recycled in situ and used in multiple steps. (Scheme 3)

Scheme 3. One-pot Hydrostannation/Stille Sequence



In order to build upon the first generation one-pot Pd-catalyzed hydrostannation/Stille coupling sequence, it is important to understand all of the three steps involved in the process. The first step is an in situ generation of tributyltin hydride.[7] (Eq. (1) in Scheme 4) The second step of the sequence involves using the in situ generated tributyltin hydride from step one in an in situ Pd-mediated hydrostannation of an alkyne.[8] (Eq. (2)) In the final step, a cross-coupling between the in situ generated vinylstannane and an electrophile occurs.[9] (Eq. (3))

Scheme 4. Three Steps in One-pot Sequence



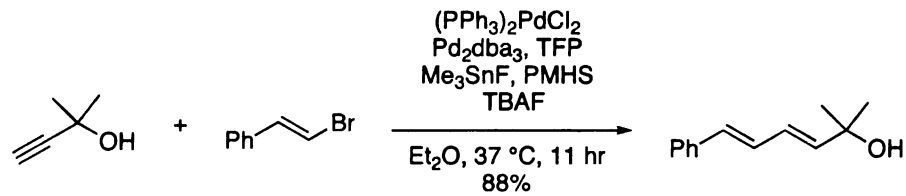
Previously we demonstrated that vinyl, aryl, and benzyl halides are all acceptable electrophiles for this sequence except acid chloride.[6] Efforts to develop a one-pot hydrostannation/Stille coupling protocol with acid chlorides as the electrophile will be discussed in Chapter 2.

CHAPTER 2. One-pot Hydrostannation/Stille Reaction with Acid Chlorides as the Electrophiles

2-1. Introduction

As discussed in Chapter 1, our group has developed one-pot Pd-catalyzed hydrostannation /Stille coupling sequences that begin with the in situ generation of triorganotin hydrides to obviate negative issues associated with handling the often unstable and/or toxic organostannanes used in these couplings. The hydrides so formed react in situ with alkynes to form vinylstannanes, which without isolation undergo Stille cross-coupling reactions.[6] (Scheme 5)

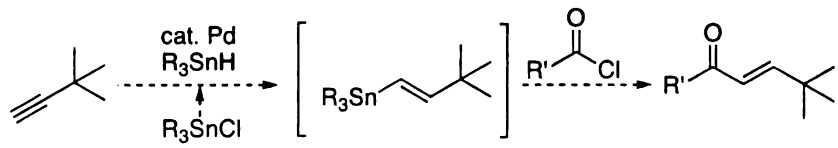
Scheme 5. One-pot Hydrostannation/Stille Sequence



2-2. One-pot Sequence with Acid Chlorides

In the studies mentioned above, we showed that vinyl, aryl, and benzyl halides were all acceptable electrophiles for this sequence. Noticeably absent from this group of electrophiles were acid chlorides. We considered this omission problematic because acid chlorides represent an important class of Stille electrophiles.[10] In Stille's earliest studies, he showed that reactions with these compounds could efficiently produce α,β-unsaturated ketones. Thus, we sought to expand the scope of the one pot hydrostannation/ Stille protocol to include acid chlorides among the viable electrophiles. (Scheme 6)

Scheme 6. Outlined Route for One-pot Hydrostannation/Stille with Acid Chlorides



As it were, the prospect of adopting a straightforward extension of our existing methodology with acid chlorides exposed a number of uncertainties. Unlike previously used electrophiles, reactions with acid chlorides face a host of potential problems. For example, under our standard conditions the triorganotin hydrides used in the hydrostannation step are prepared by the reduction of organotin halides with polymethylhydrosiloxane (PMHS) in the presence of fluoride.[11] Thus, we were confronted with the possibility of residual tin hydride or PMHS reducing the acid chloride[12] or the α,β-unsaturated ketone products.[13] In addition, while Suzuki reactions with acid chlorides have been done in water,[14] we worried about acid chloride hydrolysis. Furthermore, adventitious formation of HCl from the acid chlorides could promote competitive protiodestannylation of the vinyltin intermediates.[15] Lastly, decarbonylation[16] of the palladium(II) oxidative addition intermediate was also one of our concerns. Nonetheless, provided these problems could be defeated, achieving the synthesis of various α,β-unsaturated ketones from alkynes and acid chlorides in a single pot using an organotin salt as the initial tin source, a single load of catalyst, and unpurified vinyltin intermediates would be attractive.

2-3. One-Pot Hydrostannation/Stille Reaction with Acid Chlorides using Bu_3SnF

In starting our exploration of this putative one-pot sequence, we opted to use an anhydrous variation for the in situ generation of tributyltin hydride. Thus, Bu_3SnF, PMHS, and a catalytic amount of TBAF were reacted in the presence of an alkyne and an acid chloride. (Scheme 7)

Scheme 7. Preparation of Tin Hydride from Tin Fluoride

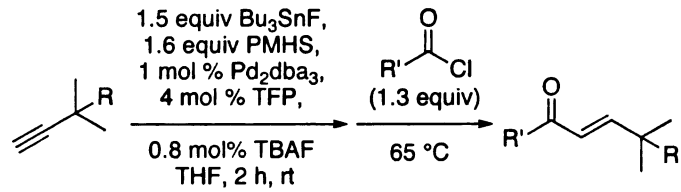
$$Bu_3SnF \;+\; 1.1 \text{ equiv PMHS} \;+\; \text{cat. TBAF} \longrightarrow Bu_3SnH$$

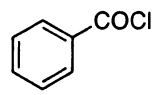
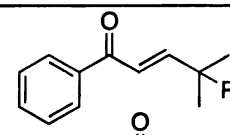
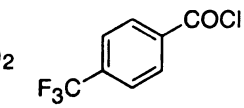
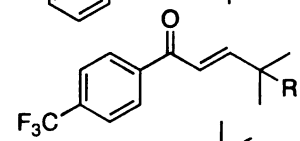
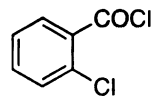
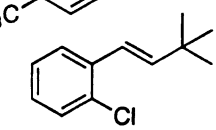
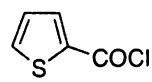
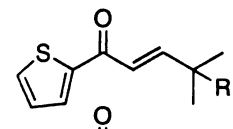
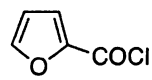
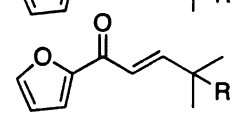
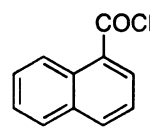
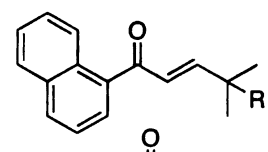
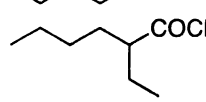
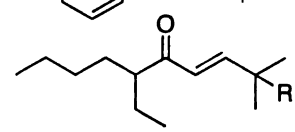
This procedure gave little of the desired α,β-unsaturated ketone as the acid chloride was consumed by the Bu_3SnF/PMHS/TBAF combination in advance of the cross-coupling. To avoid this trouble, we simply added the acid chloride (without any additional Pd-catalyst) after vinylstannane formation was complete. Under this two-step one-pot procedure a variety of α,β-unsaturated ketones could be formed. (Table 1) This first generation study only employed alkynes that were tri-substituted at the propargylic position so that our evaluation of the process would not be complicated by the formation of regioisomers. The protocol proved workable with a variety of acid chlorides. Typically cross-couplings were achieved after 6–10 h at 65 °C and the yields could be very high.

However, in some cases intrusive amounts of side products were observed. For example, reactions with either 4-trifluoromethylbenzoyl chloride (entry 3) or 2-chlorobenzoyl chloride (entry 4) witnessed the formation of the

corresponding benzaldehydes and the decarbonylated coupling products (Scheme 8). Moreover, despite our best efforts at reaction optimization some of the product yields remained moderate at best. We attributed some of these problems to the relatively slow cross-coupling times.

Table 1. One-pot Hydrostannation/Stille with Acid Chlorides using Bu_3SnF[17]



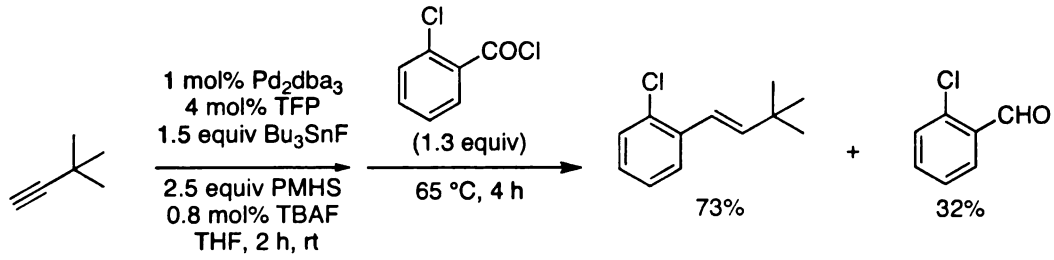
entry	R	acid chloride	Stille rxn time	product	yield [a]
1	CH_3		6 h		96%
2	$CH(CO_2Me)_2$		6 h		84%
3	$CH(CO_2Me)_2$		2 h		74% [b]
4	CH_3		6 h		73% [c]
5	CH_3		6 h		57%
6	CH_3		6 h		63%
7	CH_3		10 h		31%
8	CH_3		10 h		91%
9	$CH(CO_2Me)_2$		6 h		58%

[a] Average isolated yield over two runs. See experimental section for details.

[b] The decarbonylated product (16%) was also observed.

[c] The decarbonylated product (73%) and aldehyde (32%) are obtained.

Scheme 8. Side Reactions in One-pot Sequence

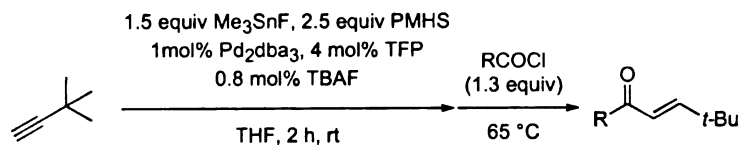


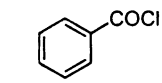
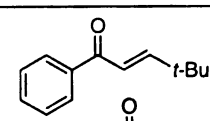
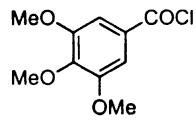
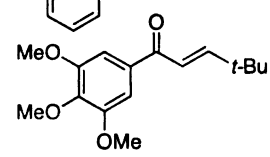
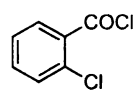
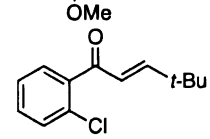
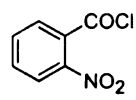
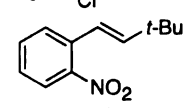
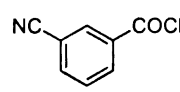
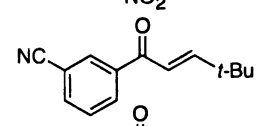
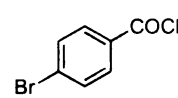
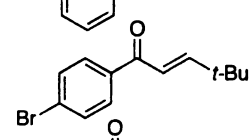
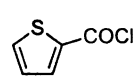
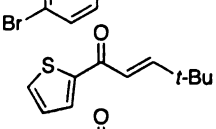
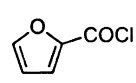
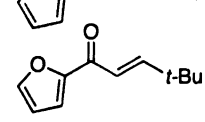
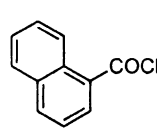
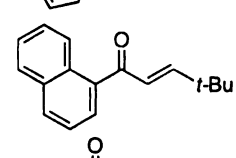
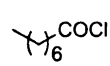
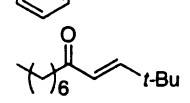
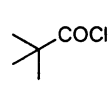
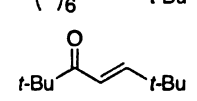
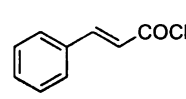
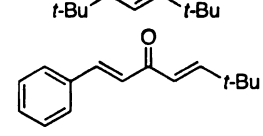
2-4. One-Pot Hydrostannation/Stille Reaction with Acid Chlorides using Me_3SnF

In our previously reported tin catalyzed hydrostannation/Stille sequence with other sp^2-halides, switching from Bu_3SnCl to the less sterically demanding Me_3SnCl gave faster reaction times and decreased byproduct formation.[18] Looking for a similar outcome for the two-step one-pot acid chloride coupling sequence, the initial tin species was changed from Bu_3SnF to Me_3SnF. We were gratified to observe a significantly improved process. As illustrated in Table 2, using Me_3SnF in place of Bu_3SnF typically decreased cross-coupling times from 6 to 2 h. More importantly, the observed increases in reaction rates were generally met with substantially higher yields and fewer visible side reactions.

For example, the previously failed coupling of 2-chlorobenzoylchloride (entry 3) could now be achieved in an over all yield of 86%. Other entries worthy of further comment include the reaction of 4-bromobenzoylchloride (entry 6).

Table 2. One-pot Hydrostannation/Stille with Acid Chlorides using Me_3SnF



Entry	Acid Chloride	Stille rxn time (h)	Product	Yield (%) [a]
1		2		94
2		2		96
3		2		86
4		2		72 [b]
5		2		98
6		4		98
7		2		99
8		2		95
9		2		92
10		2		90
11		4		92
12		4		80

[a] Average isolated yield over two runs. See experimental section for details.

[b] Decarbonylation occured even under CO atmosphere. See experimental section for details.

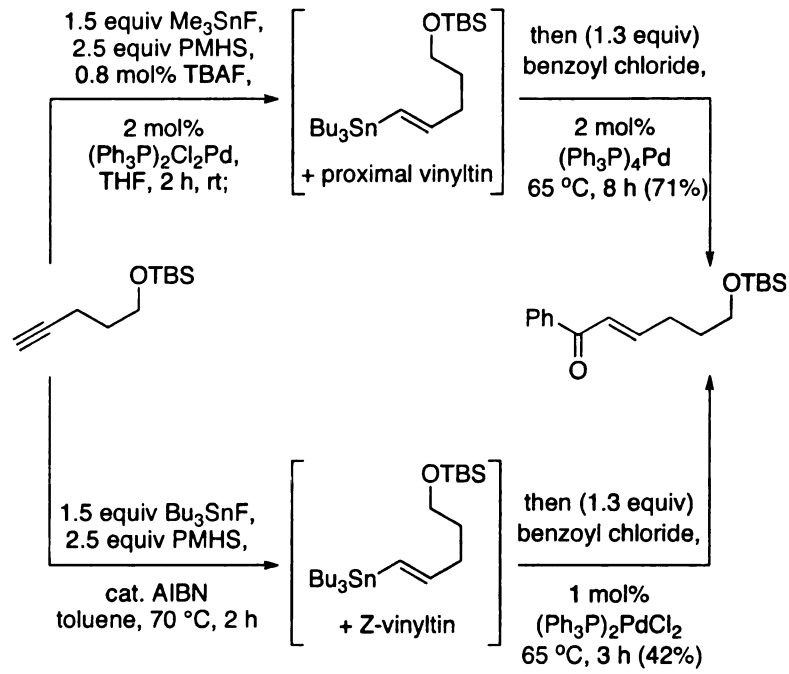
Despite its two potential coupling sites (acid chloride and aryl bromide) this substrate chemoselectively reacted with the in situ generated vinyl stannane at the acid chloride site to afford the product in near quantitative yield. Furthermore, that product did not suffer from any unwanted dehalogenation of the aryl bromide.[19] Likewise, cinnamoyl chloride afforded the 1,4-diene-3-one in 81%. Unfortunately, even under these conditions not all substrates were universally accepted. As shown in entry 4 on Table 2, 2-nitrobenzoyl chloride still gave the decarbonylated coupling product, even when the reaction was run under an atmosphere of CO.

2-5. One-Pot Sequence of Mono-substituted Alkynes with Acid Chlorides

Finally, we examined a reaction sequence that started with an alkyne that was not fully substituted at the propargylic position (Scheme 9). As previously mentioned such substrates afford measurable levels of the proximal vinylstannanes under Pd-catalyzed conditions.[20] Such vinyltins are known to be sluggish Stille partners.[21] This is reflected in the slightly diminished yield (66%) of the cross-coupled product, which arose from the partially selective cross-coupling of the distal vinyltin intermediate with the benzoyl chloride.[22] Furthermore, it must be noted that for this substrate we were also required to add an additional load of the palladium catalyst and extend the Stille reaction time to 8 h to achieve the reported yield. In an attempt to circumvent the distal/proximal regiochemical matter, we first looked at performing the Pd-catalyzed

hydrostannation step on the 1-bromoalkyne derivatives.[5] However, for reasons that remain unclear, that substrate did not work well in the hydrostannation/cross-coupling sequence. Another option involved running the hydrostannation step under free radical conditions[4] and then adding the acid chloride along with Pd-catalysts to carry out the second step.

Scheme 9. One-Pot Sequence of Mono-substituted Alkynes with Acid Chlorides



Owing to the volatility of Me_3SnH, we chose to run the radical hydrostannation with Bu_3SnH. While, this modified procedure was successful at eliminating the proximal isomer (at the cost of some Z-vinylstannane formation), recourse to the tributyltin again gave the α,β-unsaturated ketone in only modest

average overall yield (42%). Usefully, the TBS ether survived the fluoride present throughout both successful sequences.

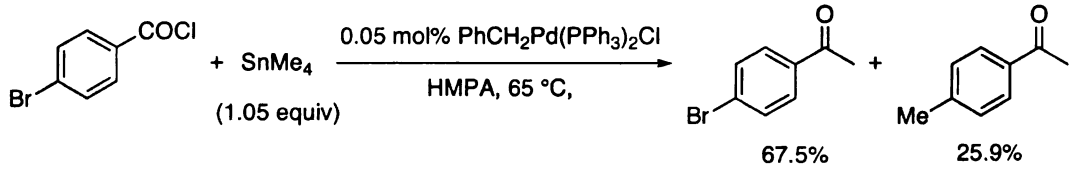
In summary, we expanded the one-pot hydrostannation/Stille coupling method to allow acid chlorides to serve as the electrophilic coupling partner. Problems associated with the use of these reactive building blocks were avoided by adding the acid chloride to the reaction after the vinylstannane was produced in situ from Me_3SnF/PMHS generated Me_3SnH and a corresponding alkyne. Both aliphatic and electronically varied aromatic acid chlorides could be employed in this one-pot synthesis of α,β-unsaturated ketones.

CHAPTER 3. One-Pot Multi-Component Stille Sequences

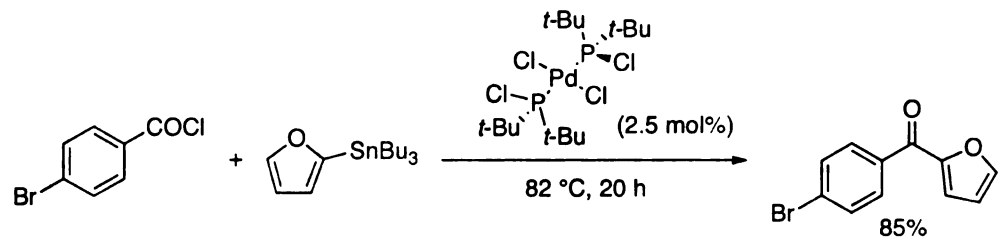
3-1. Introduction

During our development of the one-pot hydrostannation/Stille sequence with acid chlorides as the electrophile, we found that halo-substituted benzoyl chlorides cross-coupled chemoselectively at the acid chloride site, keeping the aryl halide bonds in tact (Chapter 2). This was somewhat surprising since it is shown that when Stille coupling of 4-bromobenzoyl chloride with organotin compounds give reduced yields and a significant amount of the aryl bromide coupled byproduct.[23] (Scheme 10) Moreover it was not until 2005 that Wolf's group[24] was able to define a set of generally chemoselective conditions for the Pd-catalyzed coupling of halo-bearing aryl acid chlorides with aryl/ vinyl stannanes. In these examples bis-(di-tert-butyl chloro phosphine) palladium(II) dichloride catalyzed cross-coupling of acyl chlorides with organostannanes in refluxing acetonitrile provided a means to prepare aliphatic and aromatic ketones with aryl bromide tolerance. (Scheme 11)

Scheme 10. Stille Reaction with Halo-substituted Benzoyl Chloride



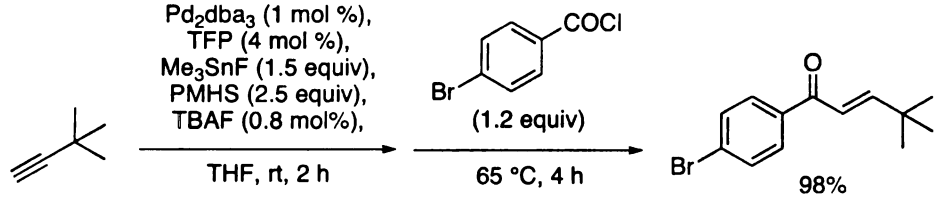
Scheme 11. Chemoselective Stille Reaction with 4-Bromo Benzoyl Chloride



3-2. Chemoselective Coupling to Acid Chloride over Aryl Bromide

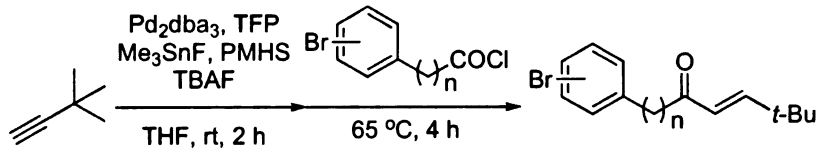
In light of these few previous reports, we were excited that our one-pot sequence not only afforded the chemoselective coupling reaction of 4-bromo benzoyl-chloride with the in situ formed vinylstannane without unwanted cross coupling at the aryl bromide, but also in that the reaction product did not suffer from any unwanted dehalogenation of the aryl bromide. (Scheme 12)

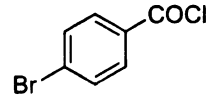
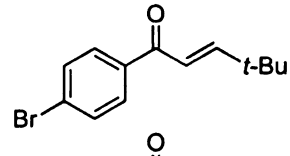
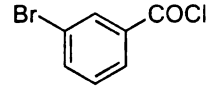
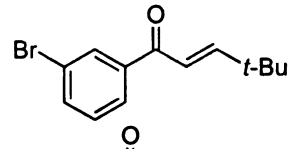
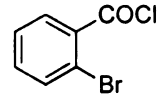
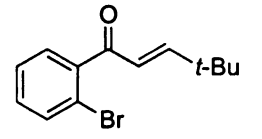
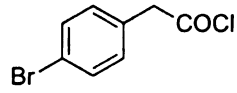
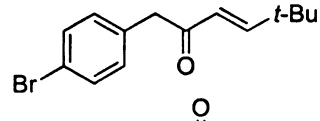
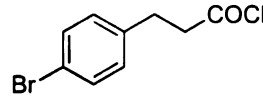
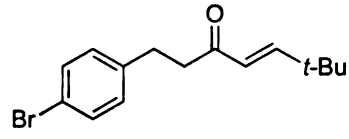
Scheme 12. Chemoselective One-pot Sequence with 4-Bromo Benzoyl Chloride



Of course, this was only a single example therefore we decided to subject an expanded set of bromo-containing acid chlorides to the reaction sequence. The results are shown below on Table 3.

Table 3. Chemoselective One-pot Hydrostannation/Stille with Bromophenyl Acid Chlorides



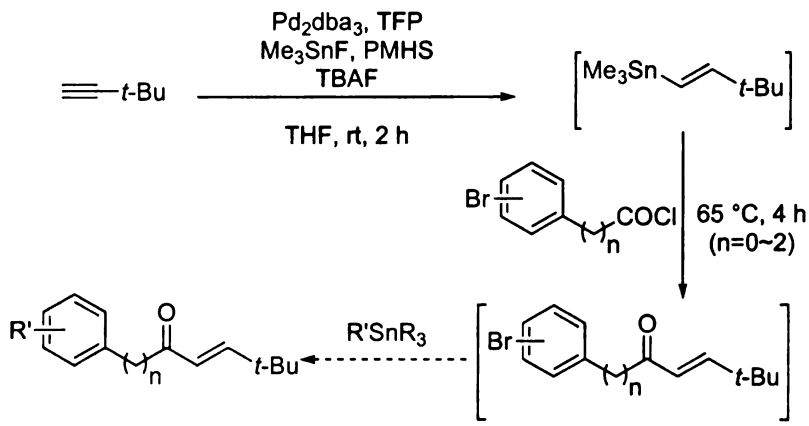
Entry	Acid Chloride	Product	Yield(%)
1			98
2			80
3			55
4			63
5			73

We found that 4-bromo benzoyl chloride underwent Pd-catalyzed ketone formation with in situ formed vinylstannane to give 4-bromophenyl ketone in 98% yield. 3-Bromo benzoyl chloride reacted in just a little bit lower 80% yield. In the case of 2-bromo benzoyl chloride the yield dropped to 55% and some side reactions were observed, namely over-reduction of the olefin and decarbonylation. Even 4-bromo-phenyl aliphatic acid chlorides worked well to give moderate to good yield for the three consecutive reactions.

3-3. One-Pot Multi-Component Stille Coupling Reactions

As the one-pot sequence afforded ketones containing an aryl bromide we asked if this reaction sequence could be subjected to a second Stille coupling at that aryl bromide site after adding another organostannane. Based on the previous results, the selective addition of two different kinds of organostannanes to halo-substituted acid chlorides to generate multi-component coupled products, without intermediate isolation, became our goal. Our strategy is shown on Scheme 13.

Scheme 13. Our Strategy for Multi-Components Coupling



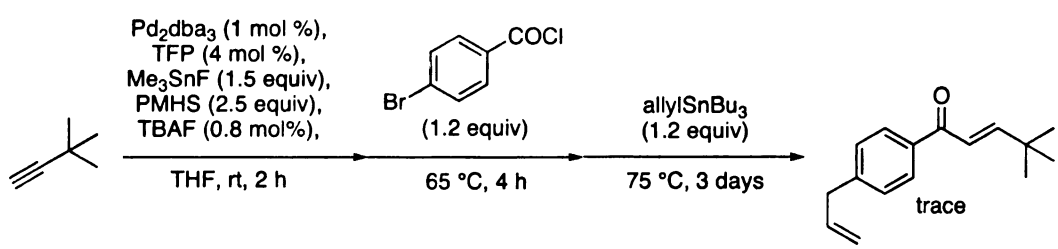
Of course there are potential problems in this sequence, including incomplete differentiation of the electrophilic sites and unwanted reactions between the first cross-coupled product or the lastly added stannanes and the reaction milieu. If these problems could be overcome, the formation of doubly-coupled α,β-unsaturated ketones in this manner would be advantageous in a number of ways. (1) No intermediate separation or isolation would be required. (2) Tin waste from all reactions could be removed in a single and final step. (3)

The protocol would allow for the rapid buildup of molecular complexity. (4) Such a sequence could be potentially adapted to automated and/or parallel syntheses.

3-4. Optimization of Reaction

We first explored the proposed sequence by simply following the first one-pot hydrostannation/Stille reaction with the addition of allylSnBu$_3$. Unfortunately that reaction did not succeed as only trace amounts of product were collected. (Scheme 14) Obviously study would be needed to achieve the desired multi-component coupling sequence.

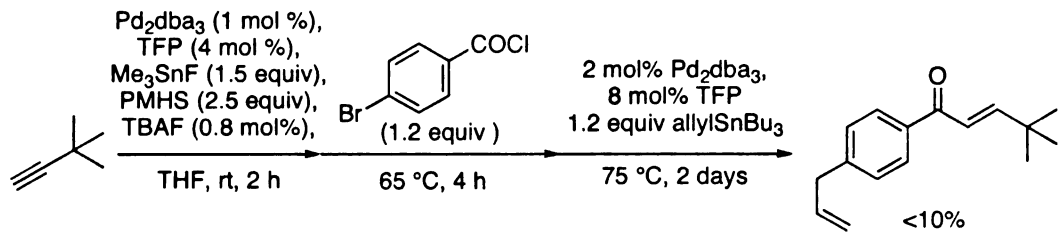
Scheme 14. Stepwise Multi-Coupling Reaction



1) Additional Fresh Pd Catalyst Loading

As simply adding the second organostannane after the first Stille reaction was unsuccessful, we hypothesized that the catalyst was dying prior to the second Stille reaction. Thus we looked at adding fresh Pd and trifuryl phosphine along with the allylSnBu$_3$. (Scheme 15) However, the reaction outcome did not get much better as we got just under 10% yield of the doubly coupled product.

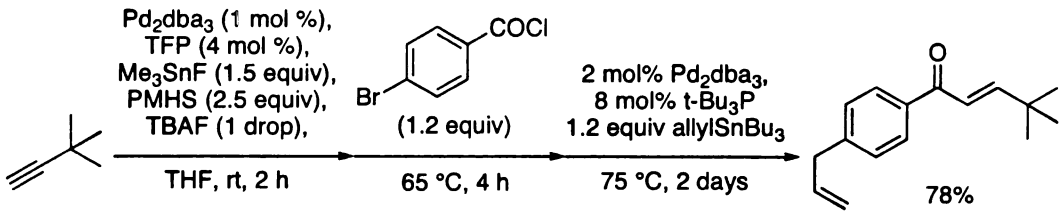
Scheme 15. Additional Fresh Pd Catalyst Loading



2) Additional Different Pd Catalyst Loading.

We next sought to overcome the sluggishness of the second Stille reaction by adding more reactive Pd/ligand combination. The literature[25] is rich with examples where Pd/*t*-Bu_3P serves as a versatile catalyst for Stille reactions. This system represented the first general method for couplings of aryl chlorides and for room-temperature couplings of aryl bromides. Therefore we looked at replacing tri-2-furylphosphine (TFP) with *t*-Bu_3P during the second Stille. This greatly improved the outcome of Scheme 16. After 2 days a 78% yield of the doubly-coupled product was obtained.

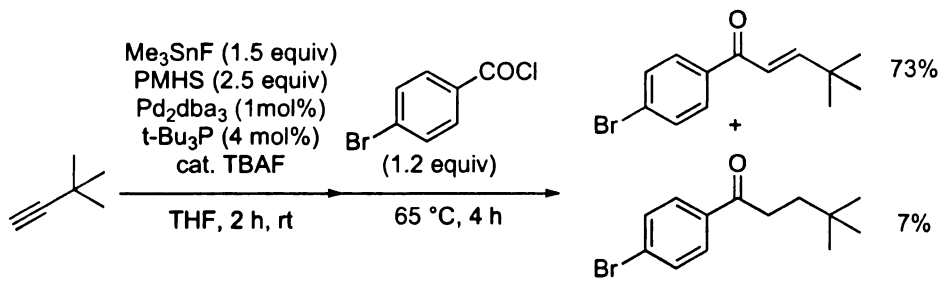
Scheme 16. Additional Different Pd Catalyst Loading.



We also examined the use of the more active tri-*tert*-butyl phosphine ligand during the first step with the hope that it would facilitate the second Stille reaction and simplify the sequence. Again though, lower yields and the over

reduced byproducts were observed at the first hydrostannation step. (Scheme 17)

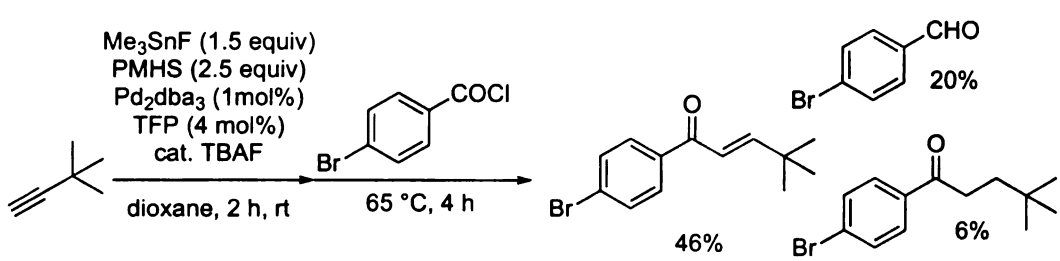
Scheme 17. Hydrostannation with Pd_2dba_3/*t*-bu_3P



3) Solvent and Temperature

Even though replacing TFP with *t*-Bu_3P gave us better results, we were not fully satisfied with reaction conditions. It is well documented that high temperatures are sometimes needed in Stile couplings.[4] However, the use of THF as solvent in the first step of the sequence limited how high the temperature could be raised. Therefore we investigated using the higher boiling solvent 1,4-dioxane at the beginning of the reaction. Unfortunately this change gave us lower yields and over-reduced byproduct during the hydrostannation/Stille reaction. (Scheme 18)

Scheme 18. Hydrostannation in 1,4-Dioxane



Scheme 19. Optimized Multi-Coupling Reaction

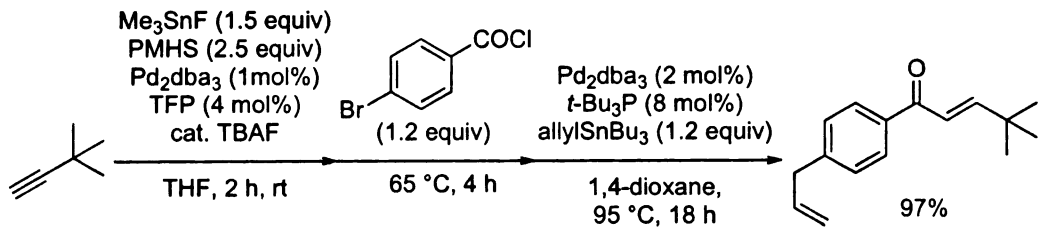
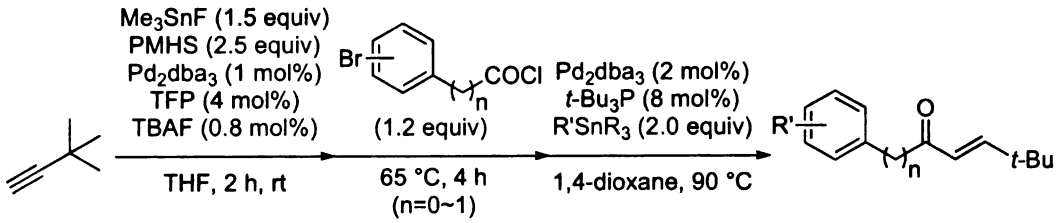
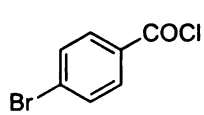
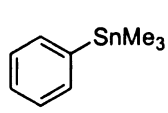
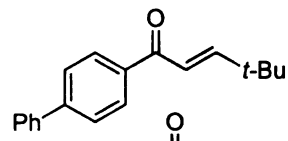
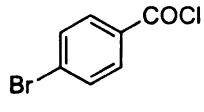
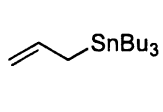
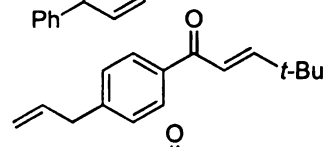
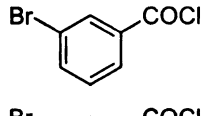
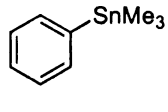
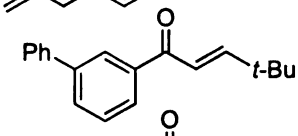
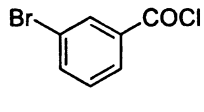
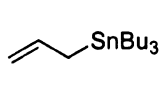
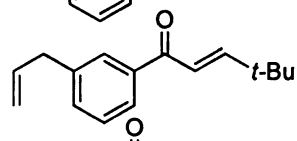
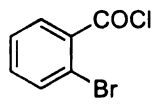
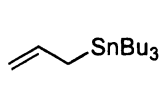
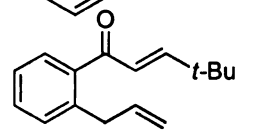
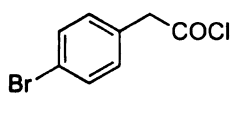
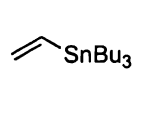
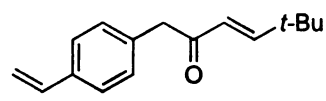


Table 4. Multi One-pot Hydrostannation/Stille with Bromophenyl Acid Chlorides



Entry	Acid Chloride	$R'SnR_3$	rxn time (h)	Product	Yield (%)
1			12		88
2			18		97
3			12		81
4			12		82
5			12		46
6			3		47

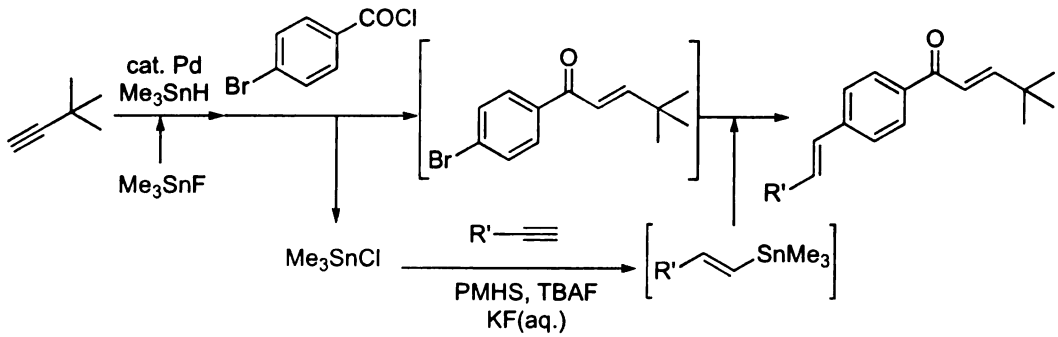
That said, adding an equivalent volume of 1,4-dioxane to the THF reaction after the first in Stille reaction and increasing oil bath temperature to 90 °C during

the second Stille coupling met with big improvements in the yield affording the product almost quantitatively. (Scheme 19) With these conditions we examined the formation of a variety of doubly-coupled α,β-unsaturated ketones. (Table 4) Bromo benzoyl chloride underwent the one-pot multi coupling reaction with vinyl, allyl, aryl stannanes to give corresponding multi-coupled ketones in yields up to 98%.

3-5. Recycling of Tin in Multi Step Sequence

In Table 4, the second Stille was always performed with newly added organostannane. In an attempt to push the limit of our multi component sequence even further, we considered the possibility of generating the second organostannane in situ. Specifically we thought that it should be possible to recycle the trimethyltin chloride formed in the first one-pot hydrostannation/Stille. (Scheme 20)

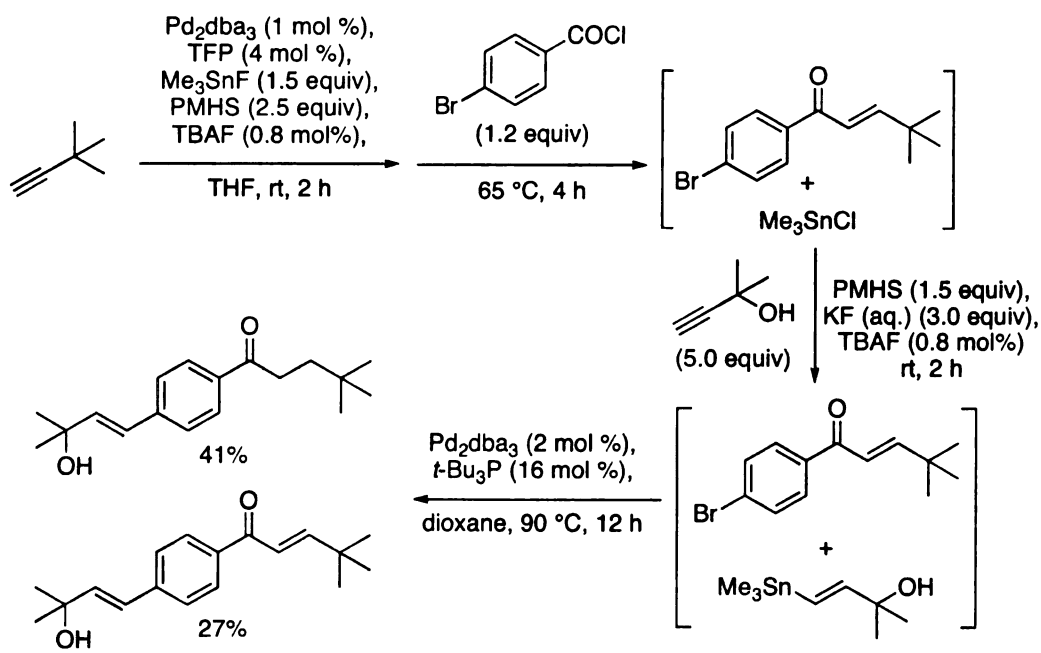
Scheme 20. Recycling Tin Multi Coupling



If the trimethyltin chloride could be converted to trimethyltin hydride then addition of an alkyne would pave the way for an in situ hydrostannation where the newly formed vinyltin could participate in the second Stille reaction. Such a process is illustrated below.

We began to explore this tin-recycling sequence by simply adding another terminal alkyne, PMHS, and KF after first hydrostannation/Stille coupling reaction, allowing 2 h for the second tin hydride formation and in situ formation of vinylstannane. After the second hydrostannation, Pd_2dba_3, *t*-Bu_3P and dioxane were added to the mixture, which was then stirred with heating to 90 °C for 12 h. (Scheme 21)

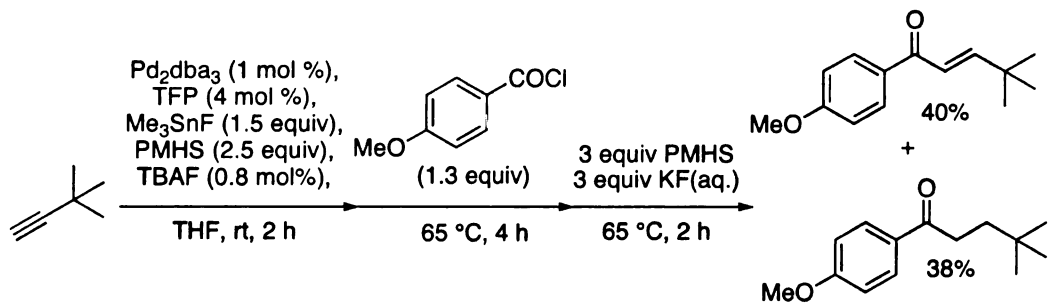
Scheme 21. Recycling Double Stille Reaction



This procedure proved moderately successful. The reaction sequence afforded 27% of the anticipated doubly-coupled product. However, 41% of the over-reduced doubly-coupled product was also produced. This product results from some of the regenerated trimethyltin hydride and/or PMHS reducing the α,β-unsaturated ketone.

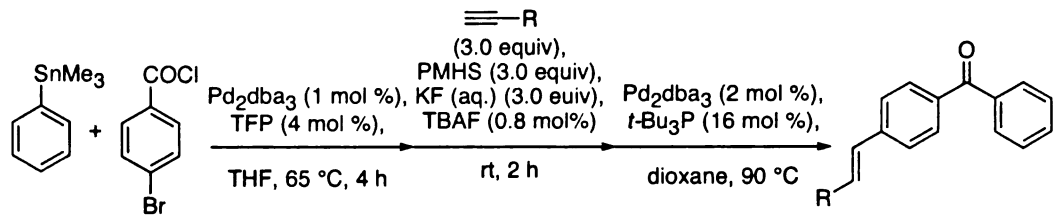
We probed this reduction by following the first Stille reaction with the addition of PMHS/KF in the absence of any alkyne. This resulted in formation of a 1:1 mixture of enone and saturated ketone.[26] (Scheme 22)

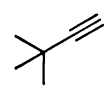
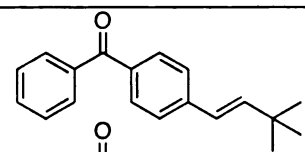
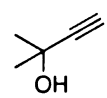
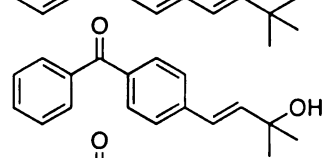
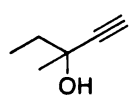
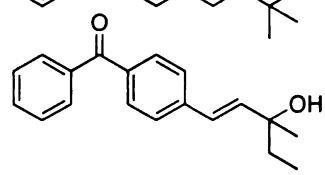
Scheme 22. Over-Reduction with in situ Formed Tin Hydride



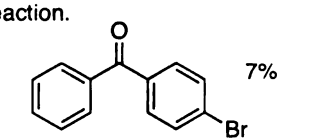
To avoid the over-reduction problem we removed the offending alkene by running the first Stille reaction with arylstannanes instead of vinylstannanes.[3] To our satisfaction this change worked well. The one-pot Stille reaction/ hydrostannation/Stille reaction with recycled trimethyltin hydride afforded the multi-component products in up to 53% yields. (Table 5) This represents an average yield of up to 85% for each step.

Table 5. Multi One-pot Hydrostannation/Stille with Recycling Tin

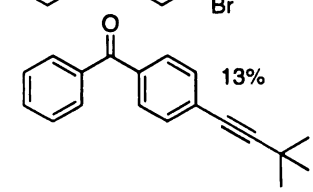


Entry	Alkyne	Time (h)	Product	Yield (%)
1		12		50 [a]
2		12		53
3		40		40

[a] Alkyne byproduct and unreacted intermediate were obtained in this reaction.



7%



13%

In summary, we have expanded the one-pot hydrostannation/Stille coupling of aromatic acid chlorides for substrates containing a halo-substituent on the aryl ring. We showed that such acid chlorides chemoselectively react with the in situ generated vinylstannane at the acid chloride site over the aryl bromide site. This selective addition enables the coupling of two different kinds of organostannanes to halo-substituted acid chlorides to generate multi-component coupled products without intermediate isolation. The tin byproduct of the first Stille reaction between an arylstannane and an acid chloride can be recycled for use in an in situ hydrostannation with an added alkyne and then the in situ

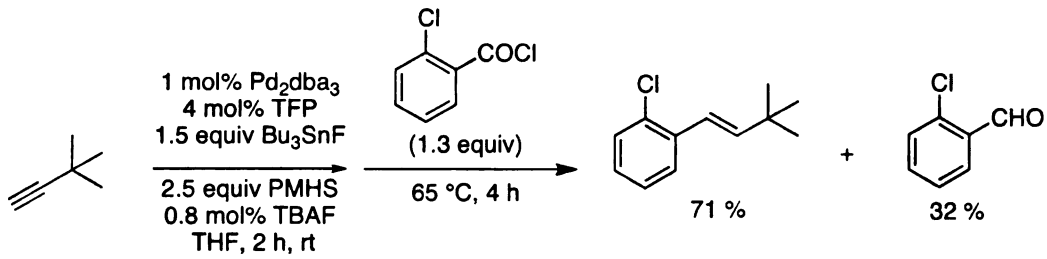
formed vinylstannane can undergo the second Stille coupling. In these last examples it must be noted that, where possible, 1,4-reduction can be competing side reaction.

CHAPTER 4. Pd (0)-Catalyzed PMHS Reductions of Acid Chlorides to Aldehydes

4-1. Introduction

As described in the Chapter 2, we have expanded the one-pot hydrostannation/Stille coupling method to allow acid chlorides to serve as the electrophilic coupling partner.[27] In the course of researching this one-pot sequence with acid chlorides as electrophiles, we obtained the intrusive amounts of aldehyde from the reduction of acid chloride. (Scheme 23) This finding prompted us to investigate this side reaction further.

Scheme 23. By-product Formation in One-pot Sequence with Bu_3SnF

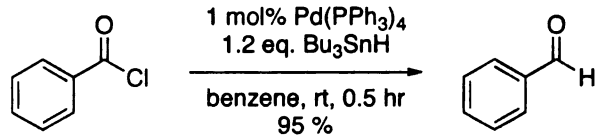


4-2. Reductions of Acid Chlorides

The reduction of acid chlorides to aldehydes is a basic and well-known functional group transformation and has been developed by various reaction conditions. Among those, reductions under Rosenmund conditions or by Li(*t*-BuO)$_3$AlH are classic means for effecting the reaction.[28] However, it was problematic due to the over-reduction to alcohols and intolerance of other

functional groups. Since that, the quest for greater selectivity and efficiency has long prompted the development of alternative methods. The effectively selective conversions from acid chloride to aldehyde have been explored including several complex metallic hydrides, and several hydride reagents.[29] The palladium-mediated organotin hydride reductions invented by Guibë have proven particularly popular.[30] (Scheme 24)

Scheme 24. Acid Chloride Reduction with Bu_3SnH under Pd Catalysis



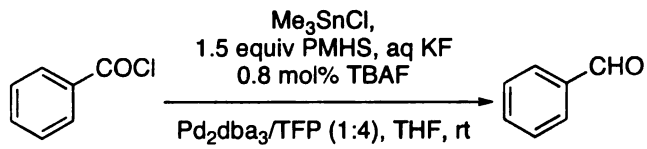
4-3. Reductions with PMHS

Of course, organotin reagents carry the baggage of being relatively toxic, expensive, unstable, etc.[31] Thus, mindful of prior reactions made catalytic in tin through the use of polymethylhydrosiloxane (PMHS) as the stoichiometric reductant,[32] we contemplated a tin-catalyzed version of Guibe's method for reducing acid chlorides to aldehydes.

As a prelude to that goal, we examined the Pd-catalyzed reduction of benzoyl chloride with a stoichiometric amount of Me_3SnH that was generated in situ by the reaction of Me_3SnCl with PMHS in the presence of aqueous KF (entry 1, Table 6).[7a] Despite the potential for hydrolysis and unwanted reactions, this combination rapidly and quantitatively afforded benzaldehyde. We next looked to

make the reaction catalytic in tin. Needless to say, we were pleased when reactions with 30 mol% and then 10 mol% tin worked nearly as well as the stoichiometric variant (entries 2-3). That satisfaction turned to surprise when, after 1 h, a tin-free control experiment (entry 4) also gave 100% benzaldehyde!

Table 6. Pd-Mediated Reduction of Benzoyl Chloride to Benzaldehyde with in situ Generated Me_3SnH



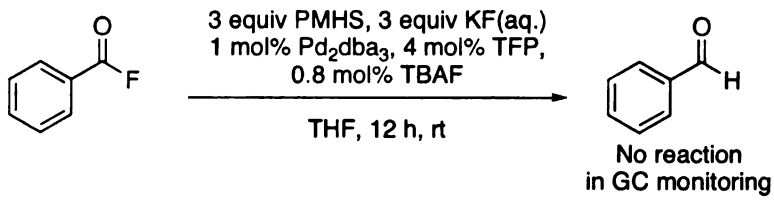
entry	Pd (0)	Me_3SnCl	KF	time	yield
1	1 mol%	1.0 eqiuv	1.5 eqiuv	0.5 h	100%
2	1 mol%	0.3 eqiuv	1.5 eqiuv	0.5 h	100%
3	1 mol%	0.1 eqiuv	1.5 eqiuv	1.0 h	100%
4	1 mol%	-	1.5 eqiuv	1.0 h	100%
5	1 mol%	-	-	24 h	12%
6	-	-	1.5 eqiuv	24 h	0%

We were caught unawares by this result because, while organosilanes have long been used to convert acid chlorides to aldehydes,[1,33] it has been over 20 years since Keinan and Greenspoon reported that acid chlorides "*cannot be reduced just with PMHS/Pd(PPh$_3$)$_4$*".[34] Their observation was later supported by Crabtree, who found that colloidal Pd formed from $Pd(hfacac)_2$ and PMHS required the presence of H_2 gas to reduce benzoyl chloride to benzaldehyde.[35]

In our system, it appeared that the presence of KF heightened the reactivity of the PMHS to where the acid chlorides can be converted to their aldehydes without the need for an additional reductant. This was supported by our own KF-free experiment (entry 5), which only gave 12% benzaldehyde after 24 h. That said, activation by KF is not sufficient to abolish the need for Pd catalysis (entry 6).

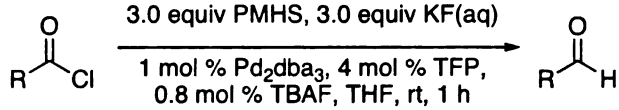
We presume the fluoride activates PMHS by making it hyper-coordinate.[36] Nonetheless, unlike acid chlorides, acid fluorides can be reduced by just PMHS/Pd(0).[37] Therefore, we had to consider if benzoyl chloride was first converted to benzoyl fluoride[38] and then reduced to benzaldehyde. However, GC monitoring never indicated the presence of benzoyl fluoride. Furthermore subjecting benzoyl fluoride to our reaction conditions failed to afford any benzaldehyde. (Scheme 25)

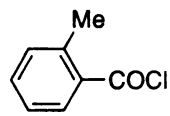
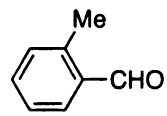
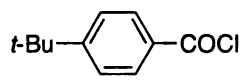
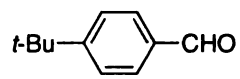
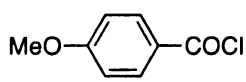
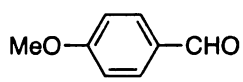
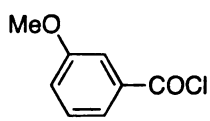
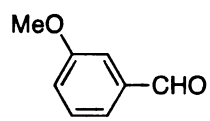
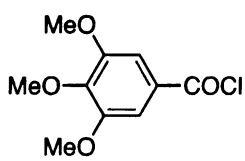
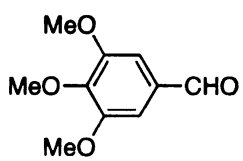
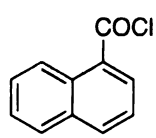
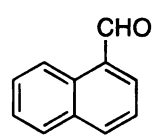
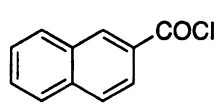
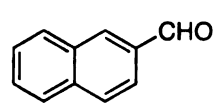
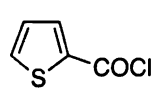
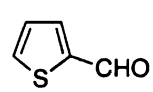
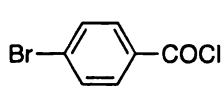
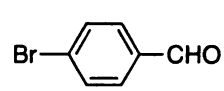
Scheme 25. Acid Chloride Reduction with Pd/PMHS/KF



With an acid fluoride intermediate ruled highly unlikely,[39] this reduction represents a noteworthy refinement of the literature. Moreover, given that PMHS is mild, safe, and cheap[6], these conditions may be attractive as a general way to convert acid chlorides to aldehydes. To assess this prospect, we tested a series of acid chlorides against the PMHS/KF/Pd(0)conditions. (Table 7.)

Table 7. Various Acid Chlorides Reduction with Pd/PMHS/KF



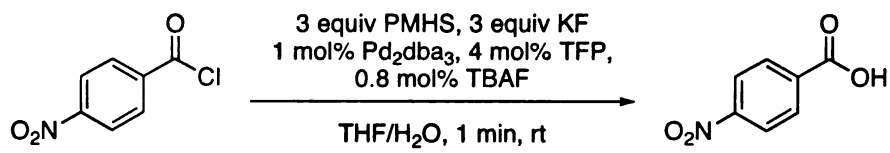
Entry	Acid Chloride	Aldehyde	Yield
1	benzoyl chloride	benzaldehyde	99%
2			83%
3			99%
4			91%
5			98%
6			82%
7			86%
8			81%
9			92%
10			68%

We soon saw that not all substrates underwent complete reaction with 1.5 equiv of PMHS. In contrast, 3.0 equiv of PMHS and aqueous KF in the company of substoichiometric amounts of Pd(0), trifurylphosphine (TFP), and TBAF[40] uniformly reduced a variety of electron-rich and neutral aryl acid chlorides (entries 1-8 in Table 7), including heterocyclic 2-thiophenoyl chloride (entry 9), to their aldehydes within 1 h at room temperature. Despite the ability of PMHS/Pd(0) to reduce aryl halides,[19,41] 4-bromobenzoyl chloride was selectively reduced to 4-bromobenzaldehyde and no benzaldehyde was detected by GC (entry 10).

4-4. Reductions of Electron Poor and Aliphatic Acid Chlorides

As shown in Table 7, the previously described reduction conditions were not universally applicable. Neither electron deficient benzoyl chlorides nor aliphatic acid chlorides were efficiently reduced. Instead the water in the reactions rapidly hydrolyzed such substrates. (Scheme 26)

Scheme 26. Fast Hydrolysis Reaction



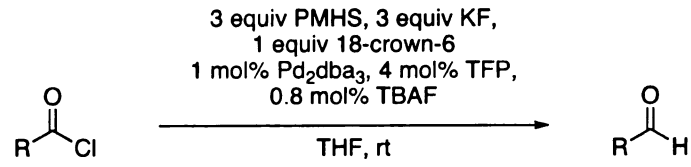
To expand this methodology to include electron deficient benzoyl chloride and aliphatic acid chloride, it was clear that water should be avoided. Among the reasons for the presence of water was the need to solubilize the potassium

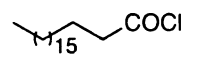
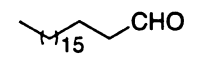
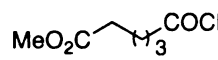
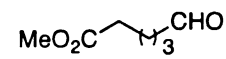
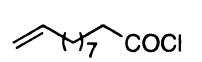
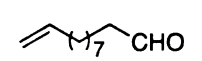
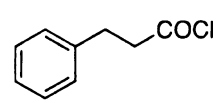
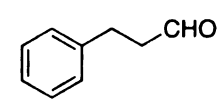
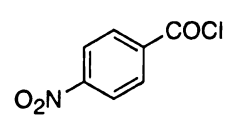
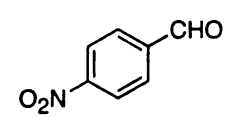
fluoride. Thus an early idea was to simply replace KF with stoichiometric amounts of TBAF. Unfortunately such amounts of TBAF promote sol-gel formation upon reaction with the PMHS.

We then looked at exchanging water with an aprotic organic solvent such as acetonitrile that could at least partially dissolve KF. Again we were disappointed when the reaction in acetonitrile did not go. Of course, we also knew that crown ethers could facilitate the movement of fluoride into other aprotic solvents. In fact coincident with these initial studies on anhydrous reduction conditions our lab established conditions for the non-aqueous hydrostannation of alkynes under Mo catalysis with Bu_3SnCl/PMHS with dry KF and 18-crown-6 in THF.[42]

With this information in hand we thought to apply similar non-aqueous reaction conditions to the reduction of aliphatic and electron-deficient aromatic acid chlorides to aldehydes. As illustrated in Table 8, reduction of such substrates with 3 equivalents of both PMHS and KF along with 1 equivalent of 18-crown-6 afforded the corresponding aldehydes. These anhydrous reactions tended to take longer (6 hours) and yields tended to be lower (50 to 71%). However, hydrolysis was shut down with trace amount of over-reduced products as the only observable byproducts.

Table 8. Non-aqueous Reduction of Electron Deficient Benzoyl Chlorides and Aliphatic Acid Chlorides



Entry	Acid Chloride	rxn time (h)	Product	Yield (%) [a]
1		6		71
2		6		53
3		6		50
4		6		71
5		6		51

[a] Average isolated yield over two runs. See experimental section for details.

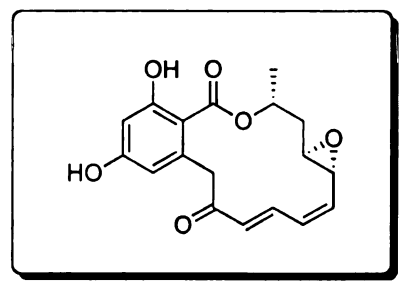
In summary, the presence of fluoride allows Pd(0)-catalyzed PMHS reductions of electron-rich and neutral aryl acid chlorides. Yields are generally high and reaction times short. Perhaps most importantly, these results amend the existing literature. Electron-rich and neutral aryl respond well to standard aqueous KF/PMHS conditions, but for electron poor or aliphatic acid chlorides KF/18-crown-6 needs to be used instead of aqueous KF to avoid acid chloride hydrolysis.

CHAPTER 5. Application of One-pot Pd-mediated Reactions in Target Synthesis

5-1. Introduction

Having developed several one-pot hydrostannation/Stille methods, we sought to validate their utility in the theater of target synthesis. The molecule chosen for this task should meet several criteria. (1) The molecule should have been previously synthesized so as to allow us a direct evaluation of any efficiency gained via the employment of our chemistry. (2) Retrosynthetic analysis of the molecule should reveal multiple opportunities to showcase our methodology. (3) The synthesis of the chosen target molecule should be instructional beyond application of the one-pot hydrostannation/Stille sequence. We deemed monocillin I a molecule that satisfied these three conditions (Figure 1).[43]

Figure 1. The Structure of Monocillin I



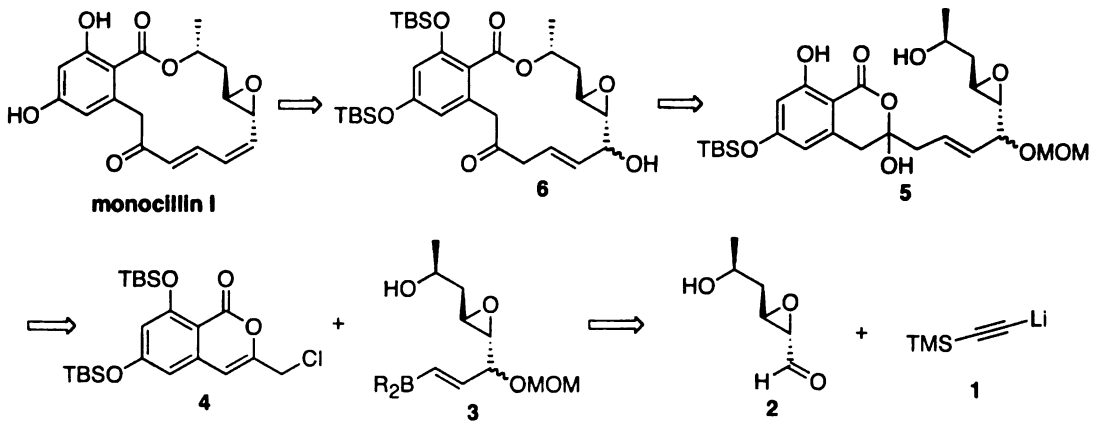
Monocillin I

5-2. Prior Synthesis

Monocillin I is a resorcylic macrolide isolated from *Monocillium nordinii*.[44] Monocillin I exhibits a variety of antifungal and antibiotic properties not shared by other members of this class of natural products. The structure of monocillin I was confirmed by its direct conversion into radicicol.[45] Affirmation of these structures was achieved by their total synthesis by Lett[46] and Danishefsky.[47]

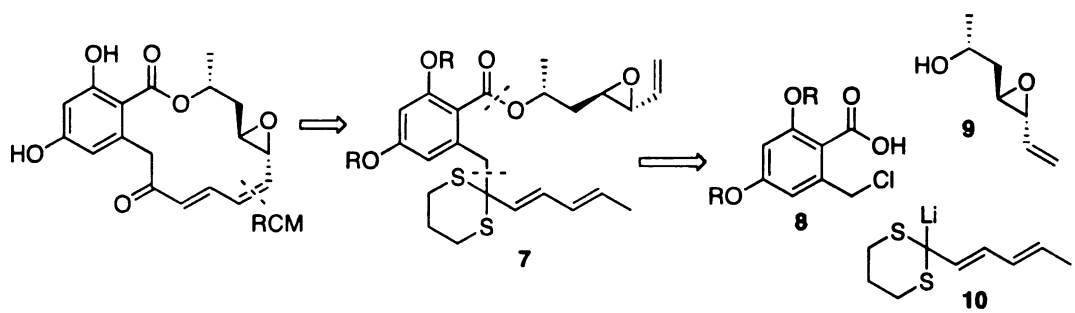
Lett's retrosynthesis is shown in Scheme 27. Lett began with a condensation between the lithiated alkyne **1** and aldehyde **2**, followed by the addition of R_2BH to afford vinylborane **3**. Isocoumarin **5** was obtained via a Suzuki-Miyaura coupling with allyl chloride **4**. Macrolide **6** was synthesized via an intramolecular Mitsunobu reaction. The conjugated *E*, Z-diene was installed by elimination of the in situ generated mesylate with Et_3N. Following deprotection, monocillin I was obtained in 15% overall yield from aldehyde **2** and TMS acetylene.

Scheme 27. Lett's Retrosynthesis



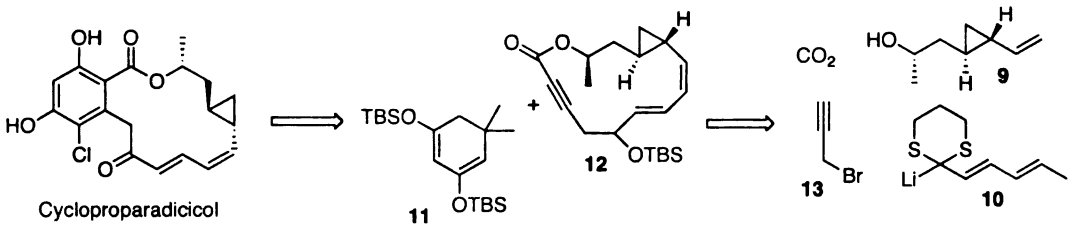
Danishefsky's retrosynthesis is outlined in Scheme 28. Danishefsky planned a convergent coupling sequence for three key intermediates. The first coupling was an esterification of benzoic acid **8** with the optically active secondary alcohol **9** containing all three stereogenic centers of monocillin I. The second coupling required a chemo- and regioselective addition of a masked acyl anion equivalent **10** to the benzyl chloride carbon in the presence of a vinyl epoxide. To complete the synthesis, a stereospecific ring-closing metathesis of **7** afforded the desired monocillin I.

Scheme 28. Danishefsky's Route I



While most syntheses of these resorcylic macrolides had begun with an intact substituted aromatic ring, he approached this synthesis differently. He used the Diels-Alder reaction shown in Scheme 29 to construct the aromatic moiety. In this regard, macrolactone ring **12** was prepared from three key starting materials, then this alkynyl macrolactone served as the dienophile in the aforementioned Diels-Alder reaction.

Scheme 29. Danishefsky's Route II using Diels-Alder Reaction

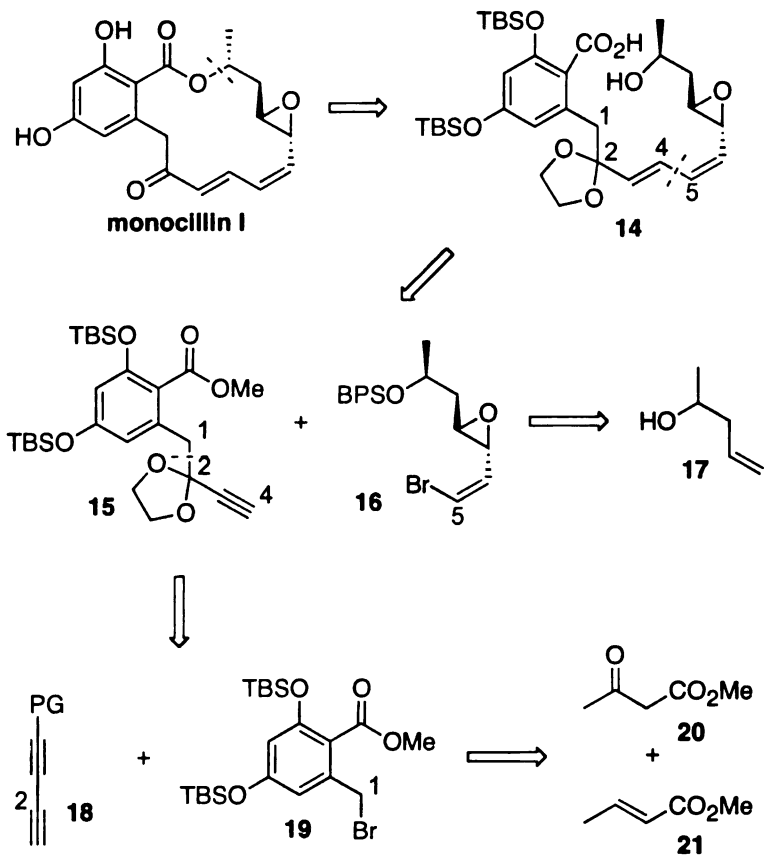


5-3. Our Retrosynthesis

Our own retrosynthetic examination of monocillin I suggested the newly developed one-pot hydrostannation/Stille chemistry described before could be applied to the formation of C1–C2, C2–C3, and/or C4–C5. In the end, it was decided that our first generation retrosynthesis involving the newly developed Stille chemistry would be applied to the construction of the C1-C2 and C4-C5 bonds. That retrosynthesis is outlined in Scheme 30. Retrosynthetic disassembly of monocillin I provided intermediate **14** as a precursor which could undergo an intramolecular Mitsunobu reaction.

The diene moiety in monocillin I would be installed via a one-pot hydrostannation/Stille sequence between alkyne **15** and *Z*-vinyl bromide **16**. The *Z*-vinyl bromide **16** could be obtained via routine synthetic operations starting from the commercially available 4-penten-2-ol **17**. The one-pot Stille protocol would then be used to form alkyne **15** from benzyl bromide **19** and diyne **18**. Benzyl bromide **19** could be synthesized via the commercially available methyl acetoacetate **20** and methyl crotonate **21**.

Scheme 30. Our Retrosynthesis

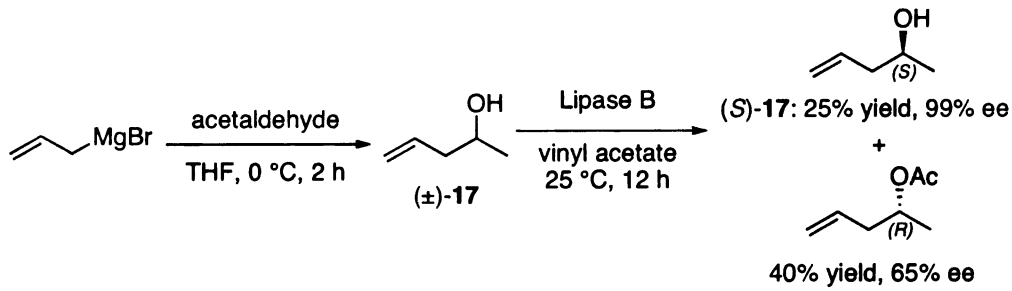


5-4. Synthesis of Vinyl Bromide 16

The first building block to be assembled was vinyl bromide **16**. Establishing the methyl group stereochemistry at what would become the C10 carbon of monocillin became our immediate goal. Towards this end optically active **17** would represent a good starting point. Although several asymmetric syntheses of **17** are known and a carbohydrate-based approach was previously developed,[48] we chose the resolve racemic **17** by way of an enzyme catalyzed kinetic resolution.[49] This decision was based on the realization that both

enantiomers could be used for the formation of the lactone through either Mitsunobu way or Yamaguchi esterifications.

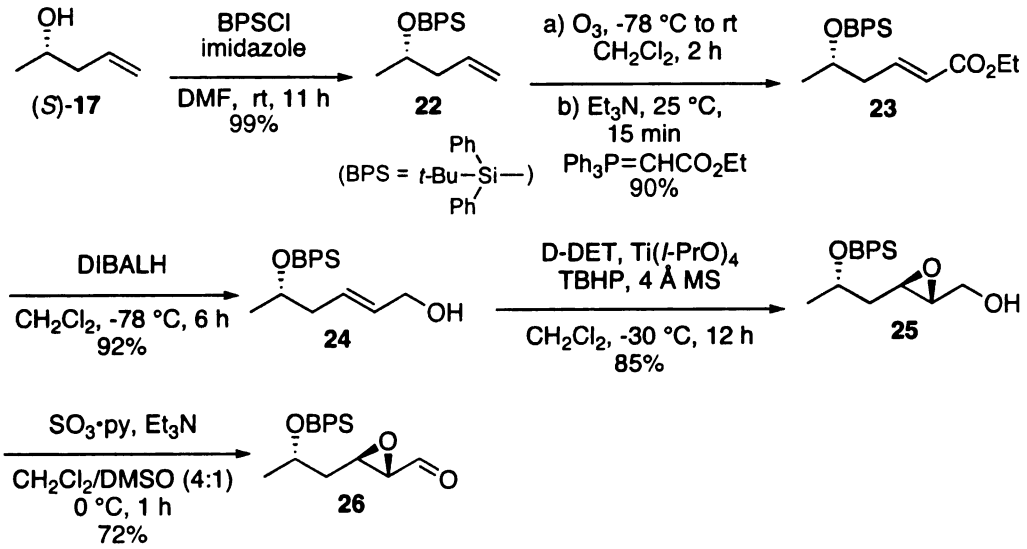
Scheme 31. Lipase Resolution of (±)-**17**



With this approach in mind (±)-**17** was prepared via a Grignard reaction between allylmagnesium bromide and acetaldehyde.[50] With racemate **17** in hand, various enzymes were explored for the desired kinetic resolution. From these experiments Novozyme emerged as the enzyme of choice. After column chromatography, (*s*)-**17** was obtained in 25% yield with a 99%ee. (Scheme 31)

The ease and cost of the protocol, as well as the high enantiomeric purity, warranted using this protocol in the total synthesis. In order to transform the newly resolved material into vinyl bromide **16**, homoallylic alcohol (*s*)-**17** was first protected as its corresponding *tert*-butyldiphenylsilyl ether **22**. The alkene moiety was then subjected to a one-pot ozonolysis-Wittig olefination to afford ester **23** in 90% yield.[51] DIBALH reduction of **23** gave the corresponding allylic alcohol **24** in 92% yield. Sharpless asymmetric epoxidation (D-DET) afforded the corresponding epoxy alcohol **25** in 85% yield. The alcohol was then oxidized[52] with SO_3• py and Et_3N to afford epoxy aldehyde **26** in 72% yield. (Scheme 32)

Scheme 32. Synthesis of gem-Dibromide **23**

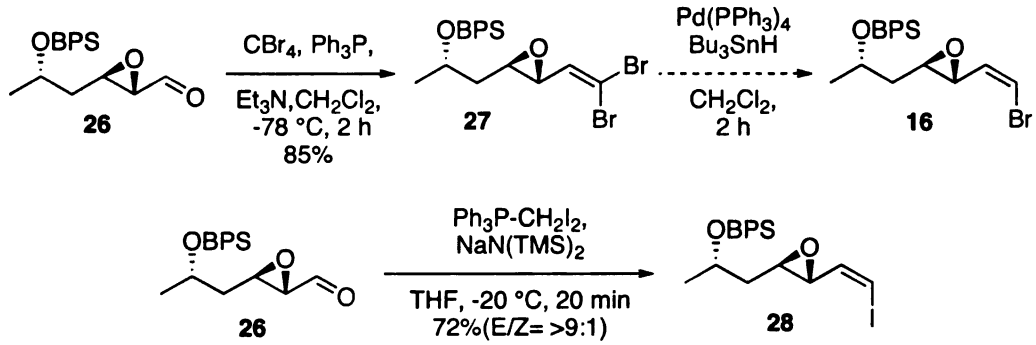


Subjection of the epoxy aldehyde **26** to a modified Corey-Fuchs protocol was necessary so the epoxide moiety would remain intact.[53] The use of Et_3N was essential for the success of the reaction. This procedure produced gem-dibromide **27** in 85% yield.

With gem-dibromide **27** in hand, the next step was to form the *Z*-vinyl bromide group. (Scheme 33) Per the literature treatment of **27** with 1.0 equiv of Bu_3SnH in the presence of $Pd(PPh_3)_4$ should afford the desired *Z*-vinyl bromide **16**.[54] However, in our hands, this protocol did not give clean vinyl bromide.

With the general dibromide approach to **16** failing, we considered alternative routes that would still use aldehyde **26** as a starting material. Among the routes consider the most successful involved construction of a (*Z*)-vinyl iodide (**28**) through a setereoselective Wittig reaction with iodomethyltriphenyl-phosphorane ($Ph_3PCH_2I_2$) to afford the vinyl halide with an E/Z ratio >9:1.[55]

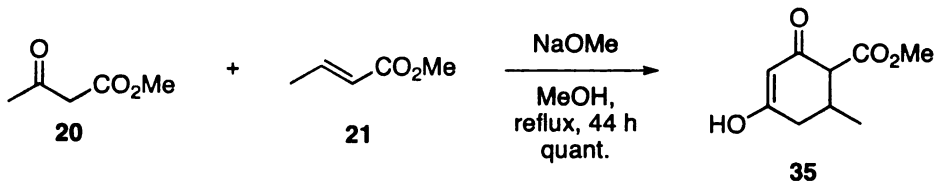
Scheme 33. *(Z)*-Vinyl Halide Preparation



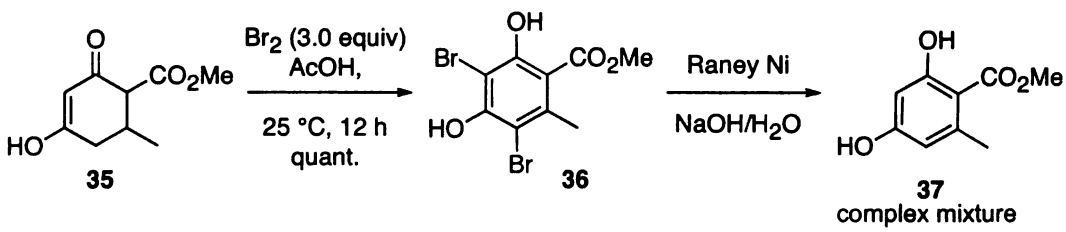
5-5. Synthesis of Benzyl Bromide 19

With one electrophilic substrate for the proposed one-pot hydrostannation/ Stille sequence synthesized, our attention turned to the remaining electrophile, benzyl bromide **19**. The key precursor to **19** was methyl orsellinate **37**. Several routes to **37** were explored. Most of these began with a methanol solution of compounds **20** and **21** was being refluxed in the presence of NaOMe, to afford methyl dihydroorsellinate (**35**) in quantitative yield. (Scheme 34)

Scheme 34. Preparation of Compound **35**

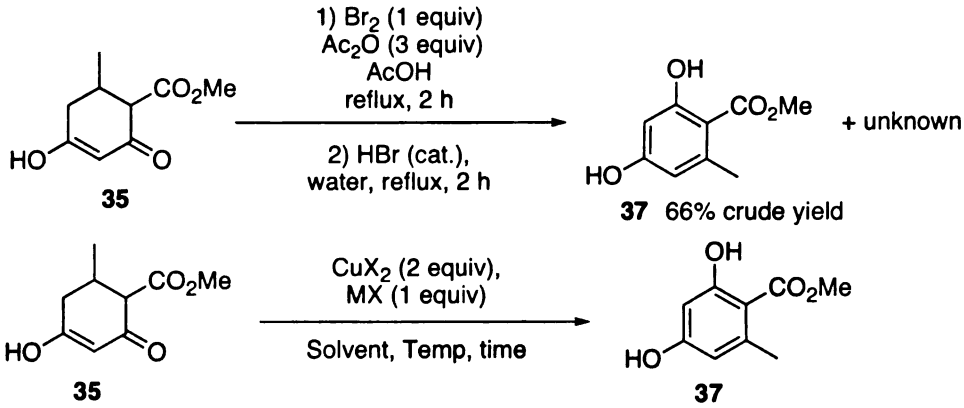


Scheme 35. Synthesis of **37**



Efficient and clean generation of methyl orsellinate (**37**) from methyl dihydro-orsellinate (**35**) proved difficult as shown in Scheme 35. While this gave the desired arene, yields were moderate and unidentifiable products contaminated the final product.

Scheme 36. Stepwise Synthesis of **37**



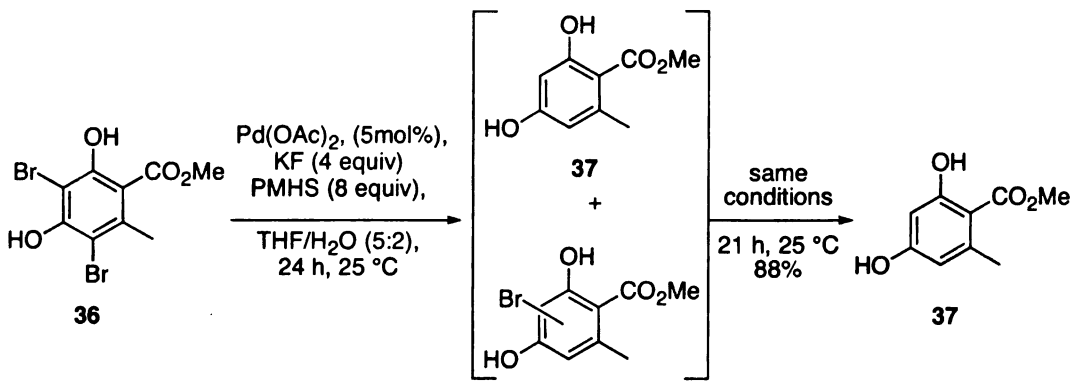
Entry	CuX_2	MX	Solvent	Temp	Time (h)	Yield
1	Br	LiBr	CH_3CN	65 °C	2	33%
2	Br	LiBr	DMF	100 °C	2	44%
3	Cl	LiCl	CH_3CN	65 °C	5	33%
4	Cl	LiCl	DMF	100 °C	5	47%
5	Cl	$MgCl_2$	CH_3CN	65 °C	12	47%

Ultimately the solution to this problem would be a more stepwise approach to **36**. Treatment of **35** with Br_2 in AcOH gave dibromide **36**. (Scheme 36) Although our initial efforts to dehalogenated **36** with Raney nickel proved irreproducible, chemistry developed in our lab worked well at transforming **36** to **37**.

Specifically, we took advantage of our group's a Pd catalyzed, PMHS/KF assisted dehalogenation procedure.[19] This method had been shown to reduce a

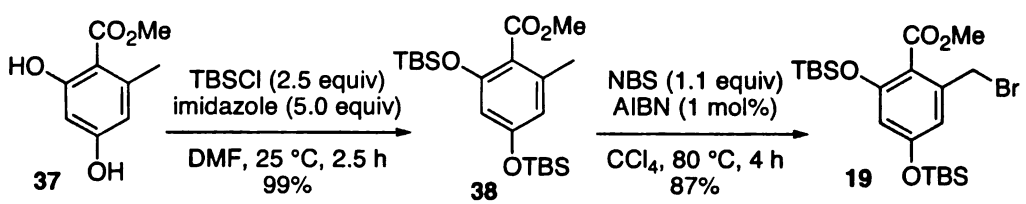
variety of aryl and vinyl halides at room temperature. When **36** was treated with 5 mol% $Pd(OAc)_2$, KF and PMHS in THF/H_2O (5:2) at 25 °C for 24 h. Crude ^1H NMR analysis indicated a 1.7:1.0 mixture of monobromide to **37**. The reaction was extracted with ether and the water was removed. The organics were then filtered to remove all of the palladium. The filtrate was then concentrated and resubjected to the same conditions. After workup and column chromatography, methyl orsellinate **37** was obtained in 88% yield. (Scheme 37)

Scheme 37. PMHS/KF Dehydrohalogenation Catalyzed by $Pd(OAc)_2$



Treatment of **37** with TBSCl (2.0 equiv) and imidazole (5.0 equiv) in DMF at 25 °C for 2.5 h afforded the bis-TBS ether **38** in 99% yield.[56] The desired benzyl bromide **19** was synthesized by treatment of **38** with NBS and catalytic AIBN in CCl_4 at 80 °C for 4 h. (Scheme 38)

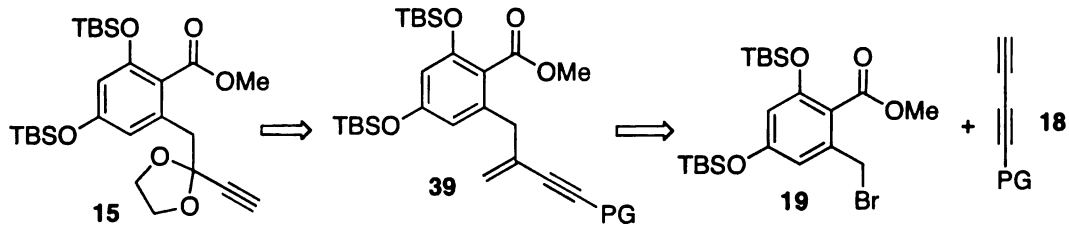
Scheme 38. TBS Protection and Benzylic Bromination



5-6. Synthesis of the Diyne Moiety

With both electrophiles in hand, the central mono-protected diyne needed to be made. In this regard, we explored several different protective groups with a focus on bulky substituents that would promote mono hydrostannation during the first of our two planed hydrostannation/Stille sequences.

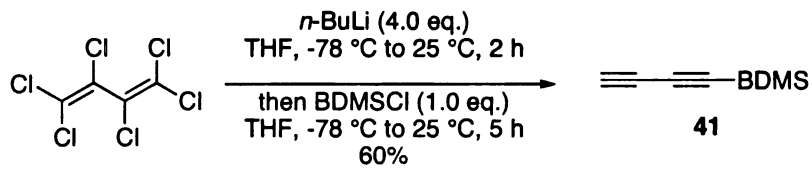
Scheme 39. Approach to Synthesis of **15**



5-6-1. Synthesis of Vinylstannane 42 from Silyldiyne 41

We first investigated the unique silyl-protecting group, biphenyldimethyl-chlorosilane (BDMSCl), owing to the ease with which its installation could be monitored and with which the final product could be isolated.[57] Diyne **41** was prepared from hexachlorobutadiene with 4.0 equiv of *n*-BuLi and 1.0 equiv of BDMSCl in THF in 60% yield.[58] (Scheme 40)

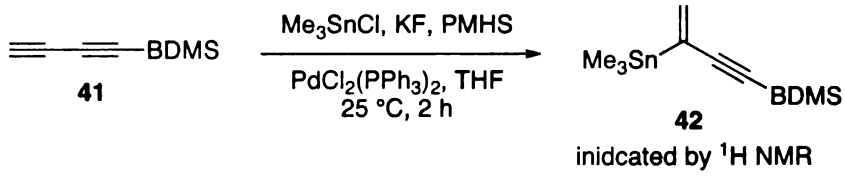
Scheme 40. Synthesis of Diyne **41**



With **41** in hand, hydrostannation of the diyne was investigated. When **41** was subject to the palladium catalyzed hydrostannation using the KF/PMHS

conditions described in Chapter 2, only the internal stannylenyne **42** was obtained, as was determined by ^{1}H NMR of a crude material. Unfortunately, all attempts to isolate this compound failed. (Scheme 41) With the undesired outcome using diyne **41**, and alternative diyne was needed.

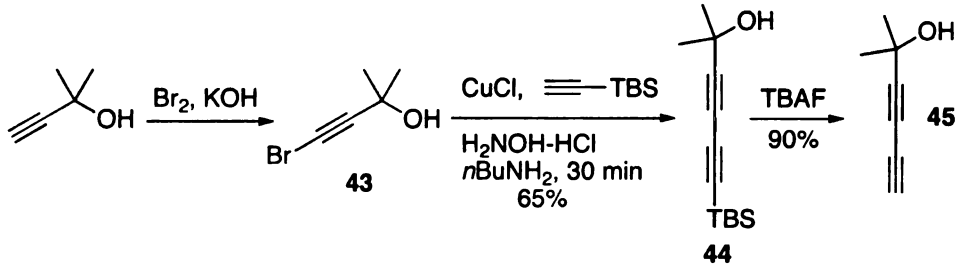
Scheme 41. Hydrostannation of Diyne **41**



5-6-2. Synthesis of Vinylstannane 46 from Diyne 45

We attributed the difficulties experienced with **41** to, or at least in part to, cleavage of the C-Si bond under the reaction conditions. Therefore a non-silicon containing protecting group would be needed. One simple and easily removable group would be acetone and for that reason diyne **45** was synthesized via the two-step protocol shown in Scheme 42.

Scheme 42. Synthesis of Diyne **45**

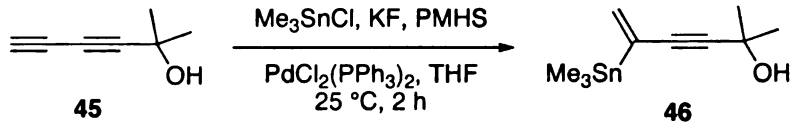


First, 2-methyl-3-butyn-2-ol was converted into bromoalkyne **43**. Using conditions developed by Marino,[59] bromoalkyne **43** was coupled with TBS-

acetylene to afford silyl diyne **44** in 65% yield. Subsequent treatment with TBAF removed the silyl group to afford diyne **45** in 90% yield. The isolation of this compound was tedious due to its volatility.

Diyne **45** was then subjected to a palladium-catalyzed hydrostannation using the KF/PMHS protocol. After two hours, the desired internal stannylenyne **46** was obtained, but again, isolation was not successful. (Scheme 43) The lack of progress in manipulating the various diynes led us to reevaluate our retrosynthesis.

Scheme 43. Hydrostannation of Diyne **45**



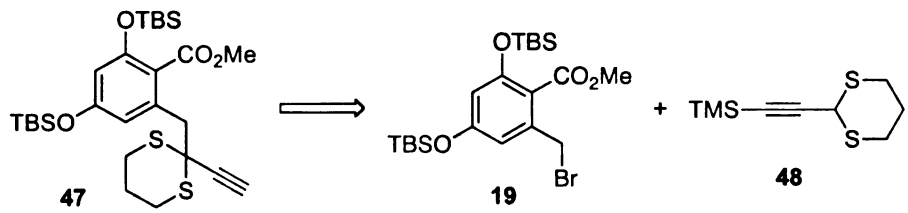
45 **46**

inidcated by ^{1}H NMR

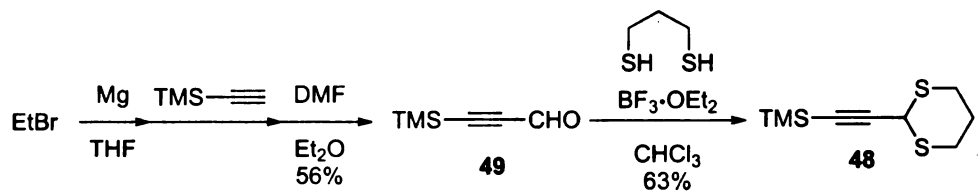
5-7. Synthesis of the Terminal Alkyne

In reevaluating our retrosynthesis we decided to forego the C1-C2 Stille coupling. This would allow us to introduce the C2 carbon at the monocillin oxidation state. We viewed an alkynyl dithiane as a substrate that would still allow us to use compound **19**, while providing us enough steric bulk for a regioselective hydrostannation. (Scheme 44) Admittedly this route held some uncertainty because we had no experience in using dithiane substrates in the one-pot hydrostannation/Stille reaction where sulfur might be problematic in Pd catalyzed coupling reaction.[60] Nonetheless this route was otherwise attractive and therefore we targeted γ-silyl ethynyldithiane **48** for synthesis.

Scheme 44. New Route for the Preparation of Terminal Alkyne

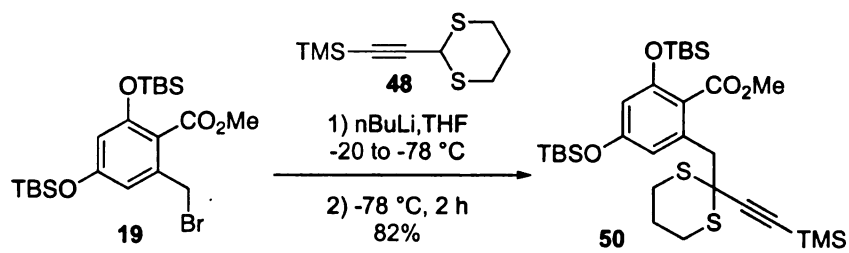


Scheme 45. Synthesis of γ-Silyl Ethynyldithiane **48**



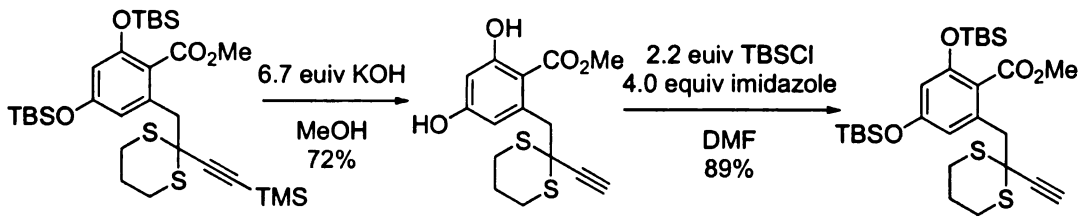
Ethyl magnesium bromide, prepared from Mg and ethyl bromide in THF, was added dropwise to a solution of trimethylsilylacetylene in THF. After refluxing for 5 min and the reaction mixture was added dropwise to a solution of DMF in THF. The solution was refluxed again for 5 min before dilute aqueous HCl was added. The resulting oil was purified by vacuum distillation to give the product in 56% yield. Conversion of 3-(trimethylsilyl)-propynal **49** to the corresponding dithiane **48** occurred in acceptable yield 63% under typical thioacetalization procedures with $BF_3 \cdot OEt_2$ and 1,3-propane dithiol. (Scheme 45)

Scheme 46. Nucleophilic Addition of Dithiane to Benzyl Bromide



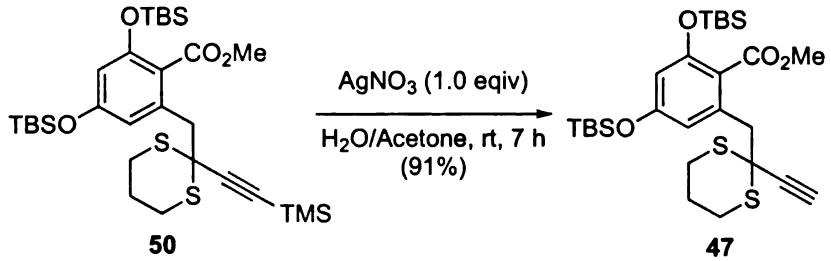
Dithiane **48** underwent rapid and stoichiometric transmetalation in the presence of n-BuLi in THF solution. Disappointingly, the addition of solution **19** in THF to the lithiumated dithiane solution did not give coupled product, only complex mixture. Fortunately changing the order of addition improved things significantly. Thus, when thioacetal **48** was converted into its lithium salt by the addition of n-BuLi and was then added dropwise to a solution of benzyl bromide **19** in THF, the alkylated thioketal **50** was obtained in 82% yield. (Scheme 46) The selective desilylation of the silyl alkyne was investigated next. When **50** was treated with 1.7 equiv of potassium hydroxide a mixture of mono-desilylated, di-desilylated and tri-desilylated products were obtained. We could simply remove three silyl groups with 6.7 equiv. of potassium hydroxide and then reprotect the two hydroxyl groups with TBSCl. (Scheme 47)

Scheme 47. Desilylation of Silyl Alkyne



However this approach wasted reagents and lacked elegance. Thus we conducted additional experiments aimed at the desired selective desilylation.[61] An interesting literature reaction involved the silver catalyzed desilylation of a silyl alkyne in the presence of a phenylsilylether. However, with compound **50** this procedure did not give good results.

Scheme 48. Chemoselective Desilylation of **50** with Silver Nitrate



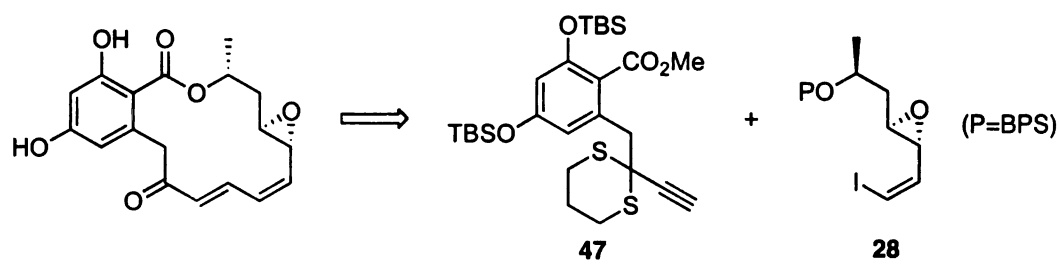
50 **47**

Instead the reaction was very slow and gave complex mixtures. It was assumed some of our problems might be coming from using only catalytic amounts of silver. Indeed we were glad to find that stoichiometric amount of silver chemoselectively desilylated product **47** with 91% yield in 7 h. (Scheme 48)

5-8. One-pot Sequence with Real Substrates

We were now ready to explore the accessibility of one-pot sequence in the synthesis of monocillin I with substrates **28** and **47**. Were we to be successful in our one-pot hydrostannation/Stille sequence, lactonization and deprotections were all that would be left for the end game of monocillin I.

Scheme 49. Close to the End Game

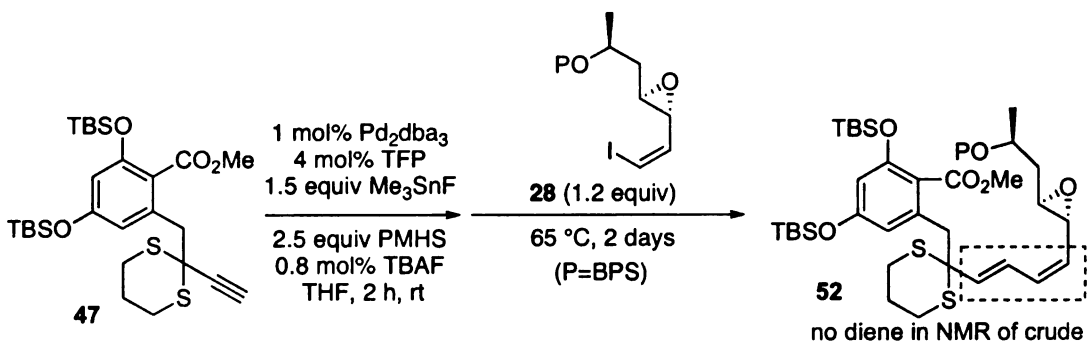


47 **28**

Exploration of the one-pot hydrostannation /Stille reaction began with a look at the stepwise sequence. (Scheme 50) Hydrostannation of **47** with in situ

formed tin hydride from trimethyltin fluoride and PMHS under the presence of Pd catalysts was followed by the addition of vinyl iodide **28** and heating to 65 °C. After 2 days, vinylstannane **47** was gone according to TLC monitoring.

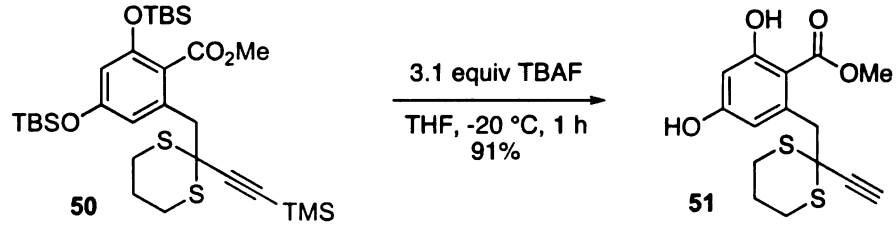
Scheme 50. One-pot Sequence with **28** and **47**



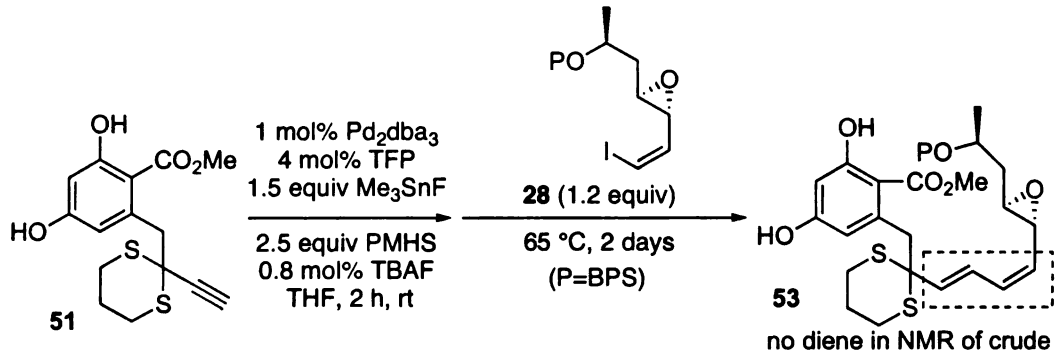
Disappointingly though, only a complex mixture of products was obtained and none of the observed compounds exhibited NMR peaks that would indicate diene formation.

Rather purification of crude reaction indicated that significant amounts of desilylation had occurred among the byproducts, presumably due to the presence of fluoride during the hydrostannation. We decided to avoid this complication by removing the TBS protecting groups on the two phenols. The treatment of compound **50** with TBAF gave the unprotected diol terminal alkyne **51** in 91% yield. (Scheme 51) Compound **51** was then subjected to our standard one-pot hydrostannation/ Stille reaction conditions, but again there were no indications of diene formation by NMR of crude materials. (Scheme 52)

Scheme 51. Desilyation of **50** with TBAF

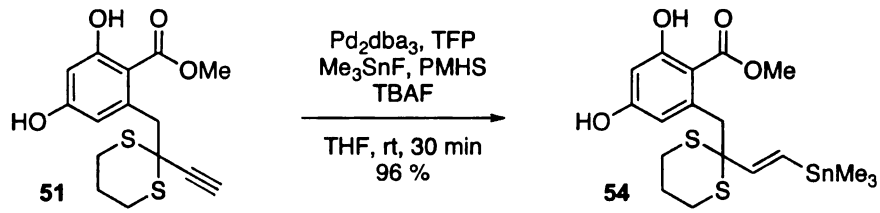


Scheme 52. Construction of Diene through Our One-pot Sequence



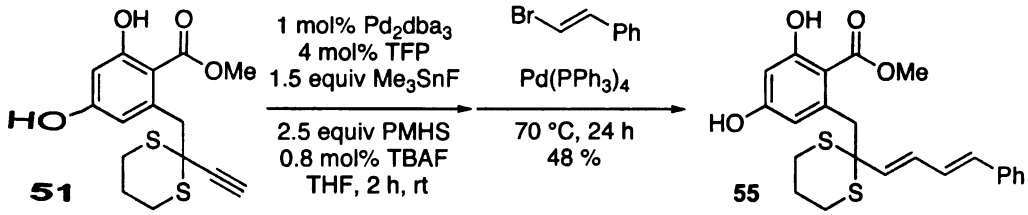
Frustrated by these failures we decide to study the individual steps of hydrostannation/Stille sequence. First, the in situ formation of the vinylstannane was investigated. Compound **51** was tested to determine whether this substrate worked well in our standard hydrostannation protocol. A hydrostannation of **51** was setup. By TLC monitoring, the starting material was gone in 30 min and a clear new spot showed up. While the acidity of the phenols made isolation via column chromatography in the presence of triethylamine difficult, the vinylstannane product **54** could be passed through the short column with 10% ethylacetate/hexane to afford pure material in 96% yield. This allowed us to conclude that the hydrostannation step with dithiane substrate **51** worked well (Scheme 53).

Scheme 53. Hydrostannation of **51**



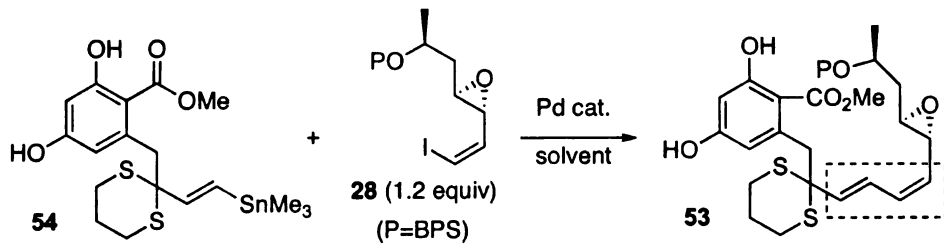
The next question became "Is the Stille coupling of in situ generated **54** problematic?" As mentioned earlier we had no prior experience with the cross-coupling of dithianes such as **51/54**.[62] With this in mind we looked into the one-pot hydrostannation/Stille coupling reaction of **51** with a simple electrophile, β-bromo-(E)-styrene. Under tetrakistriphenyl-phosphine Pd catalysis, the Stille coupling step (Scheme 54) did not afford a high yield of the product, but **55** was generated in 48% yield. These experiments suggested that dithiane **51** was not inherently a bad substrate for our one-pot sequence.

Scheme 54. One-pot Sequence with β-Bromo Styrene



Given the results described above, we concluded that the successful cross coupling of our monocillin substrates, (Z)-vinyl iodide **28** and vinylstannane **54**, would simply require a thorough screening of various Stille conditions. Unfortunately this did not prove to be the case.

Table 9. Search for the Stille Reaction Condition

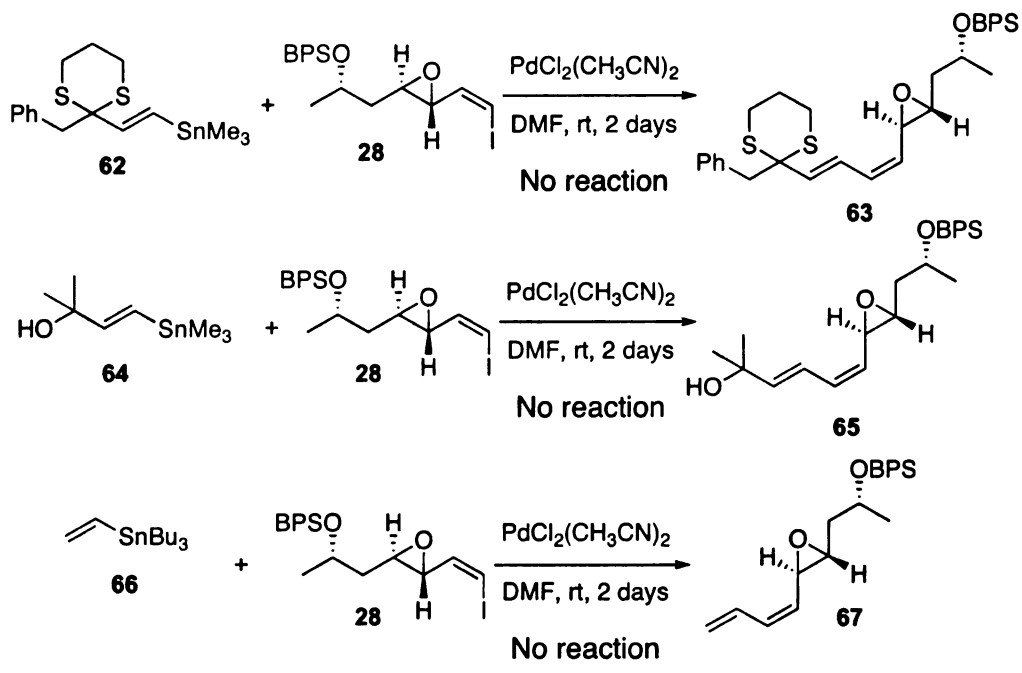


Entry	Pd cat.	solvent	Aditives	temp	time	Yield
1	$PdCl_2(CH_3CN)_2$	DMF		rt	5 days	no diene
2	$PdCl_2(CH_3CN)_2$	NMP		rt	2 days	no diene
3	$PdCl_2(CH_3CN)_2$	NMP	CuI(1.0 eq.)	rt	2 days	no diene
4	$Pd_2dba_3/AsPh_3$	NMP	LiCl(2.0 eq.)	60 °C	2 days	no diene

Table 9 showed some of the catalyst, solvent, additive, condition's combinations studied. For these and all other variations tried NMR of the crude materials never suggested diene formation. Owing to all of the unsuccessful results plus the successful control experiment with **51/54**, we began to suspect vinyl iodide substrate **28** as the cause of our problems. The literature does not offer any examples of a substrate bearing an epoxide group right next to a (Z)-vinyl iodide participating in any Pd-catalyzed coupling reactions.

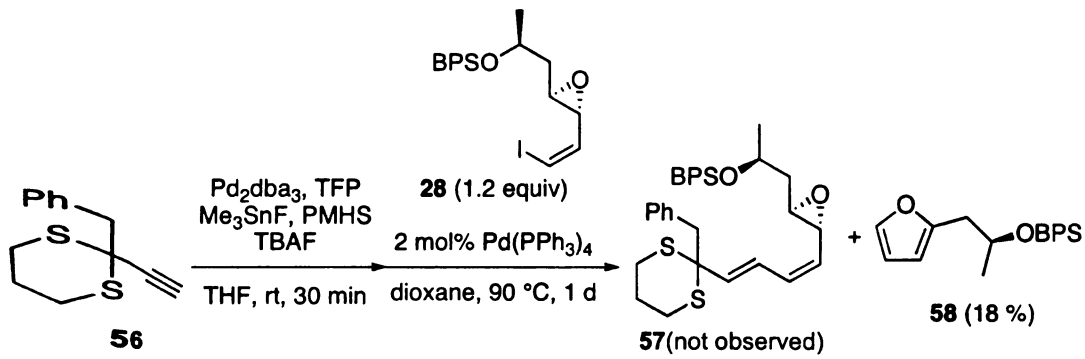
Therefore we decided to investigate the coupling of substrate **28** with simplified vinyltins. (Scheme 55) Again, we did not get the cross-coupled products. Instead NMR analysis of the crude reaction and TLC monitoring indicated consumption of the vinyl iodide plus homocoupling of stannane **62** and **64**.[63]

Scheme 55. Our One-pot Sequence with Simply Modified Vinylstannanes



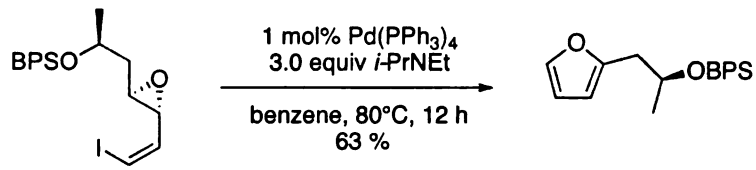
Somewhat surprisingly when we subjected alkyne **56** and substrate **28** to the full one-pot hydrostannation/Stille reaction sequence a new product was observed. (Scheme 56) Again this was not the expected cross-coupled product, but furan **58**.

Scheme 56. Furan Formation

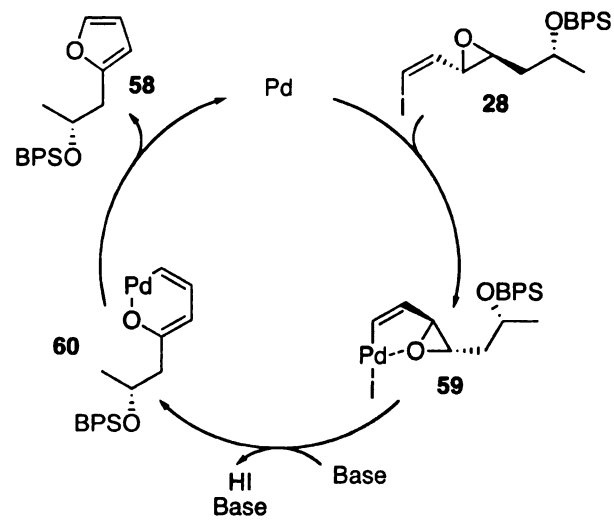


We wondered what among the reaction conditions led epoxy (Z)-vinyl iodide **28** to be converted into the furan ring. When epoxy (Z)-vinyl iodide **28** and $(PPh_3)_4Pd$ were mixed in benzene, then heated at 80°C for 12 h, the mixture did not give any furan formation. However, we got furan product **58** in 62% yield from epoxy (Z)-vinyl iodide **28** in presence of the tetrakis Pd catalyst and Hunig's base. (Scheme 57) Presumably either the PMHS or TBAF was playing the role of the Hunig's base during the reaction of Scheme 56.

Scheme 57. Furan Formation from **29**



Scheme 58. The Proposed Mechanism for Furan Formation

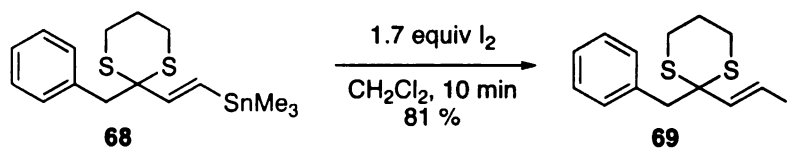


While the furan formation mechanism has not been experimentally elucidated, a putative mechanism is put forth in Scheme 58. After oxidative

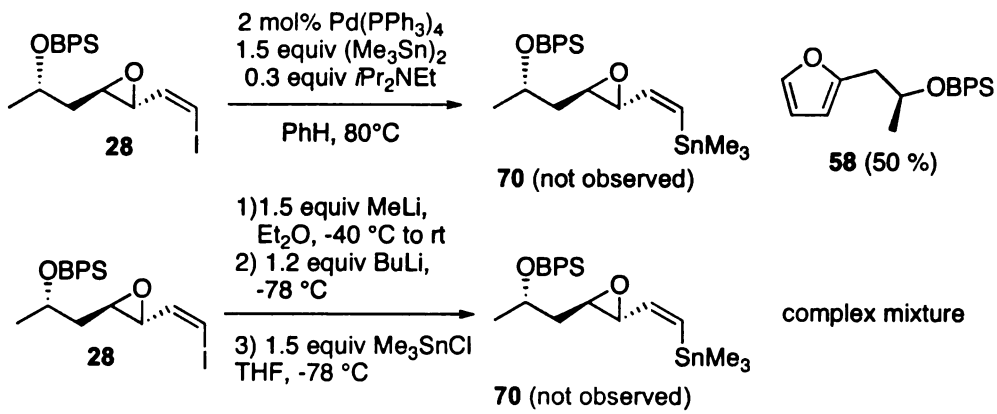
addition by Pd into the vinyl iodide bond, the epoxide oxygen could coordinate after which epoxide opening would lead to cationic π allyl Pd. Base would promote formation of intermediate **61**, which upon reductive elimination would afford the furan ring of **58**.

Assuming that our mechanistic picture was at least correct in oxidative addition initiating the furan forming sequence we considered switching the reactive ends of the Stille partners. While this switch would be incompatible with our goal of forming the C4-C5 bond via our one-pot hydrostannation/Stille cross coupling sequence, the information gained by studying such a reaction would otherwise still be instructive.

Scheme 59. Switch from Vinylstannane to Vinyl Iodide



Scheme 60. Stannylation of Vinyl Iodide **28** to Vinylstannane



The vinyl stannane easily was switched to the corresponding vinyl iodide with iodine in CH_2Cl_2 in 81% yield. (Scheme 59) Unfortunately converting vinyl iodide **28** into epoxy (Z)-vinyl stannane **70** was not readily realized. (Scheme 60)

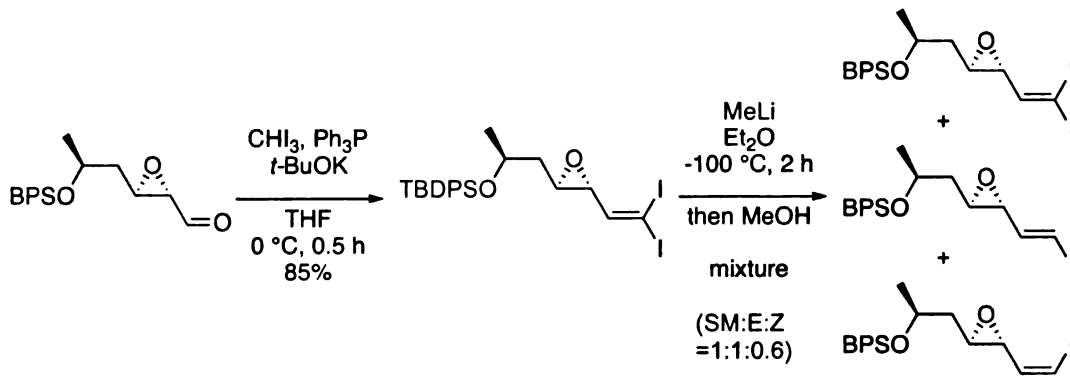
Pd-catalyzed stannylation,[64] intended to afford the vinylstannane, did not provide any of the corresponding vinylstannane, but again by-product, furan formation was witnessed in 50% yield. In another approach, lithiation of **23** with methyl lithium and then butyl lithium at -78 °C and subsequent treatment with trimethylstannyl chloride was also examined. This too did not afford epoxy (Z)-vinylstannane but resulted in generating complex mixture. Because the Sn/I partner swap was as mentioned above outside the scope of our synthetic aim no additional effort was extended to the preparation of **70**.

We questioned if the geometry of the (Z)-vinyl iodide was necessary for furan formation. To answer this query we sought to make and cross-coupled the (E)-epoxy vinyl iodide. Thus, the epoxy aldehyde in Scheme 61 was subjected to a diiodination. Then lithium-halogen exchange reactions gave us a mixture of diiodide, (E) and (Z) vinyl iodides in a ratio of 1:1:0.6. (Scheme 61)

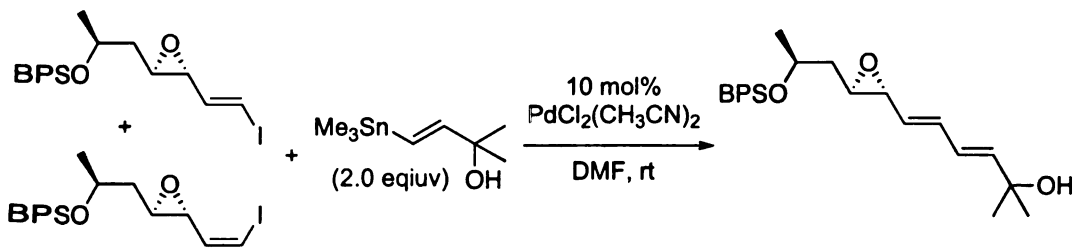
Attempted Isolation of pure (E) vinyl iodide by column chromatography failed, but did allow for the removal of the diiodo compound. So, a 1:0.6 mixture of (E) and (Z) vinyl iodides was used and a Stille coupling with organostannane. (Scheme 62) The reaction was monitored by kinetic studies of ^1H NMR. This NMR monitoring showed that (E)-vinyl iodide consumed and coupled with vinylstannane with the diene formation. However (Z)-vinyl iodide stayed un-

reactive. Through these experiments we concluded that the (Z) geometry is problematic.

Scheme 61. Preparation of (E) Epoxy Vinyl Iodide



Scheme 62. Stille Cross-Coupling Reaction of Mixture of the (E) and (Z)-Epoxy Vinyl Iodide



Moreover the fact that the (Z)-vinyl iodide epoxide was not viable as intermediate in our retrosynthetic scheme also forced us to acknowledge that demonstrating a successful one-pot hydrostannation/Stille sequence as part of the planned approach to monocillin would be unlikely. As a full reworking of the synthetic approach to monocillin would extend beyond the scope of this dissertation, work in this area is concluded until it is taken up as part of a future dissertation project.

<Reference>

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2. Stille's early studies were built on the foundation of his prior work in the area of transitions metal oxidative addition chemistry (Stille, J. K. *Acc. Chem. Res.* **1977**, *10*, 434-442) as well as the preliminary reports of Kosugi et al. See: (a) Kosugi, M.; Shimizu, Y.; Migita, T. *J. Organomet. Chem.* **1977**, *129*, C36–C38. (b) Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977,** 301–302. (c) Kosugi, M.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 1423–1424.

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Experimental Details

Materials and Methods

All reactions were carried out in oven-dried glassware, with magnetic stirring, and monitored by thin-layer chromatography with 0.25-mm precoated silica gel plates or capillary GC, unless otherwise noted. All commercial reagents were used without purification. All solvents were reagent grade. Diethyl ether and THF were freshly distilled from sodium/benzophenone under nitrogen. Benzene, toluene, DMSO, diisopropyl-ethylamine and cyclohexane were freshly distilled from calcium hydride under nitrogen. Tetrahydrofuran was freshly distilled from sodium/benzophenone under nitrogen. Tris(dibenzylideneacetone)-dipalladium (0), dichlorobis(triphenyl- phosphine)palladium (II), tetrakis(triphenyl-phosphine)palladium (0), anhydrous A.C.S grade potassium fluoride, polymethyl-hydrosiloxane (PMHS), tetrabutylammonium fluoride (1M solution in THF), and 3,3-dimethyl-1-butyne were purchased and used without purification unless otherwise mentioned. 2-Thiophenecarbonyl chloride, 2-furoyl chloride, 3,4,5-trimethoxybenzoyl chloride, and 2-nitrobenzoyl chloride, were prepared following literature procedures and used after distillation. The remaining acid chlorides were purchased and used without purification.

Flash chromatography was performed with silica gel 60 Å (particle size 230-400 mesh ASTM). High performance liquid chromatography (HPLC) was performed with Ranin component analytical/ semiprep system. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise

stated. Melting points were determined on a Thomas-Hoover Apparatus, uncorrected. Infrared spectra were recorded on a Nicolet IR/42 spectrometer. Proton and carbon NMR spectra were recorded on a Varian Gemini-300, VXR 500 or INOVA 600 spectrometer. Chemical shifts for ^{1}H NMR and ^{13}C NMR are reported in parts per million (ppm) relative to $CDCl_3$ (δ = 7.24 ppm for ^{1}H NMR or δ = 77.0 ppm for ^{13}C NMR). Optical rotations were measured with a Perkin-Elmer Model 341 polarimeter. High resolution mass spectra (HRMS) data were obtained at either the Michigan State University Mass Spectrometry Service Center or at the Mass Spectrometry Laboratory of the University of South Carolina, Department of Chemistry & Biochemistry. GC/MS were performed with a fused silica column (30 m by 0.25 mm i.d.). ICP analysis was performed on a Micromass Platform Inductively Coupled Plasma-Mass Spectrometer at the ICP-Hex-MS Laboratory at the department of Geological Sciences at Michigan State University.

Chapter 2. One-pot Hydrostannation/Stille Reaction with Acid Chlorides as the Electrophiles

Procedure for the Preparation of Tri-2-furylphosphine (TFP): $CeCl_3 \cdot 7H_2O$ (60 g, 161 mmol) was placed into a 3 neck 1-L flask containing a stir bar. The flask was places into a 150 °C oil bath and was then places under vacuum (~1 mmHg) until a fine powder was obtained. The flask was then cooled to 25 °C under N_2 and THF (200 mL) was added. In a separate flask, a solution of furan (20 g, 294 mmol) in THF (100 mL) was cooled to 0 °C. To this solution was added *n*-BuLi (100 mL of a 1.6 M solution in hexanes, 160 mmol). After the addition was complete, the mixture was stirred at 25 °C for 1 h. The flask containing the dried $CeCl_3$ in THF was cooled to –78 °C and then the α-furyl lithium solution was added via cannula. Once the addition was complete, the solution was allowed to stir at –78 °C for 1 h and then PCl_3 (3.50 mL, 40.1 mmol) was added and the cold bath was removed. The mixture was then allowed to warm to 25 °C overnight with stirring. The mixture was then poured into sat. aq. NH_4Cl (300 mL). The layers were separated and the aqueous layer was extracted with Et_2O. The combined organics were dried ($MgSO_4$), filtered and concentrated (not to dryness). The residue was purified by column chromatography [silica; 90:10 hexane/EtOAc] to afford tri-2-furylphosphine (5.36 g, 58%) as a white crystalline solid (mp 64 °C; lit.[1] mp 59-64 °C). The product

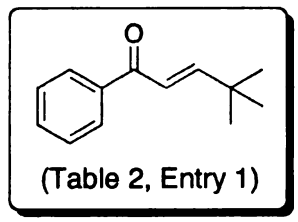
could also be recrystallized from hexanes (3x). All spectral data match those reported in the literature.[2]

Preparation of Trimethyltin Fluoride: THF (30 mL) was placed in a 250 mL flask and KF (150 mmol, 8.71 g) dissolved in H_2O (20 mL) was added. Me_3SnCl 1 M solution in THF (50 mL) was added with vigorous stirring. During this time the exothermicity of the reaction made the flask warm to touch. The reaction was stirred for 2 h, at which time then flask was no longer warm to touch. The reaction was filtered and the white solid was washed with H_2O and Et_2O. After air-drying, the remaining volatiles were removed by drying the solid dried under high vacuum to afford the Me_3SnF as a white solid in quantitative yield.[3]

General Procedure for the One-pot Hydrostannation/Stille Reaction using Me_3SnF:

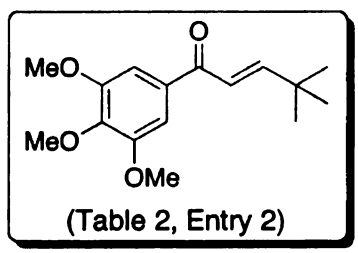
Pd_2dba_3 (0.01 mmol, 9.2 mg) and TFP (0.04 mmol, 9.3 mg) were added to THF (5 mL) and the resulting mixture was stirred at rt for 15 min. At that time, 3,3-dimethyl 1-butyne (1 mmol, 0.125 mL), Me_3SnF (1.5 mmol, 274 mg), PMHS (2.5 mmol, 0.15 mL), and TBAF (1 drop of a 1 M solution in THF (~0.008 mmol)) were added successively. The reaction was then allowed to stir at rt for 2 h, at which time the hydrostannation was complete by GC. The acid chloride (1.3 mmol) was then added and the mixture was allowed to reflux (~65 °C) until the cross-coupling was judged complete by TLC (2–4 h). At that time, the reaction was

diluted with saturated aq. KF (2 mL) and stirred for 0.5 h. The reaction was extracted with Et_2O and H_2O and the aqueous phase was back extracted with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by silica gel chromatography to afford the corresponding α,β-unsaturated ketone.


(Table 2, Entry 1)

(*E*)-4,4-Dimethyl-1-phenylpent-2-en-1-one: Subjection of benzoyl chloride (1.3 mmol, 0.15 mL) to the general procedure afforded after column chromatography (silica gel, hexane/EtOAc: 90/10) 0.179 g (95%) of (*E*)-4,4-dimethyl-1-phenylpent-2-en-1-one as a colorless oil. Second run gave 93% yield.

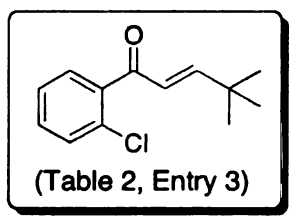
IR (neat) 2963, 1669, 1620, 1304 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.90 (dd, *J* = 6.9, 1.6 Hz, 2H), 7.52–7.41 (m, 3H), 7.06 (d, *J* = 15.7 Hz, 1H), 6.78 (d, *J* = 15.7 Hz, 1H,), 1.12 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.4, 159.5, 138.2, 132.4, 128.4, 121.0, 34.1, 28.7 ppm; HRMS (EI) m/z 189.1279 [(M+H), calcd. for $C_{13}H_{17}O$ 189.1285] Physical and spectral data were consistent with those previously reported.[4]


(Table 2, Entry 2)

(*E*)-1-(3,4,5-Trimethoxyphenyl)-4,4-dimethylpent-2-en-1-one: Subjection of 3,4,5-trimethoxybenzoyl chloride (1.3 mmol, 0.3 g) to the general procedure afforded after column chromatography (silica gel,

hexane/EtOAc: 90/10) 0.267 g (97%) of (*E*)-1-(3,4,5-trimethoxyphenyl)-4,4-dimethylpent-2-en-1-one as a white solid. Second run gave 95% yield. mp 57–58 °C.

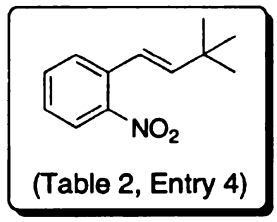
IR (KBr) 2963, 1665, 1582, 1414 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.12 (s, 2H), 7.00 (d, *J* = 15.7 Hz, 1H), 6.67 (d, *J* = 15.9 Hz, 1H), 3.86 (s, 9H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm: δ = 190.3, 159.2, 152.9, 142.2, 133.3, 120.6, 106.2, 60.7, 56.2, 34.0, 28.6 ppm; HRMS (EI) m/z 279.1596 [(M+H), calcd. for $C_{16}H_{23}O_4$ 279.1574]



(Table 2, Entry 3)

(*E*)-1-(2-Chlorophenyl)-4,4-dimethylpent-2-en-1-one: Subjection of 2-chlorobenzoyl chloride (1.3 mmol, 0.17 mL) to the general procedure afforded after column chromatography (silica gel, hexane/EtOAc: 90/10) 0.203 g (91%) of (*E*)-1-(2-chlorophenyl)-4,4-dimethylpent-2-en-1-one as a colorless liquid. Second run gave 81% yield.

IR (neat) 1667, 1618, 1300 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.22 (m, 4H), 6.69 (d, *J* = 16.2 Hz, 1H), 6.38 (d, *J* = 15.9 Hz, 1H), 1.06 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.6, 161.4, 138.8, 130.8, 129.8, 128.9, 126.4, 125.2, 33.8, 28.2 ppm; HRMS (EI) m/z 223.0896 [(M+H), calcd. for $C_{13}H_{16}ClO$ 223.0890]

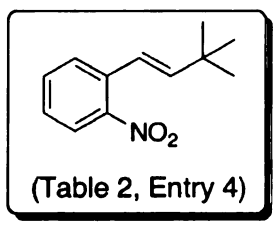


(Table 2, Entry 4)

1-((*E*)-3,3-Dimethylbut-1-enyl)-2-nitrobenzene:

Subjection of 2-nitrobenzoyl chloride (1.3 mmol, 0.17 mL) to the general procedure afforded after column chromatography (silica gel, hexane/EtOAc: 90/10) 0.152 g (74%) of 1-((*E*)-3,3-dimethylbut-1-enyl)-2-nitrobenzene as a yellow liquid along with a trace amount of the corresponding enone.

IR (neat) 2963, 1524, 1346 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, J = 8.2 Hz, 1H), 7.56–7.45 (m, 2H), 7.31–7.26 (t, J = 6.6 Hz, 1H), 6.77 (d, J = 15.9 Hz, 1H), 6.22 (d, J = 15.9 Hz, 1H), 1.10 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.1, 133.6, 132.7, 128.4, 127.2, 124.2, 120.2, 33.8, 29.2 ppm

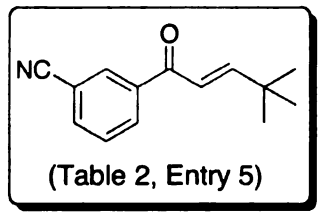


(Table 2, Entry 4)

Reaction under CO Atmosphere:

1-((*E*)-3,3-Dimethylbut-1-enyl)-2-nitrobenzene:

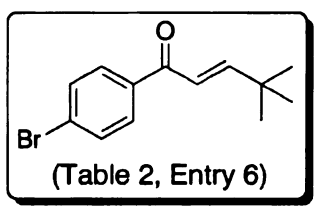
Subjection of 2-nitrobenzoyl chloride (1.3 mmol, 0.17 mL) to the general procedure with CO gas bubbling to the reaction mixture afforded after column chromatography (silica gel, hexane/EtOAc: 90/10) 0.152 g (74%) of 1-((*E*)-3,3-dimethylbut-1-enyl)-2-nitrobenzene as a yellow liquid along with a trace amount of the corresponding enone.



(Table 2, Entry 5)

3-(*E*)-4,4-Dimethylpent-2-enoyl)benzonitrile: Subjection of 3-cyanobenzoyl chloride (1.3 mmol, 0.216 g) to the general procedure afforded after column chromatography (silica gel, hexane/EtOAc: 90/10) 0.211g (99%) of 3-((*E*)-4,4-dimethylpent-2-enoyl) benzonitrile as a white crystalline solid. Second run gave 97% yield. mp 74–75 °C.

IR (KBr) 2230, 1678, 1612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.14 (s, 1H), 8.11 (d, J = 7.7 Hz, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.59 (t, J = 7.14 Hz, 1H), 7.09 (d, J = 15.7 Hz, 1H), 6.72 (d, J = 15.7 Hz, 1H), 1.12 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.1, 161.5, 138.9, 135.4, 132.4, 132.0, 129.5, 119.9, 118.0, 112.9, 34.3, 28.5 ppm

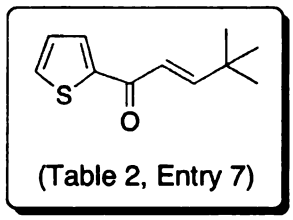


(Table 2, Entry 6)

(*E*)-1-(4-Bromophenyl)-4,4-dimethylpent-2-en-1-one: Subjection of 4-bromobenzoyl chloride (1.3 mmol, 0.216 g) to the general procedure afforded after 4 h Stille reaction and column chromatography (silica gel, hexane/EtOAc: 90/10) 0.264g (99%) of (*E*)-1-(4-bromophenyl)-4,4-dimethylpent-2-en-1-one as a white crystalline solid. mp 43–44 °C. Second run gave 97% yield.

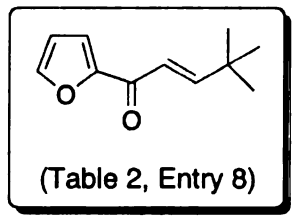
IR (KBr) 1671, 1620, 1580, 1108, 1004 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.9 Hz, 2H), 7.06 (d, J = 15.7 Hz, 1H), 6.72 (d, J = 15.7 Hz, 1H), 1.13 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.3, 160.2,

136.9, 131.7, 130.0, 127.6, 120.5, 34.2, 28.7 ppm; HRMS (EI) m/z 267.0375 [(M+H), calcd. for $C_{13}H_{15}BrO$ 267.0385]


(Table 2, Entry 7)

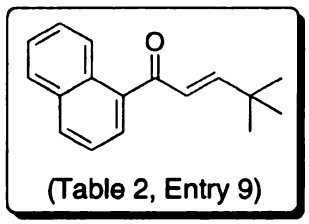
(*E*)-4,4-Dimethyl-1-(thiophen-2-yl)pent-2-en-1-one: Subjection of 2-thiophenoyl chloride (1.3 mmol, 0.14 mL) to the general procedure afforded after column chromatography (silica gel, hexane/EtOAc: 90/10) 0.193g (99%) of (*E*)-4,4-dimethyl-1-(thiophen-2-yl)pent-2-en-1-one as a bright yellow liquid. Second run gave 99% yield.

IR (neat) 1659, 1617, 1414, 723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.72 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.59 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.10–7.04 (m, 2H), 6.67 (d, *J* = 15.7 Hz, 1H), 1.09 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.8, 158.6, 145.2, 133.5, 131.7, 128.0, 120.3, 33.9, 28.6 ppm; HRMS (EI) m/z 195.0846 [(M+H), calcd. for $C_{11}H_{14}OS$ 195.0844]


(Table 2, Entry 8)

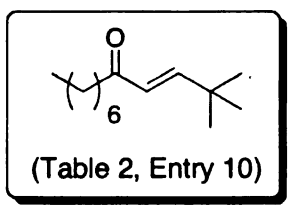
(*E*)-1-(Furan-2-yl)-4,4-dimethylpent-2-en-1-one: Subjection of 2-furanoyl chloride (1.3 mmol, 0.13 mL) to the general procedure afforded after column chromatography (silica gel, hexane/EtOAc: 90/10) 0.171g (96%) of (*E*)-1-(furan-2-yl)-4,4-dimethylpent-2-en-1-one as a dark brown liquid. Second run gave 94% yield.

IR (neat) 1667, 1616, 1468 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.55 (s, 1H), 7.18 (d, *J* = 3.6 Hz, 1H), 7.11 (d, *J* = 15.9 Hz, 1H), 6.67 (d, *J* = 15.7 Hz, 1H), 6.49 (m, 1H), 1.07 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.5, 158.6, 153.3, 146.3, 119.8, 117.3, 112.2, 33.9, 28.5 ppm; HRMS (EI) m/z 179.1074 [(M+H), calcd. for $C_{11}H_{15}O_2$ 179.1072]


(Table 2, Entry 9)

(*E*)-4,4-Dimethyl-1-(naphthalen-5-yl)pent-2-en-1-one: Subjection of 2-furanoyl chloride (1.3 mmol, 0.2 mL) to the general procedure afforded after column chromatography (silica gel, hexane/EtOAc: 90/10) 0.216 g (93%) of (*E*)-4,4-dimethyl-1-(naphthalen-5-yl)pent-2-en-1-one as a bright brown crystalline solid. Second run gave 91% yield. mp 37–38 °C.

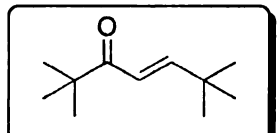
IR (neat) 1669, 1615, 1508, 1298, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 7.1 Hz, 1H), 7.66 (d, *J* = 6.9 Hz, 1H), 7.56–7.46 (m, 3H), 6.88 (d, *J* = 15.9 Hz, 1H), 6.59 (d, *J* = 15.9 Hz, 1H), 1.11 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.7, 161.1, 137.0, 133.7, 131.3, 130.5, 128.3, 127.2, 127.1, 126.3, 126.1, 125.6, 124.4, 34.1, 28.6 ppm; HRMS (EI) m/z 239.1436 [(M+H), calcd. for $C_{17}H_{19}O$ 239.1442]


(Table 2, Entry 10)

(*E*)-6,6-Dimethylhept-4-en-3-one: Subjection of 1-octanoyl chloride (1.3 mmol, 0.22 mL) to the general procedure afforded after column chromatography (silica

gel, hexane/EtOAc: 90/10) 0.189g (90%) of (*E*)-6,6-dimethylhept-4-en-3-one as a bright brown liquid. Second run gave 90% yield.

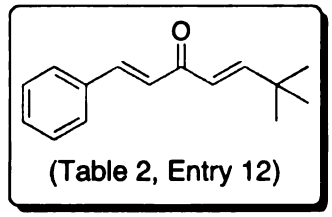
IR (neat) 1676, 1626 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.80 (d, J = 16.2 Hz, 1H), 5.99 (d, J = 16.2 Hz, 1H), 2.50 (t, J = 7.7 Hz, 2H), 1.59 (m, 2H), 1.24 (brs, 8H), 1.04 (s, 9H), 0.84 (brs, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.5, 156.7, 125.4, 40.3, 33.6, 31.7, 29.2, 29.1, 28.7, 24.3, 22.6, 14.0 ppm; HRMS (EI) m/z 211.2053 [(M+H), calcd. for $C_{14}H_{27}O$ 211.2062]


(Table 2, Entry 11)

(*E*)-2,2,6,6-Tetramethylhept-4-en-3-one: Subjection of trimethylacetyl chloride (1.3 mmol, 0.16 mL) to the general procedure afforded after 4 h Stille reaction and column chromatography (silica gel, hexane/EtOAc: 90/10) 0.155 g (92%) of (*E*)-2,2,6,6-tetramethylhept-4-en-3-one as a bright brown crystalline solid. Second run gave 92% yield. mp 42 °C. (lit. 42–43°C)[5]

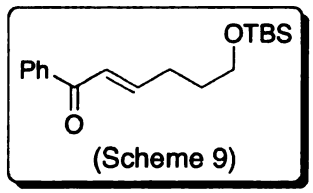
IR (KBr) 1688, 1628, 1086 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 6.92 (d, J = 15.4 Hz, 1H), 6.38 (d, J = 15.7 Hz, 1H), 1.12 (s, 9H), 1.04 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.8, 157.2, 119.0, 43.0, 33.7, 28.8, 26.3 ppm; HRMS (EI) m/z 169.1592 [(M+H), calcd. for $C_{11}H_{21}O$ 169.1592]

Physical and spectral data were consistent with those previously reported.[6]


(Table 2, Entry 12)

(1*E*,4*E*)-6,6-Dimethyl-1-phenylhepta-1,4-dien-3-one : Subjection of cinnamoyl chloride (1.3 mmol, 0.217 g) to the general procedure afforded after 4 h Stille reaction and column chromatography (silica gel, hexane/EtOAc: 90/10) 0.173g (81%) of (1*E*,4*E*)-6,6-dimethyl-1-phenylhepta-1,4-dien-3-one as a bright brown liquid. Second run gave 79% yield.

IR (neat) 1659, 1628, 1601 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, 1H), 7.55 (m, 2H), 7.36 (m, 3H), 7.00 (d, J = 15.9 Hz, 2H), 6.34 (d, J = 15.9 Hz, 1H), 1.12 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.7, 157.8, 142.9, 134.8, 130.3, 128.8, 128.2, 124.8, 124.4, 33.9, 28.7 ppm; HRMS (EI) m/z 215.1436 [(M+H), calcd. for $C_{15}H_{19}O$ 215.1423] Physical and spectral data were consistent with those previously reported.[7]


(Scheme 9)

(*E*)-6-(*tert*-Butyldimethylsilyloxy)-1-phenylhex-2-en-1-one: 5-(*tert*-Butyldimethylsilyloxy)-1-pentyne (199 mg, 1.0 mmol), Me_3SnF (1.5 mmol, 274 mg), $(PPh_3)_2Cl_2Pd$ (0.02 mmol, 14.0 mg), PMHS (1.5 mmol, 0.09 mL), and TBAF (1 drop of a 1 M solution in THF (~0.008 mmol)) were added to Et_2O (5 mL) and the resulting mixture was stirred at rt for 2 h, at which time the hydrostannation was complete by TLC. Then $(PPh_3)_4Pd$ (11.3 mg, 0.01 mmol) and benzoyl chloride (0.15 mL, 1.3 mmol) in THF (5 mL) was added and the mixture was allowed to reflux (~65 °C) until the cross-coupling was judged complete by TLC (8 h). At that time, the

reaction was diluted with saturated aq. KF (2 mL) and stirred for 10 min. The reaction was extracted with Et_2O and H_2O and the aqueous phase was back extracted with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc: 90/10) to afford 0.219 g (71%) of (*E*)-6-(*tert*-butyldimethylsilyloxy)-1-phenylhex-2-en-1-one along with a trace of the α-isomer as a bright yellow liquid as a colorless oil.

IR (neat) 1672, 1622,1099, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 6.9 Hz, 2H), 7.54–7.39 (m, 3H), 7.08–7.01 (m, 1H), 6.89 (d, *J* = 15.4 Hz, 1H), 3.64 (t, *J* = 6.0 Hz, 2H), 2.40 (overlapping q, *J* = 7.1 Hz, 2H), 1.76 (quint, *J* = 6.3 Hz, 2H) 0.88 (s, 9H), 0.04 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.7, 149.4, 138.0, 132.5, 128.4, 126.1, 62.1, 31.2, 29.2, 25.9, 18.2, -5.4 ppm

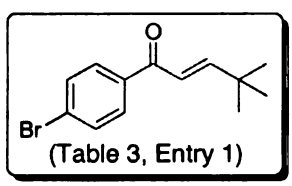
Procedure for the One-pot Radical Hydrostannation/Stille Reaction: A round-bottom flask containing a solution of 5-(*tert*-butyldimethylsilyloxy)-1-pentyne (199 mg, 1.0 mmol), Bu_3SnCl (0.33 mL, 1.2 mmol), aq. KF (175 mg, 3.0 mmol; 0.25 mL H_2O), PMHS (0.07 mL, 1.2 mmol), and AIBN (8 mg, 0.05 mmol) in toluene (5 mL) was immersed in a preheated (~75 °C) oil bath for 10 min. After stirring for 2 h at this temperature, the reaction mixture was cooled, then $(PPh_3)_4Pd$ and distilled benzoyl chloride (0.15 mL, 1.3 mmol) were added. The mixture was allowed to stir at reflux (~75 °C) until the cross-coupling was judged complete by TLC (2.5 h). At that time, the reaction was diluted with saturated aq.

KF (2 mL) and stirred for 10 min. The reaction was extracted with Et_2O and H_2O and the aqueous phase was back extracted with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc: 90/10) to afford 0.128 g (42%) of (*E*)-6-(*tert*-butyldimethylsilyloxy)-1-phenylhex-2-en-1-one as a colorless oil. For spectroscopic data see above.

Chapter 3. One-pot Multi-Component Stille Sequences

General Procedure for the One-pot Hydrostannation/Stille Reaction using Me_3SnF:

Pd_2dba_3 (0.01 mmol, 9.2 mg) and TFP (0.04 mmol, 9.3 mg) were added to THF (5 mL) and the resulting mixture was stirred at rt for 15 min. At that time, 3,3-dimethyl 1-butyne (1 mmol, 0.125 mL), Me_3SnF (1.5 mmol, 274 mg), PMHS (2.5 mmol, 0.15 mL), and TBAF (1 drop of a 1 M solution in THF (~0.008 mmol)) were added successively. The reaction was then allowed to stir at rt for 2 h, at which time the hydrostannation was complete by GC. The acid chloride (1.3 mmol) was then added and the mixture was allowed to reflux (~65 °C) until the cross-coupling was judged complete by TLC (2–4 h). At that time, the reaction was diluted with saturated aq. KF (2 mL) and stirred for 0.5 h. The reaction was extracted with Et_2O and H_2O and the aqueous phase was back extracted with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by silica gel chromatography to afford the corresponding α,β-unsaturated ketone.

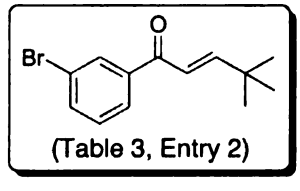


(Table 3, Entry 1)

(*E*)-1-(4-Bromophenyl)-4,4-dimethylpent-2-en-1-one: Subjection of 4-bromobenzoyl chloride (1.3 mmol, 0.216 g) to the general procedure afforded after 4 h Stille

reaction and column chromatography (silica gel, hexane/EtOAc: 90/10) 0.264 g (99%) of (*E*)-1-(4-bromophenyl)-4,4-dimethylpent-2-en-1-one as a white crystalline solid. mp 43–44 °C.

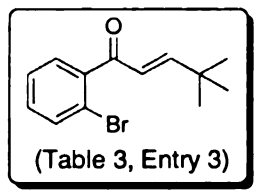
IR (KBr) 1671, 1620, 1580, 1108, 1004 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.77 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.9 Hz, 2H), 7.06 (d, J = 15.7 Hz, 1H), 6.72 (d, J = 15.7 Hz, 1H), 1.13 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.3, 160.2, 136.9, 131.7, 130.0, 127.6, 120.5, 34.2, 28.7 ppm; HRMS (EI) m/z 267.0375 [(M+H), calcd. for $C_{13}H_{16}BrO$ 267.0385]



(Table 3, Entry 2)

(*E*)-1-(3-Bromophenyl)-4,4-dimethylpent-2-en-1-one: Subjection of 3-bromobenzoyl chloride (1.3 mmol, 0.216 g) to the general procedure afforded after 4 h Stille reaction and column chromatography (silica gel, hexane/EtOAc: 90/10) 0.211g (80%) of (*E*)-1-(3-bromophenyl)-4,4-dimethylpent-2-en-1-one as a bright brown liquid.

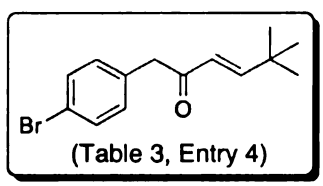
IR (neat) 3068, 2960, 1687, 1568, 1312, 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.01 (t, J = 1.9 Hz, 1H), 7.80 (dt, J = 8.0 and 1.1 Hz, 1H), 7.64 (dq, J = 8.0 and 1.1 Hz, 1H), 7.31(t, J = 8.0 Hz, 1H), 7.05 (d, J = 15.7 Hz, 1H), 6.69 (d, J = 15.7 Hz, 1H), 1.13 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.0, 160.6, 140.0, 135.4, 131.5, 130.1, 127.0, 122.8, 120.5, 34.3, 28.7 ppm.



(Table 3, Entry 3)

(*E*)-1-(2-Bromophenyl)-4,4-dimethylpent-2-en-1-one: Subjection of 2-bromobenzoyl chloride (1.3 mmol, 0.216 g) to the general procedure afforded after 4 h Stille reaction and column chromatography (silica gel, hexane/EtOAc: 90/10) 0.147g (55%) of (*E*)-1-(2-bromophenyl)-4,4-dimethylpent-2-en-1-one as a bright brown liquid and a trace amount of the decarbonylated byproduct was observed.

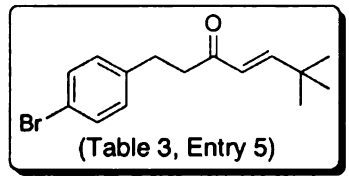
IR (neat) 3056, 2961, 1660, 1616, 1298 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, J = 8.0 Hz, 1H), 7.23–7.36 (m, 3H), 6.63 (d, J = 15.7 Hz, 1H), 6.32 (d, J = 15.7 Hz, 1H), 1.06 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.5, 161.9, 141.1, 133.2, 131.0, 128.9, 127.1, 125.3, 119.2, 34.1, 28.4 ppm



(Table 3, Entry 4)

(E)-1-(4-Bromophenyl)-5,5-dimethylhex-3-en-2-one: Subjection of 2-(4-bromophenyl) acetyl chloride (1.3 mmol, 0.306 g) to the general procedure afforded after 4 h Stille reaction and column chromatography (silica gel, hexane/EtOAc: 90/10) 0.177g (63%) of (E)-1-(4-bromophenyl)-5,5-dimethylhex-3-en-2-one as a white crystalline solid. mp 69–70 °C.

IR(PTFE) 2957, 1696, 1672, 1629, 1487 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 8.3 Hz, 2H), 6.90 (d, J = 16.1 Hz, 1H), 6.05 (d, J = 16.1 Hz, 1H), 3.78 (s, 2H), 1.06 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.4, 158.4, 133.5, 131.7, 131.2, 124.5, 120.9, 46.7, 33.9, 28.6 ppm



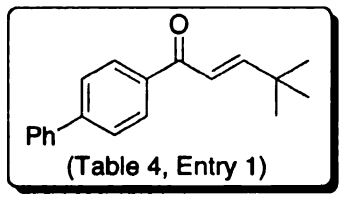
(Table 3, Entry 5)

(E)-1-(4-Bromophenyl)-6,6-dimethylhept-4-en-3-one: Subjection of 3-(3-bromophenyl) propanoyl chloride (1.3 mmol, 0.322 g) to the general procedure afforded after 4 h Stille reaction and column chromatography (silica gel, hexane/EtOAc: 90/10) 0.215g (73%) of (E)-1-(4-bromophenyl)-6,6-dimethylhept-4-en-3-one as a white crystalline solid. mp 156–157 °C

IR(KBr) 3041, 3024, 2962, 1696, 1671, 1626, 1488, 1364, 1107, 1011, 811 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 6.78 (d, *J* = 15.8 Hz, 1H), 5.99 (d, *J* = 16.2 Hz, 1H), 2.84 (m, 4H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.6, 157.4, 140.3, 131.5, 130.2, 15.3, 119.8, 41.5, 33.7, 29.4, 28.6

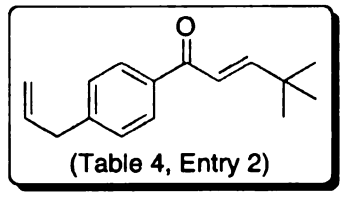
General Procedure for the Multiple Hydrostannation/Stille Reaction: Pd_2dba_3 (0.01 mmol, 9.2 mg) and TFP (0.04 mmol, 9.3 mg) were added to THF (5 mL) and the resulting mixture was stirred at rt for 15 min. At that time, 3,3-dimethyl 1-butyne (1 mmol, 0.125 mL), Me_3SnF (1.5 mmol, 274 mg), PMHS (2.5 mmol, 0.15 mL), and TBAF (1 drop of a 1 M solution in THF (~0.008 mmol)) were added successively. The reaction was then allowed to stir at rt for 2 h, at which time the hydrostannation was complete by GC. The bromo benzoyl chloride (1.3 mmol) was then added and the mixture was allowed to reflux (~65 °C) until the cross-coupling was judged complete by TLC (2–4 h). At that time, Pd_2dba_3, *t*-Bu_3P, organostannanes (2.0 equiv) and 1,4-dioxane (5 mL) were added and

refluxed at ~90 °C until the cross-coupling was judged complete by TLC. The reaction was diluted with saturated aq. KF (2 mL) and stirred for 0.5 h. The reaction was extracted with Et_2O and H_2O and the aqueous phase was back extracted with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by silica gel chromatography to afford the corresponding α,β-unsaturated ketone.



(Table 4, Entry 1)

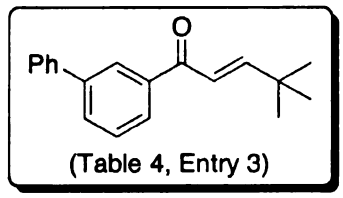
(E)-1-(Biphenyl-4-yl)-4,4-dimethylpent-2-en-1-one: Subjection of Me_3SnPh (2.0 mmol, 0.36 mL) to the general procedure afforded after column chromatography (silica gel, hexane/EtOAc: 90/10) 0.233 g (88%) of (E)-1-(biphenyl-4-yl)-4,4-dimethylpent-2-en-1-one as a white crystal. mp 127–129 °C IR (PTFE) 1661, 1614, 1600, 1303 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.6 Hz, 2H), 7.68 (d, *J* = 8.7 Hz, 2H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.7 Hz, 1H), 7.09 (d, *J* = 15.8 Hz, 1H), 6.82 (d, *J* = 15.7 Hz, 1H), 1.16 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.0, 159.5, 145.3, 140.0, 136.9, 129.1, 128.9, 128.1, 127.3, 127.2, 120.9, 34.2, 28.8 ppm; HRMS (EI) m/z 264.1516 [(M+), calcd. for $C_{19}H_{20}O$ 264.1514]



(Table 4, Entry 2)

(E)-1-(4-Allylphenyl)-4,4-dimethylpent-2-en-1-one: Subjection of allylSnBu$_3$ (2.0 mmol, 0.16 mL) to the general procedure afforded after column chromatography (silica gel, hexane/EtOAc: 90/10) 0.222 g (97%) of (E)-1-(4-allylphenyl)-4,4-dimethylpent-2-en-1-one as a colorless liquid.

IR (neat) 1667, 1618, 1300 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.04 (d, J = 15.6 Hz, 1H), 6.77 (d, J = 15.6 Hz, 1H), 5.97 (m, 1H), 5.11 (s, 1H), 5.09 (d, J = 7.8 Hz, 1H), 3.44 (d, J = 6.6 Hz, 2H), 1.13 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.1, 145.2, 136.4, 136.3, 128.8, 128.7, 121.0, 116.5, 40.1, 34.1, 28.8 ppm; HRMS (EI) m/z 228.1511 [(M+), calcd. for $C_{16}H_{20}O$ 228.1514]

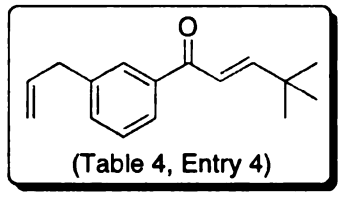


(Table 4, Entry 3)

(E)-1-(Biphenyl-3-yl)-4,4-dimethylpent-2-en-1-one: Subjection of Me_3SnPh (2.0 mmol, 0.36 mL) to the general procedure afforded after column chromatography (silica gel, hexane/EtOAc: 90/10) 0.214 g (81%) of (E)-1-(biphenyl-3-yl)-4,4-dimethylpent-2-en-1-one as a liquid.

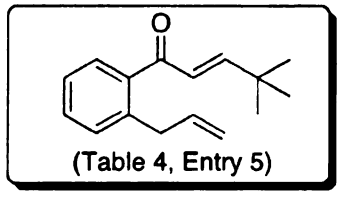
IR (neat) 3060, 3031, 2960, 1669, 1618, 1309, 1206 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H) 7.77 (d, J = 7.8 Hz, 1H) 7.62 (d, J = 7.8 Hz, 1H) 7.54(t, J = 7.6 Hz, 1H) 7.47 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 7.6 Hz, 1H), 7.10 (d, J = 15.9 Hz, 1H), 6.82 (d, J = 15.9 Hz, 1H), 1.16 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.5, 159.8, 141.6, 140.3, 138.8, 131.2,

128.9(2), 127.7, 127.3, 127.2(2), 121.1, 34.2, 28.7 ppm; HRMS (EI) m/z 264.1514 [(M+), calcd. for $C_{19}H_{20}O$ 264.1514]


(Table 4, Entry 4)

(E)-1-(3-Allylphenyl)-4,4-dimethylpent-2-en-1-one: Subjection of allylSnBu_3 (2.0 mmol, 0.16 mL) to the general procedure afforded after column chromatography (silica gel, hexane/EtOAc: 90/10) 0.187 g (82%) of (E)-1-(3-allylphenyl)-4,4-dimethylpent-2-en-1-one as a liquid.

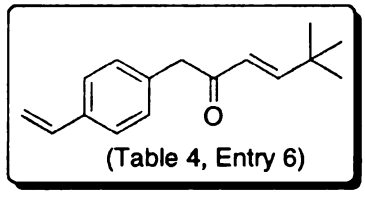
IR (neat) 1667, 1618, 1300 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.12 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H) 7.77 (d, J = 7.8 Hz, 1H) 7.62 (d, J = 7.8 Hz, 1H) 7.54(t, J = 7.6 Hz, 1H) 7.47 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 7.6 Hz, 1H), 7.10 (d, J = 15.9 Hz, 1H), 6.82 (d, J = 15.9 Hz, 1H), 1.16 (s, 9H) ppm; HRMS (EI) m/z 228.1513 [(M+), calcd. for $C_{16}H_{20}O$ 228.1514]


(Table 4, Entry 5)

(E)-1-(2-Allylphenyl)-4,4-dimethylpent-2-en-1-one: Subjection of allylSnBu_3 (2.0 mmol, 0.16 mL) to the general procedure afforded after column chromatography (silica gel, hexane/EtOAc: 90/10) 0.105 g (46%) of (E)-1-(2-allylphenyl)-4,4-dimethylpent-2-en-1-one as a liquid.

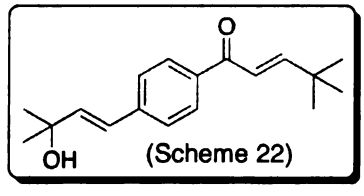
IR (neat) 3067, 2960, 2924, 2853, 1653, 1616, 1297, 1019 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.20 (m, 4 H), 6.69 (d, J = 16.0 Hz, 1H), 6.38 (d, J = 15.9 Hz, 1H), 5.96–5.83 (m, 1 H), 5.01–4.93 (m, 2 H), 3.47 (d, J = 6.6 Hz, 1 H), 1.11

(s, 9 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.6, 161.2, 139.3, 138.5, 137.1, 130.4, 130.2, 128.0, 126.1, 125.7, 116.0, 37.3, 34.0, 28.6 ppm


(Table 4, Entry 6)

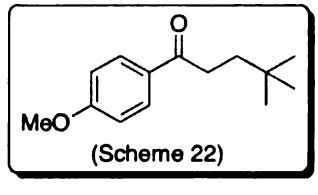
(E)-5,5-Dimethyl-1-(4-vinylphenyl)hex-3-en-2-one: Subjection of vinyl$SnBu_3$ (2.0 mmol, 0.16 mL) to the general procedure afforded after column chromatography (silica gel, hexane/EtOAc: 90/10) 0.107 g (47%) of (E)-5,5-dimethyl-1-(4-vinylphenyl)hex-3-en-2-one as a liquid.

IR (neat) 3064, 2960, 1694, 1280 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.2 Hz, 2 H), 7.17 (d, *J* = 8.0 Hz, 2 H), 6.73 (dd, *J* = 17.6, 6.6 Hz, 1H), 6.07 (d, *J* = 16.2 Hz, 1H) 5.74 (d, *J* = 17.6 Hz, 1 H), 5.23 (d, *J* = 10.7 Hz, 1H), 3.81 (s, 2H), 1.05 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.8, 157.9, 136.4, 136.1, 134.1, 129.5, 126.4, 124.4, 113.5, 47.2, 33.7, 28.5 ppm


(Scheme 22)

(*E*)-1-(4-((*E*)-3-Hydroxy-3-methylbut-1-enyl)-phenyl)-4,4-dimethylpent-2-en-1-one: Pd_2dba_3 (0.01 mmol, 9.2 mg) and TFP (0.04 mmol, 9.3 mg) were added to THF (5 mL) and the resulting mixture was stirred at rt for 15 min. At that time, 3,3-dimethyl 1-butyne (1 mmol, 0.125 mL), Me_3SnF (1.5 mmol, 274 mg), PMHS (2.5 mmol, 0.15 mL), and TBAF (1 drop of a 1 M solution in THF (~0.008 mmol)) were added successively. The reaction was then allowed to stir at rt for 2 h, at which time the hydrostannation was complete by GC. The

bromo benzoyl chloride (1.3 mmol) was then added and the mixture was allowed to reflux (~65 °C) until the cross-coupling was judged complete by TLC (4 h). At that time, alkyne (3 mmol), PMHS (3.0 mmol, 0.18 mL), and potassium fluoride (3 mmol in 1ml H_2O) TBAF (1 drop of a 1 M solution in THF (~0.008 mmol)) were added successively. The reaction was then allowed to stir at rt for 2 h, at which time the hydrostannation was complete by GC. Then, Pd_2dba_3, *t*-Bu_3P and 1,4-dioxane were added and refluxed at ~90 °C until the cross-coupling was judged complete by TLC. The reaction was diluted with saturated aq. KF (2 mL) and stirred for 0.5 h. The reaction was extracted with Et_2O and H_2O and the aqueous phase was back extracted with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (silica gel, hexane/EtOAc: 90/10) to afford the inseparable mixture of product (27%) and corresponding 1,4-reduction byproduct (41%).

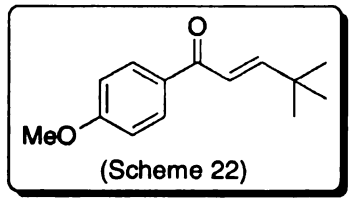


(Scheme 22)

Procedure for the Reduction after One-pot Sequence with 4-Methoxybenzoyl Chloride: Pd_2dba_3 (0.01 mmol, 9.2 mg) and TFP (0.04 mmol, 9.3 mg) were added to THF (5 mL) and the resulting mixture was stirred at rt for 15 min. At that time, 3,3-dimethyl 1-butyne (1 mmol, 0.125 mL), Me_3SnF (1.5 mmol, 274 mg), PMHS (2.5 mmol, 0.15 mL), and TBAF (1 drop of a 1 M solution in THF (~0.008 mmol)) were added successively. The reaction was then allowed to stir at rt for 2 h, at which time the hydrostannation was complete by GC. The 4-Methoxybenzoyl Chloride (1.3 mmol) was then added and the mixture was

allowed to reflux (~65 °C) until the cross-coupling was judged complete by TLC (4 h). At that time, PMHS (3.0 mmol, 0.18 mL), and potassium fluoride (3 mmol in 1mL H_2O) TBAF (1 drop of a 1 M solution in THF (~0.008 mmol)) were added successively. The reaction was then allowed to stir at 65 °C for 2 h, at which time the reduction did not go further by TLC. The reaction was diluted with saturated aq. KF (2 mL) and stirred for 0.5 h. The reaction was extracted with Et_2O and H_2O and the aqueous phase was back extracted with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by silica gel chromatography to afford the product (40%) and corresponding α, β-unsaturated ketone (38%). mp 63–66 °C.

IR (KBr) 3074, 2948, 2865, 2841, 1668, 1605, 1260, 1032, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.93 (m, 2 H), 6.92 (m, 2 H), 3.85 (s, 3 H), 2.86 (m, 2 H), 1.61 (m, 2 H), 0.94 (s, 9 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.3, 130.3, 130.2, 113.7, 55.4, 38.4, 34.0, 30.2, 29.2 ppm

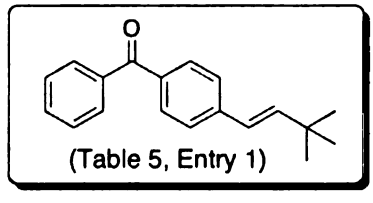


(Scheme 22)

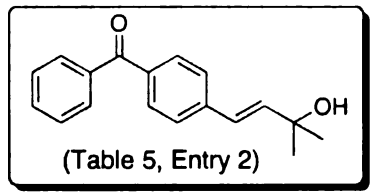
IR (neat) 3071, 2960, 2905, 2866, 2840, 1667, 1617, 1600, 1260, 1169, 1024, 832 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.96 (dd, *J* = 6.8, 2.2 Hz, 2 H), 7.06 (d, *J* = 15.6 Hz, 1 H), 6.96 (dd, *J* = 6.9, 2.2 Hz, 2 H), 6.81 (d, *J* = 15.7 Hz, 1 H), 3.88 (s, 3 H), 1.16 (s, 9 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.7, 163.2, 158.5, 131.1, 130.8, 120.5, 113.7, 55.4, 34.0, 28.8 ppm

General Procedure for the Multiple Hydrostannation/Stille Reaction Recycling Tin: Typical reaction procedure: Pd_2dba_3 (0.01 mmol, 9.2 mg) and

TFP (0.04 mmol, 9.3 mg) were added to THF (5 mL) and the resulting mixture was stirred at rt for 15 min. At that time, $PhSnMe_3$ and 4-Br-benzoyl chloride were added successively. The reaction was then allowed to stir at 65 °C for 4 h, at which time the coupling reaction was complete by TLC. At that time, alkyne (3 mmol), PMHS (3.0 mmol, 0.18 mL), and potassium fluoride (3 mmol in 1mL H_2O) TBAF (1 drop of a 1 M solution in THF (~0.008 mmol)) were added successively. The reaction was then allowed to stir at rt for 2 h, at which time the hydrostannation was complete by GC. At that time, Pd_2dba_3, *t*-Bu_3P and 1,4-dioxane were added and refluxed at ~90 °C until the cross-coupling was judged complete by GC. The reaction was diluted with saturated aq. KF (2 mL) and stirred for 0.5 h. The reaction was extracted with Et_2O and H_2O and the aqueous phase was back extracted with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by silica gel chromatography to afford the corresponding α,β-unsaturated ketone.


(Table 5, Entry 1)

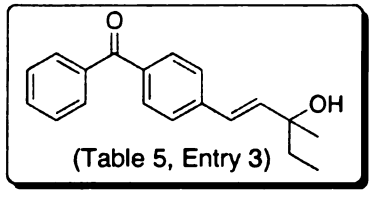
(E)-(4-(3,3-Dimethylbut-1-enyl)phenyl)-(phenyl)methanone: Subjection of 3,3-dimethylbut-1-yne (3.0 mmol, 0.25 mL) to the general procedure afforded after column chromatography (silica gel, hexane/EtOAc: 80/20) 0.132 g (50%) of (E)-(4-(3,3-dimethylbut-1-enyl)phenyl)(phenyl)methanone as a liquid with inseparable byproduct.



(Table 5, Entry 2)

(E)-(4-(3-Hydroxy-3-methylbut-1-enyl)phenyl)-(phenyl)methanone: Subjection of 2-methylbut-3-yn-2-ol (3.0 mmol, 0.29 mL) to the general procedure afforded after column chromatography (silica gel, hexane/EtOAc: 80/20) 0.141 g (53%) of (E)-(4-(3-hydroxy-3-methylbut-1-enyl)phenyl)(phenyl)-methanone as a liquid.

IR (neat) 3448 (br), 3058, 2972, 1652, 1600, 1316, 1281 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.77 (m, 4H), 7.56 (m, 1H) 7.47 (m, 4H) 6.66 (d, J = 16.1 Hz, 1H) 6.49(t, J = 16.1 Hz, 1H) 1.43 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.1, 141.2, 140.4, 137.8, 136.2, 132.2, 130.6, 129.9, 128.2, 126.2, 125.5, 71.1, 29.9 ppm



(Table 5, Entry 3)

(E)-(4-(3-Hydroxy-3-methylpent-1-nyl)phenyl)-(phenyl)methanone: Subjection of 3-methylpent-1-yn-3-ol (3.0 mmol, 0.34 mL) to the general procedure afforded after column chromatography (silica gel, hexane/EtOAc: 80/20) 0.112 g (40%) of (E)-(4-(3-hydroxy-3-methylpent-1-nyl)phenyl)(phenyl) methanone as a liquid.

IR (neat) 3466 (br), 3059, 2967, 1652, 1600, 1446, 1316, 1281 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.78 (m, 4H), 7.57 (m, 1H) 7.48 (m, 4H) 6.67 (d, J = 16.1 Hz, 1H) 6.41 (t, J = 16.1 Hz, 1H) 1.73 (m, 3H), 1.42 (s, 3H), 0.98 (t, J = 7.3 Hz,

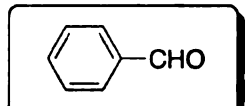
3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.1, 141.3, 139.4, 137.8, 136.1, 132.2, 130.6, 129.9, 128.2, 126.4, 126.1, 73.5, 35.3, 27.7, 8.2 ppm

Chapter 4. Pd (0)-Catalyzed PMHS Reductions of Aromatic Acid Chlorides to Aldehydes

General Procedure for Reductions with Me_3SnCl/PMHS/KF/Pd(0): Pd_2dba_3 (0.01 mmol, 9.2 mg) and TFP (0.04 mmol, 9.3 mg) were added to THF (5 mL) and the resulting mixture was stirred at rt for 15 min. At that time, acid chloride (1 mmol), Me_3SnCl (0.1–1.0 mmol), PMHS (1.5 mmol, 0.09 mL), aq. KF (1.5 mmol, 87.3 mg in 1 mL H_2O) and TBAF (1 drop of a 1 M solution in THF (~0.008 mmol)) were added successively. The reaction was then allowed to stir at rt until the reduction was judged complete by GC (~0.5 to 1 h). At that time, the reaction was diluted with saturated aq. KF (3 mL) and stirred for 0.5 h. The reaction was then extracted with Et_2O and the aqueous phase was back extracted with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (10% Et_2O/pentane) to afford the aldehyde.

General Procedure for Reductions with PMHS/KF/Pd(0): Pd_2dba_3 (0.01 mmol, 9.2 mg) and trifurylphosphine (TFP) (0.04 mmol, 9.3 mg) were added to THF (5 mL) and the resulting mixture was stirred at rt for 15 min. At that time, acid chloride (1 mmol), PMHS (3.0 mmol, 0.18 mL), aq. KF (3.0 mmol, 174.5 mg in 1 mL H_2O) and TBAF (1 drop of a 1 M solution in THF (~0.008 mmol)) were added successively. The reaction was then allowed to stir at rt until the reduction was complete by GC monitoring (~1 h). At that time, the reaction was extracted

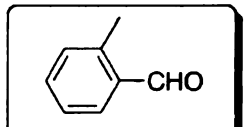
with Et_2O and the aqueous phase back extracted with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (10% Et_2O/pentane) to afford the aldehyde.



(Table 7, Entry 1)

Benzaldehyde: Subjection of benzoyl chloride (1.0 mmol, 0.141 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et_2O/pentane) 0.105 g (99%) of benzaldehyde as a colorless liquid.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.98 (s, 1H), 7.85 (dd, J = 8.0, 1.1 Hz, 2H), 7.62 (m, 1H), 7.51 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.2, 136.3, 134.3, 129.6, 128.9 ppm. Physical and spectral data were consistent with those obtained from a commercial sample.

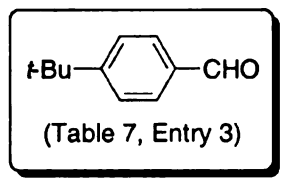


(Table 7, Entry 2)

2-Methylbenzaldehyde: Subjection of 2-methyl-benzoyl chloride (1.0 mmol, 0.155 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et_2O/pentane) 0.100 g (83%) of 2-methyl-benzaldehyde as a colorless liquid.

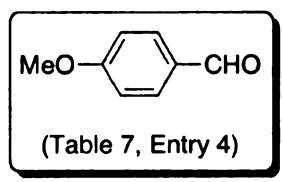
^1H NMR (300 MHz, $CDCl_3$): δ = 10.24 (s, 1H), 7.78 (d, J = 7.4 Hz, 1H), 7.48 (m, 1H), 7.35 (m, 1H), 7.23 (d, J = 7.4 Hz, 1H), 2.64 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.8, 140.6, 134.2, 133.6, 132.0, 131.7, 126.3, 19.5 ppm. Physical

and spectral data were consistent with those obtained from a commercial sample.



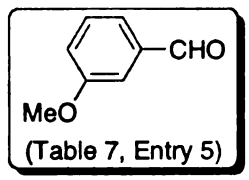
(Table 7, Entry 3)

4-*tert*-Butylbenzaldehyde: Subjection of 4-*tert*-butylbenzoyl chloride (1.0 mmol, 197 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et_2O/pentane) 0.161 g (99%) of 4-*tert*-butylbenzaldehyde as a colorless liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.96 (s, 1H), 7.81 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 1.32 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.9, 158.4, 134.1, 129.6, 125.9, 35.3, 31.0 ppm. Physical and spectral data were consistent with those obtained from a commercial sample.



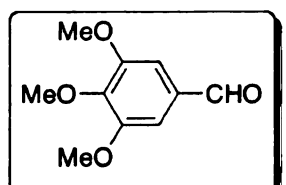
(Table 7, Entry 4)

4-Methoxybenzaldehyde: Subjection of 4-methoxybenzoyl chloride (1.0 mmol, 0.171 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et_2O/pentane) 0.124 g (91%) of 4-methoxybenzaldehyde as a colorless liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.84 (s, 1H), 7.81 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.7, 164.6, 131.9, 129.9, 114.3, 55.5 ppm. Physical and spectral data were consistent with those obtained from a commercial sample.



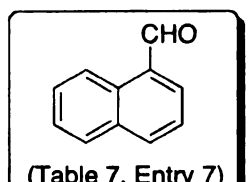
(Table 7, Entry 5)

3-Methoxybenzaldehyde: Subjection of 3-methoxy-benzoyl chloride (1.0 mmol, 0.171 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et_2O/pentane) 0.133 g (98%) of 3-methoxybenzaldehyde as a colorless liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.92 (s, 1H), 7.40 (m, 2H), 7.33 (s, 1H), 7.14 (m, 1H), 3.81 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.0, 160.1, 137.7, 129.9, 123.4, 121.4, 112.0, 55.3 ppm. Physical and spectral data were consistent with those obtained from a commercial sample.



(Table 7, Entry 6)

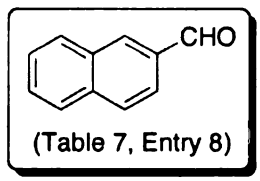
3,4,5-Trimethoxybenzaldehyde: Subjection of 3,4,5-trimethoxybenzoyl chloride (1.0 mmol, 231 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et_2O/pentane) 0.160 g (82%) of 3,4,5-trimethoxybenzaldehyde as a white crystal. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.84 (s, 1H), 7.01 (s, 2H), 3.91 (s, 3H), 3.90 (s, 6H,) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.0, 153.6, 143.7, 131.7, 106.7, 61.0, 56.3 ppm; mp 71–72 °C. Physical and spectral data were consistent with those obtained from a commercial sample.



(Table 7, Entry 7)

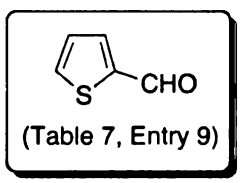
1-Naphthaldehyde: Subjection of 1-naphthoyl chloride (1.0 mmol, 0.191 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et_2O/pentane) 0.134 g (86%) of 1- naphthaldehyde as a colorless liquid. ^1H NMR (300 MHz, $CDCl_3$): δ

= 10.36 (s, 1H), 9.25 (d, J = 8.5 Hz, 1H), 8.06 (d, J = 8.2 Hz, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.67 (t, J = 8.5 Hz, 1H), 7.59 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.3, 136.5, 135.1, 133.6, 131.3, 130.4, 128.9, 128.4, 126.8, 124.7 (2C) ppm. Physical and spectral data were consistent with those obtained from a commercial sample.



(Table 7, Entry 8)

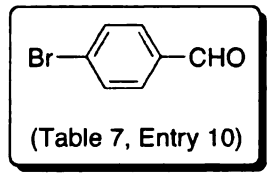
2-Naphthaldehyde: Subjection of 2-naphthoyl chloride (1.0 mmol, 0.191 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et_2O/pentane) 0.126 g (81%) of 2- naphthaldehyde as a white crystal. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.12 (s, 1H), 8.30 (s, 1H), 7.95–7.85 (m, 4H), 7.63–7.52 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.8, 136.1, 134.1, 133.7, 132.3, 129.1, 128.7 (2C), 127.7, 126.7 ppm, 122.4; mp 57–58 °C. Physical and spectral data were consistent with those obtained from a commercial sample.



(Table 7, Entry 9)

2-Thiophenecarboxaldehyde: Subjection of 2-thiophene-carbonyl chloride (1.0 mmol, 0.147 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et_2O/pentane) 0.103 g (92%) of 2-thiophenecarboxaldehyde as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.90 (s, 1H), 7.75 (m, 2H), 7.19 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.9, 144.0, 136.2, 135.0, 128.2 ppm.

Physical and spectral data were consistent with those obtained from a commercial sample.



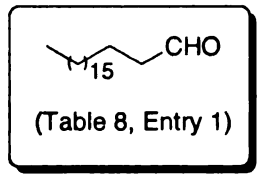
(Table 7, Entry 10)

4-Bromobenzaldehyde: Subjection of 4-bromo-benzoyl chloride (1.0 mmol, 220 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et_2O/pentane) 0.126 g (68%) of 4-bromo-benzaldehyde as a white crystal. mp 54–56 °C

^1H NMR (300 MHz, $CDCl_3$): δ = 9.93 (s, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.9, 135.0, 132.4, 130.9, 129.7 ppm. Physical and spectral data were consistent with those obtained from a commercial sample.

General Procedure for Reductions with PMHS/KF/18-crown-6/Pd(0): Pd_2dba_3 (0.01 mmol, 9.2 mg) and trifurylphosphine (TFP) (0.04 mmol, 9.3 mg) were added to THF (5 mL) and the resulting mixture was stirred at rt for 15 min. At that time, acid chloride (1 mmol), PMHS (1.5 mmol, 0.09 mL), aq. KF (2.0 mmol, 174.5 mg), 18-crown-6 (1mmol, 260 mg) and TBAF (1 drop of a 1 M solution in THF (~0.008 mmol)) were added successively. The reaction was then allowed to stir at rt until the reduction was complete by GC monitoring. At that time, the reaction was filtered through cotton and evaporated. The resulting

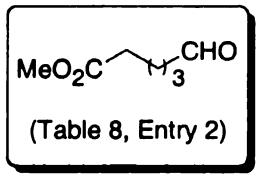
residue was purified by silica gel chromatography (10% Et_2O/pentane) to afford the aldehyde.



(Table 8, Entry 1)

Stearaldehyde: Subjection of stearoyl chloride (1.0 mmol, 303 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et_2O/pentane) 180 mg (67%) of stearaldehyde as a white crystal. mp 42–43 °C.

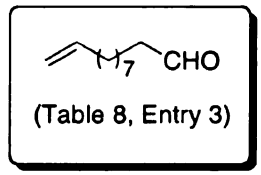
IR (KBr) 2952, 1737, 1437 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 9.75 (s, 6 H), 2.42 (m, 2 H), 1.23 (m, 30 H), 0.86 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 203.0, 43.9, 31.9, 29.69, 29.65, 29.63, 29.57, 29.42, 28.36, 29.16, 22.69, 22.07, 14.12 ppm. Physical and spectral data were consistent with those obtained from a commercial sample.



(Table 8, Entry 2)

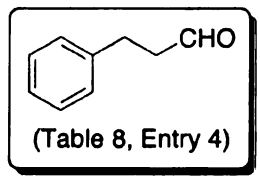
Methyl 6-Oxobutanoate: Subjection of methyl 6-chloro-6-oxohexanoate (1.0 mmol, 179 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et_2O/pentane) 77 mg (53%) of methyl 6-oxohexanoate as colorless liquid.

IR (neat) 2952, 2725, 1737, 1198 cm-1; ^1H NMR (500 MHz, $CDCl_3$): δ = 9.74 (m, 1H), 3.64 (s, 3 H), 2.44 (m, 2 H), 2.31 (m, 2 H), 1.64 (m, 4 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.0, 173.7, 51.5, 43.5, 33.7, 24.3, 21.4 ppm. Physical and spectral data were consistent with those obtained from a commercial sample.



(Table 8, Entry 3)

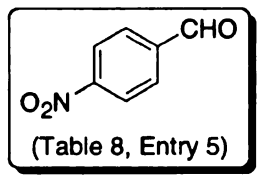
Undec-10-enal: Subjection of undec-10-enoyl chloride (1.0 mmol, 203 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et_2O/pentane) 84 mg (50%) of undec-10-enal as colorless liquid. IR (neat) 3076, 2927, 2716, 1727, 1640 cm-1; ^1H NMR (500 MHz, $CDCl_3$): δ = 9.74 (s, 1 H), 5.82–5.74 (m, 1 H), 4.99–4.89 (m, 2 H), 2.41 (dt, *J* = 7.3, 1.9 Hz, 2 H), 2.03 (m, 2 H), 1.61 (m, 2 H), 1.29 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.9, 139.1, 114.1, 43.8, 33.7, 29.26, 29.22, 29.1, 29.0, 28.8, 22.0 ppm. Physical and spectral data were consistent with those obtained from a commercial sample.



(Table 8, Entry 4)

3-Phenylpropanal: Subjection of 3-phenylpropanoyl chloride (1.0 mmol, 169 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et_2O/pentane) 95 mg (71%) of 3-phenylpropanal as colorless liquid.

IR (KBr) 3027, 2927, 1723, 1496, 1453, 699 cm-1; ^1H NMR (300 MHz, $CDCl_3$): δ = 9.81 (m, 1 H), 7.30–7.18 (m, 4H), 2.95 (t, *J* = 7.6 Hz, 2 H), 2.78 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.7, 140.3, 128.6, 128.3, 126.3, 45.2, 28.1 ppm. Physical and spectral data were consistent with those obtained from a commercial sample.

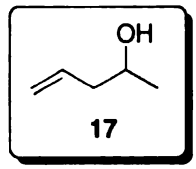


(Table 8, Entry 5)

4-Nitrobenzaldehyde: Subjection of 4-nitrobenzoyl chloride (1.0 mmol, 186 mg) to the general procedure afforded after column chromatography (silica gel, 10% Et_2O/pentane) 77 mg (51%) of 4-bromo-benzaldehyde as a white crystal. mp 102–103 °C

IR (KBr): 3107, 1709, 1606, 1536, 1347 cm-1; ^1H NMR (300 MHz, $CDCl_3$): δ = 10.14 (s, 1H), 8.39 (m, 2 H), 8.07 (m, 2 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.3, 140.0, 130.5, 124.3 ppm. Physical and spectral data were consistent with those obtained from a commercial sample.

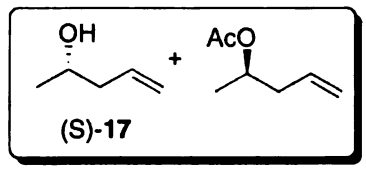
CHAPTER 5. Application of One-pot Pd-mediated Reactions in Target Synthesis



17

Preparation of (+/-)-4-Penten-2-ol: A flask was charged with Mg turnings (110 g, 4.5 mol) and dry Et_2O (187 mL). While this mixture was stirring, a solution of allyl bromide (173 mL, 2.0 mol) in Et_2O (1.0 L) was added slowly so as to keep the reaction temperature ~30 °C. Once the addition was complete, the solution was allowed to stir for 1 h. The solution of allylmagnesium bromide was cooled with an ice bath and a solution of acetaldehyde (100 mL, 1.8 mol) in Et_2O (100 mL) was added via an addition funnel. Once the addition was complete, the reaction was refluxed for 3 h. The reaction was then poured into ice water and quenched by the addition of dilute H_2SO_4. The mixture was then extracted with Et_2O. The organics were dried ($MgSO_4$), filtered and concentrated (NO HEAT on rotovap). The resulting residue was purified by distillation [bp 112-116 °C @ 760 mmHg] to afford (+/-)-4-penten-2-ol (170 g, 98%) as a clear liquid.

Spectra matched those of commercial material.



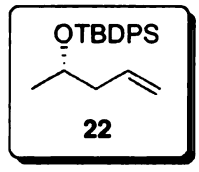
(S)-17

Preparation of (*S*)-4-Penten-2-ol and (*R*)-4-Penten-2-yl Acetate: (+/-)-4-Penten-2-ol (77.86 g, 904 mmol) was dissolved into freshly distilled vinyl acetate (83.3 mL, 904 mmol) and Novozyme 435 (8.22 g) was added. This slurry

was stirred at room temperature for ~12 h. The reaction was then filtered and the filtrate was loaded onto a column of silica and was eluted with 90:10 Pentane/Et_2O and once the acetate was off, 70:30 pentane/Et_2O was used to obtain the (*S*)-alcohol. The relevant fractions were rotovaped (NO HEAT!!!!) to afford (*S*)-4-penten-2-ol (19.49 g, 25%; 99% ee) and (*R*)-4-penten-2-yl acetate (46 g, 40%; 65 % ee).

^1H NMR (300 MHz, $CDCl_3$) δ = 1.18 (d, J = 6.2 Hz, 3H), 1.97 (bs, 1H), 2.09-2.21 (m, 2H), 3.68 (m, 1H), 5.04-5.08 (m, 2H), 5.72-5.81 (m, 1H) ppm; ^{13}C (75 MHz, $CDCl_3$) δ = 22.6, 43.6, 66.8, 117.9, 134.7 ppm

Spectra matched those of commercial material.



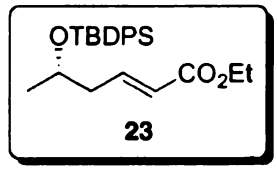
22

Preparation of (*S*)-*tert*-Butyl(pent-4-en-2-yloxy)diphenylsilane: (*S*)-4-Penten-2-ol (11.97 g, 139 mmol) was dissolved into DMF (140 mL) and imidazole (20.82 g, 306 mmol) was added followed by TBDPSCl (35.8 mL, 138 mmol). After stirring at room temperature for 10 h, the reaction was poured into sat. aq. NH_4Cl and then was extracted with Et_2O. The combined organics were dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by column chromatography [silica; hexanes] to afford (*S*)-*tert*-butyl(pent-4-en-2-yloxy)diphenylsilane (44.95 g, 99%) as a clear oil.

IR (neat) 3072 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 1.10 (m, 12 H), 2.24 (m, 2 H), 3.95 (m, 1 H), 4.96-5.03 (m, 2 H), 5.74-5.86 (m, 1 H), 7.35-7.48 (m, 6 H), 7.69-

7.75 (m, 4 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.3, 22.8, 27.0, 43.9, 69.2, 116.7, 127.4, 127.5, 129.4, 129.5, 134.5, 134.8, 135.1, 135.8, 135.9 ppm; $[\alpha]_D^{23}$ = + 16.8 (c = 2.07, CH_2Cl_2) All data matched those of the literature.[8]

Preparation of $Ph_3P{=}CHCO_2Et$. Ethyl-2-bromoacetate (111 mL, 1 mol), was added dropwise during 30 min to a stirred solution of PPh_3 (262 g, 1 mol) in benzene at 25 °C. This mixture was stirred for 5 h and then was allowed to stand overnight. The precipitate was filtered off and was successively washed with benzene and hexanes and then dried in vacuo to yield the corresponding bromide. This solid was then dissolved into cold water and 2 N NaOH was added dropwise until the mixture was alkaline to phenolphthalein. The precipitate was filtered off and air-dried to give the phosphorane as a white solid (312 g, 90%).



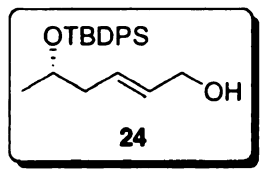
23

Preparation of (*S*)-(*E*)-Ethyl 5-(*tert*-Butyldiphenylsiloxy)-2-hexenoate: (*S*)-*tert*-Butyl(pent-4-en-2-yloxy) diphenylsilane (1.0 g, 3.08 mmol) was dissolved into CH_2Cl_2 (15 mL). This solution was then purged with N_2 and then cooled to –78 °C. O_3 was bubbled through the solution at –78 °C until a blue color persisted. The excess O_3 was removed by purging the solution with N_2. The reaction was then allowed to warm to room temperature and a condenser was added. Once at room temperature, a solution of Et_3N (0.47 mL, 3.4 mmol) and $Ph_3P{=}CHCO_2Et$ (1.18 g, 3.4 mmol) in CH_2Cl_2 (15 mL) was added to the solution. Once the

addition was complete, the mixture was stirred for 20 min. The reaction was then concentrated and purified by column chromatography [silica; 95:5 hexane/EtOAc] to afford (*S*)-(*E*)-ethyl 5-(*tert*-butyldiphenylsiloxy)-2-hexenoate (1.10 g, 90%) of light yellow oil.

IR (neat) 3071, 3049, 2963, 1721, 1656, 1427, 1264, 1175 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.67 (d, *J* = 7.7 Hz, 4 H), 7.47–7.27 (m, 6 H), 6.99–6.89 (m, 1 H), 5.80 (dd, *J* = 15.7, 1.4 Hz, 1 H), 4.23–4.15 (q, *J* = 7.1 Hz, 2 H), 4.00–3.94 (m, 1 H), 2.35 (m, 2 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.07 (s, 9 H) ppm; ^{13}C (125 MHz, $CDCl_3$) δ = 166.4, 145.5, 135.8, 134.3, 133.9, 129.65, 129.56, 127.57, 127.49, 123.4, 68.5, 60.1, 42.1, 26.9, 23.2, 19.2, 14.2 ppm; $[\alpha]^D_{25}$ = -34.2 (c = 0.87, CH_2Cl_2)

All data matched those of the literature.[9]



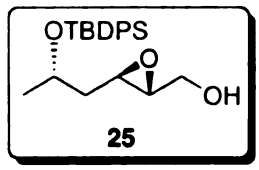
24

Preparation of (*S*)-(*E*)-5-(*tert*-Butyldiphenylsiloxy)hex-2-en-1-ol: (*S*)-(*E*)-Ethyl 5-(*tert*-butyldiphenylsiloxy)-2-hexenoate (44.57 g, 113 mmol) was dissolved into CH_2Cl_2 (560 mL) and the solution was cooled to –78 °C. DIBALH (236 mL of a 1M solution in hexanes, 236 mmol) was added dropwise via an addition funnel. Once the addition was complete, the reaction was allowed to stir for 6 h at –78 °C. The reaction was quenched by the addition of water and Rochelle's salt. The reaction was then allowed to warm to room temperature for several hours (overnight if needed). The phases were separated and the aqueous phase was

extracted with CH_2Cl_2 (4x). The combined organics were dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] to afford (*S*)-(*E*)-5-(*tert*-butyldiphenylsiloxy)-hex-2-en-1-ol (36.64 g, 92%) as a colorless oil.

IR (neat) 3320(br), 3070, 2963, 2857, 1427, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.69–7.65 (m, 4 H), 7.42–7.33 (m, 6 H), 5.59–5.55 (m, 2 H), 4.00 (m, 2 H), 3.90 (q, J = 6.0 Hz, 1 H), 2.18 (m, 2 H), 1.05 (s, 9 H) ppm; ^{13}C (125 MHz, $CDCl_3$) δ 163.2, 135.9, 134.6, 134.4, 131.3, 129.53, 129.48, 129.38, 127.5, 127.4, 69.2, 63.7, 42.2, 27.0, 23.1, 23.1, 19.2 ppm; HRMS (EI) *m/z* 355.2093 [(M^+), calcd. for $C_{22}H_{31}O_2Si$ 355.2113]; $[\alpha]^{25}_D$ = -21.5 (c = 0.67, CH_2Cl_2) All data matched those of the literature.[10,11]

Procedure for the Preparation of Anyhydrous *tert*-Butylhydrogen Peroxide (TBHP) in Toluene. To 1 L sep. funnel was added 360 mL of TBHP (30% aqueous solution) and 440 mL of toluene. The solution was swirled, not shaken. The aqueous phase was separated and the organic phase was transferred to a 1 L flask equipped with a Dean-Stark trap and reflux condenser. Boiling chips were added and the solution was refluxed for 4 h; during which ~120 mL of distillate was removed. The head temperature was ~80 °C. After cooling, the remaining TBHP/toluene solution was transferred to a brown glass bottle and stored at 25 °C over activated 4Å MS.



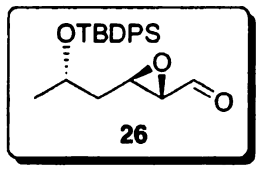
25

Preparation of (*S*, *R*, *R*)-(3-(2-(*tert*-Butyldiphenylsiloxy)-propyl)oxiran-2-yl)methanol: To a suspension of 4Å MS (4 g) in CH_2Cl_2 (125 mL) at –30 °C was added in sequential fashion: D-DET (0.73 mL, 4.22 mmol), Ti(*i*-PrO)$_4$ (1.03 mL, 3.52 mmol) and dropwise addition of TBHP (14 mL of a 3.86 M solution in toluene, 54 mmol). After stirring at –30 °C for 30 min, a solution of (*S*)-(*E*)-5-(*tert*-butyldiphenylsiloxy)-hex-2-en-1-ol (12.47 g, 35.2 mmol) in CH_2Cl_2 (18 mL) was added via a syringe so as to keep the reaction temperature at –30 °C. Once the addition was complete, stirring was stopped and the mixture was left at –30 °C for 12 h. The reaction was then warmed to –20 °C and quenched by the addition of 10% NaOH/brine (25 mL). Upon further warming to –10 °C, the reaction was diluted with Et_2O and $MgSO_4$ (15 g) and celite (4.0 g) were added and this mixture was stirred for 20 min. The reaction was then allowed to settle for ~1 h before filtering through celite. The filter cake was rinsed with Et_2O and the filtrate was concentrated. The residue was purified by column chromatography [silica; 80:20 to 70:30 hexane/EtOAc] to afford (*S*, *R*, *R*)-(3-(2-(*tert*-butyldiphenylsiloxy)-propyl)oxiran-2-yl)methanol (11.12 g, 85%) as a clear oil.

IR (neat) 3430(br), 3070, 2931, 2857, 1472, 1427, 1110 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.68 (m, 4 H), 7.40 (m, 6 H), 4.08 (m, 1 H), 3.82 (m, 1 H), 3.54 (m, 1H), 3.04 (m, 1 H), 2.81 (m, 1 H), 1.76 (m, 2 H), 1.62 (m, 1 H), 1.11 (d, *J* = 6.1 Hz, 3 H), 1.05 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.2, 23.8, 26.9, 41.6,

53.2, 58.7, 61.5, 67.6, 127.5, 129.6, 134.3, 135.8 ppm; HRMS (EI) *m/z* 371.2042 [(M+H), calcd. for $C_{22}H_{31}O_3Si$ 371.2050]; $[\alpha]^{25}_D$= + 2.0 (c = 0.76, CH_2Cl_2)

All data matched those of the literature.[11]



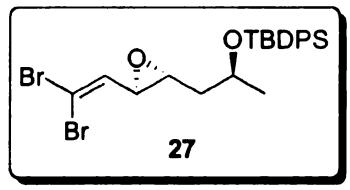
26

Preparation of 3-(2-(*tert*-Butyldiphenylsiloxy)-propyl)-oxirane-2-carbaldehyde: A solution of (*S*, *R*, *R*)-(3-(2-(*tert*-butyldiphenylsiloxy)-propyl)oxiran-2-yl)methanol (10.66 g, 28.77 mmol) and Et_3N (20 mL, 141 mmol) in 4:1 mixture of CH_2Cl_2/DMSO (300 mL) at 0 °C was treated with SO_3•py (16.08 g, 101 mmol) and this mixture was stirred at room temperature for 1 h. The reaction was then diluted with EtOAc, washed with water, sat. aq. $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography [silica; 95:5 hexane/EtOAc] to afford 3-(2-(*tert*-butyldiphenylsiloxy)-propyl)oxirane-2-carbaldehyde (7.68 g, 72%) as a yellow oil.

IR (neat) 3071, 2931, 2857, 1730, 1427, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 8.91 (d, *J* = 6.3 Hz, 1 H), 7.69–7.65 (m, 4 H), 7.44–7.36 (m, 6 H), 4.14–4.09 (m, 1 H), 3.28 (m, 1 H), 3.03 (dd, *J* = 6.3, 2.0 Hz, 1 H), 1.85–1.79 (m, 1 H), 1.66–1.61 (m, 1 H), 1.14 (d, *J* = 6.3 Hz, 3 H), 1.06 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 198.1, 135.81, 135.77, 134.12, 133.76, 129.77, 129.67, 127.68, 127.55, 67.4, 59.3, 54.1, 41.1, 26.9, 23.7, 19.2 ppm

$[\alpha]^{25}_D$= -42.0 (c = 1.12, CH_2Cl_2)

All data matched those of the literature.[11]



27

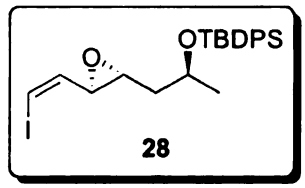
Preparation of 2-(2,2-Dibromovinyl)-3-(2-(*tert*-butyl-diphenylsiloxy)propyl)oxirane.

To a mixture of CBr_4 (14.51 g, 43.76 mmol) in CH_2Cl_2 (120 mL) at 0 °C under Ar was added a solution of PPh_3 (22.96 g, 87.53 mmol) in CH_2Cl_2 (40 mL). After 20 min at 0 °C, the solution was cooled to –78 °C and Et_3N (3.2 mL, 22.92 mmol) was added. A solution of 3-(2-(*tert*-butyldiphenylsiloxy)-propyl)oxirane-2-carbaldehyde (7.68 g, 20.84 mmol) in CH_2Cl_2 (70 mL) was added dropwise over 10 min. After 2 h, hexanes (120 mL) were added and the mixture was allowed to stir for 1 h. Filtering and concentration afforded a mixture of bromohydrin and epoxy dibromide. This mixture was then dissolved into THF (100 mL) and treated with TBAF (22 mL of a 1M solution in THF, 22 mmol) and stirred for 1 min at room temperature. The mixture was then washed with water, brine, dried ($MgSO_4$), filtered and concentrated to afford 2-(2,2-dibromovinyl)-3-(2-(*tert*-butyldiphenylsiloxy)propyl)oxirane (9.25 g, 85%) as a yellow oil.

Data for bromohydrin: $[\alpha]^{25}_D$= -77.8 (c = 1.12, $CHCl_3$)

IR (neat) 3458 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.10 (m, 9 H), 1.18 (d, J = 6.2 Hz, 3 H), 1.62 (m, 2 H), 3.13 (m, 1 H), 4.18 (m, 1 H), 4.62 (m, 1 H), 6.80 (d, J = 10.2 Hz, 1 H), 7.34-7.52 (m, 6 H), 7.64-7.79 (m, 4 H); ^{13}C (125 MHz, $CDCl_3$) δ 19.1, 23.0, 27.0, 41.8, 56.2, 67.7, 71.1, 95.1, 127.6, 127.8, 129.8, 129.9, 133.3, 133.7, 134.6, 135.8, 135.9; HRMS (EI) *m/z* 601.9492 [(M^+), calcd. for $C_{23}H_{29}Br_3O_2Si$ 601.9487].

Data for epoxy dibromide: $[\alpha]^{25}_{D}$= -7.6 (c = 1.08, $CHCl_3$); IR (neat) 3071 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.6 (m, 9 H), 1.11 (d, *J* = 6.2 Hz, 3 H), 1.58-1.80 (m, 2 H), 3.00 (td, *J* = 2.1, 6.2 Hz, 1 H), 3.27 (dd, *J* = 2.1, 7.8 Hz, 1 H), 4.07 (m, 1 H), 6.06 (d, *J* = 10.2 Hz, 1 H), 7.33-7.47 (m, 6 H), 7.64-7.74 (m, 4 H); ^{13}C (75 MHz, $CDCl_3$) δ 19.2, 23.8, 25.9, 26.5, 26.9, 41.6, 56.7, 57.8, 67.4, 93.4, 127.5, 127.6, 127.7, 129.5, 129.6, 129.7, 133.8, 134.3, 134.7, 135.7, 135.8; HRMS (EI) *m/z* 522.0222 [(M^+), calcd. for $C_{23}H_{28}Br_2O_2Si$ 522.0225].



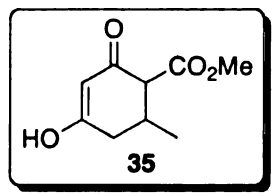
28

Preparation of *tert*-Butyl((*S*)-1-((2R,3R)-3-((*Z*)-2-iodovinyl) oxiran-2-yl)propan-2-yloxy)diphenylsilane. To a suspension of iodomethyltriphenylphosphonium iodide (0.65 mmol, 345 mg) in THF/DMF (2 mL/2 mL) at -20 °C was slowly added sodium bis-(trimethylsilyl)amide (0.65 mmol, 0.65 mL) in THF. After stirring for 5 min the solution was cooled to -20 °C and the aldehyde (0.5 mmol, 185 mg) in THF (1 ml) was added. The reaction was maintained at -20 °C for 25 min. The reaction mixture was diluted with EtOAc and workup with water and brine. The combined organics were dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product, which was purified by flash chromatography (95:5 hex/EtOAc) to afford product (dr: Z/E= >9/1) in 72% yield.

IR (neat) 3070, 2930, 1427, 1111 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.68 (m, 4H), 7.43–7.37 (m, 6H), 6.48 (d, *J* = 7.8 Hz, 1 H), 5.94 (t, *J* = 7.8 Hz, 1 H), 4.12–4.06 (m, 1 H), 3.32 (d, *J* = 7.6 Hz, 1 H), 3.04 (m, 1 H), 1.82–1.77 (m, 1H), 1.70–

1.63 (m, 1H), 1,13(d, J = 6.1 Hz, 3 H), 1.06 (s, 9H) ppm; ^{13}C (125 MHz, $CDCl_3$) δ = 138.3, 135.83, 135.82, 134.4, 134.0, 129.7, 129.6, 127.6, 127.5, 84.6, 67.6, 60.7, 56.7, 41.7, 27.0, 23.8, 19.2 ppm; $[\alpha]^{25}_D$= -28.7 (c = 2.15, $CHCl_3$)

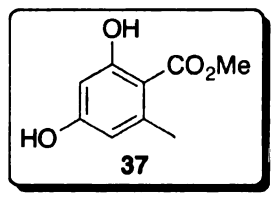
Preparation of Methyl 2,4-Dihydroxy-6-methylbenzoate: Methyl acetoacetate (5.2 mL, 48 mmol) and CaO (2.73 g, 48.7 mmol) were dissolved in THF (35 mL) under nitrogen and then were heated to 50 °C for 1 h. Diketene (stabilized with $CuSO_4$) (3.70 mL, 4.04 mmol) was added dropwise while the mixture was being cooled with a water bath to keep the temperature between 30-40 °C. Once the addition was complete, the reaction was refluxed for 8 h and then cooled to room temperature. The THF was removed (rotovap) and ether (50 mL) was added followed by enough 2 M HCl to dissolve the residual CaO in the mixture. After extracting with ether (3x), water was added and the aqueous phase was adjusted to pH 6.0 with 10% NaOH and then the mixture was extracted with ether (3x). The solvent was removed to provide a complex mixture of products that were not identifiable.



35

Preparation of Methyl Dihydroorsellinate: Na (18.4 g, 800 mmol) was added with stirring in small pieces to dry MeOH (275 mL). After the reaction had subsided, methyl acetoacetate (86 mL, 800 mmol) was added dropwise followed by the dropwise addition of methyl crotonate (85 mL, 800 mmol). After the addition was complete,

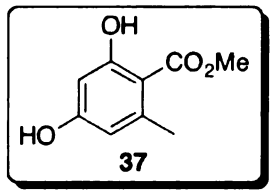
the reaction was refluxed for 44h. At this time the MeOH was carefully removed in the original flask with the rotovap. The resulting residue was then cooled to 0 °C and ether (400 mL) was added with stirring. The solid formed was then removed by filtration and the filter cake was then washed with ether (100 mL). The solid was hen dissolved into water (275 mL), cooled to 0 °C, and then concentrated HCl was added until the aqueous phase turned the pH paper red (pH 3). This solution was then allowed to sit in the ice bath for ~1 h. The white solid was then filtered and washed with ice water (300 mL). This solid was then dried under vacuum for ~1 day to afford methyl dihydroorsellinate (120 g, 82%) as a white solid (mp 125-127 °C).[12]



37

Procedure using Br_2/Ac_2O/AcOH and Catalytic HBr -Preparation of Methyl 2,4-Dihydroxy-6-methylbenzoate: Methyl dihydroorsellinate (18.42 g, 100 mmol) was dissolved in a mixture of AcOH (60 mL) and Ac_2O (30 mL) by warming and once dissolved cooled to 0 °C (ice bath). A solution of Br_2 (5.12 mL, 100 mmol) in AcOH (10 mL) was added dropwise at 0 °C. A stream of N_2 was allowed to bubble through the solution as the temperature was brought to reflux (~125 °C). This mixture was then allowed to reflux for 2h. The authors suggest bubbling N_2 through the mixture during reflux, but this has to be watched carefully! The solution was then cooled to 25 °C and water (60 mL) was added followed by the addition of 48% HBr (1 mL). This solution was then refluxed for 2 h. After

cooling, the mixture was poured into water and extracted with ether (7x). The organics were washed with water, sat. aq. $NaHCO_3$, water, dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] to afford methyl 2,4-dihydroxy-6-methylbenzoate (12.05 g, 66%) as a white solid contaminated with an unknown product. mp 138 °C (lit. 136–138 °C)[13] All spectroscopic data matched those of the literature.

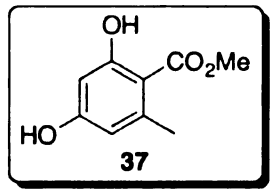


37

Procedure for the Use of $CuBr_2$ and LiBr[15] – Preparation of Methyl 2,4-Dihydroxy-6-methylbenzoate

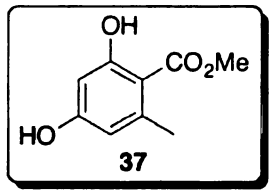
Methyl dihydroorsellinate (1.84 g, 10 mmol), $CuBr_2$ (4.46 g, 20 mmol) and LiBr (0.86 g, 10 mmol) were dissolved into CH_3CN (20 mL). This mixture was then refluxed for 2 h. After cooling to 25 °C, the reaction was poured into a solution of 10% HCl (50 mL) and ether (100 mL). The layers were separated and the aqueous phase was extracted with ether (2x). The combined organics were dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] to afford methyl 2,4-dihydroxy-6-methylbenzoate (600 mg, 33%) as a white solid.[14]

IR (KBr) 3368, 3311, 1641, 1445, 1326, 1268, 1159 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ = 10.75 (brs, 1H), 6.17 (m, 2H), 3.78 (s, 3H), 2.27 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.4, 161.4, 161.3, 141.1, 110.4, 107.5, 100.6, 51.9, 22.2 ppm



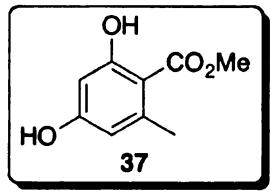
37

Procedure for the Use of $CuBr_2$ and LiBr using DMF as Solvent[15] - Preparation of Methyl 2,4-Dihydroxy-6-methylbenzoate: Applying the above conditions except this entry used DMF (20 mL) as solvent at 100 °C. The resulting residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] to afford methyl 2,4-dihydroxy-6-methylbenzoate (800 mg, 44%) as a white solid.



37

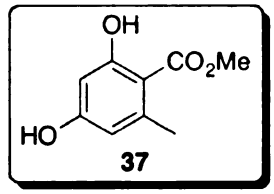
Procedure for the Use of $CuCl_2$ and LiCl[15] in CH_3CN - Preparation of Methyl 2,4-Dihydroxy-6-methylbenzoate: Methyl dihydroorsellinate (10.0 g, 54.3 mmol), $CuCl_2$ (29.20 g, 217 mmol) and LiCl (4.60 g, 109 mmol) were dissolved into CH_3CN (200 mL). This mixture was then refluxed for 5 h. After cooling to 25 °C, the reaction was poured into a solution of 10% HCl (50 mL) and ether (100 mL). The layers were separated and the aqueous phase was extracted with ether (2x). The combined organics were dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] to afford methyl 2,4-dihydroxy-6-methylbenzoate (3.30 g, 33%) as a white solid.



37

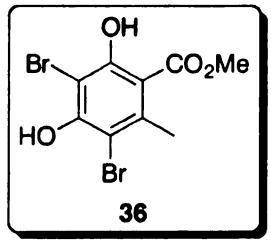
Procedure for the Use of $CuCl_2$ and LiCl[15] in DMF - Preparation of Methyl 2,4-Dihydroxy-6-methylbenzoate Applying the above conditions using

DMF as the solvent at 100 °C for 5 h after column chromatography [silica; 80:20 hexane/EtOAc] afforded methyl 2,4-dihydroxy-6-methylbenzoate (4.47 g, 47%) as a white solid.



37

Procedure for the Use of $CuCl_2$ and $MgCl_2$[15] - Preparation of Methyl 2,4-Dihydroxy-6-methylbenzoate: Methyl dihydroorsellinate (5.0 g, 27.15 mmol), $CuCl_2 \cdot 2H_2O$ (9.26 g, 54.30 mmol) and $MgCl_2 \cdot 6H_2O$ (2.76 g, 13.60 mmol) were dissolved into CH_3CN (30 mL). This mixture was then refluxed for 12 h. After cooling to 25 °C, the reaction was poured into a solution of 10% HCl (50 mL) and ether (100 mL). The layers were separated and the aqueous phase was extracted with ether (2x). The combined organics were dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] to afford methyl 2,4-dihydroxy-6-methylbenzoate (3.0 g, 60%) contaminated with an unknown product.



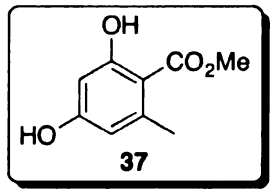
36

Preparation of Methyl 3,5-Dibromo-2,4-dihydroxy-6-methyl-benzoate: Br_2 (56 mL, 1090 mmol) was added to a solution of methyl dihydroorsellinate (66.35 g, 360 mmol) in AcOH (212 mL) at such a rate to keep the temperature between 40-45 °C. This mixture was allowed to stir for ~1h and then allowed to stand for ~10 h. Water was then added to this mixture and the solid was

collected by filtration (course glass frit) and was washed with copious amounts of water. The white solid obtained was dried to afford methyl 3,5-dibromo-2,4-dihydroxy-6-methyl-benzoate (142 g, 93%) as a white solid (mp 106 °C, lit 112–114 °C)[15b].

IR (neat) 3619, 3425, 2957, 1652, 1588, 1404, 1320, 1252 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 12.16 (s, 1H), 6.46 (s, 1H), 3.97 (s, 3H), 2.65 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 171.2, 159.4, 153.8, 140.4, 107.5, 105.4, 96.3, 52.8, 23.2 ppm

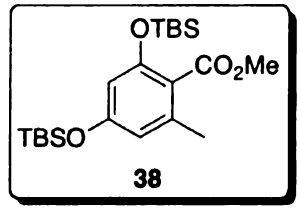
All spectroscopic data matched those of the literature.[16]



37

Procedure for PMHS/KF Dehydrohalogenation catalyzed by $Pd(OAc)_2$ - Preparation of Methyl 2,4-Dihydroxy-6-methylbenzoate: Methyl 3,5-dibromo-2,4-dihydroxy-6-methyl-benzoate (117 g, 345 mmol) was dissolved into THF (1725 mL) and was purged with N_2. $Pd(OAc)_2$ (3.87 g, 17.25 mmol), KF (80.18 g, 1380 mmol) and H_2O (~690 mL) were all added under N_2. PMHS (166 mL, 2760 mmol) was then slowly added (*add the PMHS via an additional funnel and allow the PMHS to flow as a thin stream while using a mechanical stirrer. Also use a reflux condenser as the reaction is exothermic*) and once the addition was complete, the reaction was allowed to stir at 25 °C for 24 h. Crude ^1H NMR analysis indicated a 1.7:1.0 ratio of product to monobromide. This reaction was then diluted with Et_2O and the layers were separated. The aqueous portion was

extracted with Et_2O (3x). The combined organics were then concentrated to about ½ volume. This solution was then filtered through a pad of silica gel with celite on top. The filter cake was rinsed with Et_2O until TLC analysis (80:20 hexane/EtOAc) showed no product. The filtrate was then concentrated to dryness. This residue was then dissolved into THF (1725 mL) and was purged with N_2. $Pd(OAc)_2$ (3.87 g, 17.25 mmol), KF (80.18 g, 1380 mmol) and H_2O (~690 mL) were all added under N_2. PMHS (166 mL, 2760 mmol) was then slowly added and this mixture was allowed to stir at 25 °C for 21 h. Crude ^1H NMR analysis indicated that the reaction was complete. After diluting with Et_2O, the reaction was allowed to stand overnight (~10 h). The layers were separated and the aqueous portion was extracted with Et_2O. The combined organics were dried ($MgSO_4$), filtered through celite and then concentrated. The resulting residue was purified by column chromatography [silica; 80:20 hexane/EtOAc] to afford methyl 2,4-dihydroxy-6-methylbenzoate (55.3 g, 88%) of a white solid.

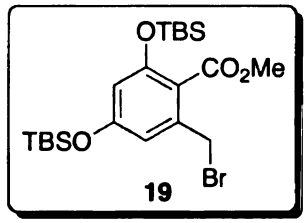


38

Preparation of Methyl 2,4-Di-(*t*-butyldimethylsiloxy)-6-methylbenzoate. Methyl 2,4-dihydroxy-6-methylbenzoate (15.73 g, 86.35 mmol) was dissolved into DMF (130 mL). Imidazole (29.40 g, 432 mmol) was added followed by TBSCl (32.54 g, 216 mmol). The reaction was then allowed to stir at 25 °C fro 2.5 h. The reaction was then poured into water and then extracted with EtOAc. The combined organics were washed with sat. aq. $NaHCO_3$, sat. aq. NH4Cl,

brine, dried (MgSO4), filtered and concentrated. The resulting residue was purified by column chromatography [silica; 98:2 hexane/EtOAc] to afford methyl 2,4-di-(*t*-butyldimethylsiloxy)-6-methylbenzoate (35.01 g, 99%) as a clear oil.

IR (neat) 2957 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 0.18 (s, 6 H), 0.20 (s, 6 H), 0.96 (s, 9 H), 0.97 (s, 9 H), 2.22 (s, 3 H), 3.82 (s, 3 H), 6.16 (s, 1 H), 6.29 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = -4.4, 18.0, 18.2, 19.7, 25.5, 25.6, 51.7, 108.5, 114.9, 119.8, 137.9, 153.8, 156.9, 168.8; HRMS (EI) 410.2305 *m/z* 410.2305 [(M^+), calcd. for $C_{21}H_{38}O_4Si$ 410.2309.



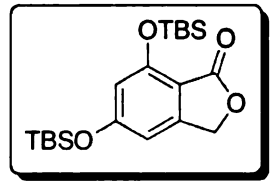
19

Preparation of Methyl 2-(Bromomethyl)-4,6-di-(*t*-butyldimethylsiloxy)-benzoate: Methyl 2,4-di-(*t*-butyldimethyl siloxy)-6-methylbenzoate (1.0 g, 2.44 mmol), NBS (477 mg, 2.68 mmol) and AIBN (4 mg, 0.024 mmol) were added to freshly distilled CCl4 (20 mL). This mixture was gently refluxed for 3.5 h. The reaction was then filtered, while still warm, through a pad of celite and the filtrate was concentrated. The resulting residue was purified by column chromatography [silica; 95:5 hexane/EtOAc] to afford methyl 2-(bromomethyl)-4,6-di-(*t*-butyldimethylsiloxy)-benzoate (1.03 g, 87%) as an oil.

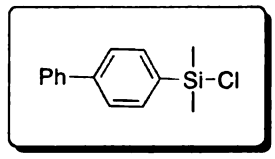
IR (neat) 2957 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 0.18 (s, 6 H), 0.20 (s, 6 H), 0.96 (s, 9 H), 0.97 (s, 9 H), 2.22 (s, 3 H), 3.82 (s, 3 H), 6.16 (s, 1 H), 6.29 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ= -4.4, 18.0, 18.2, 19.7, 25.5, 25.6, 30.5, 51.7,

111.2, 115.1, 138.0, 154.5, 156.9, 167.7; HRMS (EI) *m/z* 488.1410 [(M^+), calcd. for $C_{21}H_{37}BrO_4Si$ 488.1414.

**Note: If this compound is left to stand for a long period of time, another product forms. The product has been identified as 5,7-bis(*tert*-butyldimethylsiloxy)-isobenzofuran-1(3H)-one.



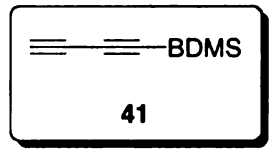
Data for 5,7-Bis(*tert*-butyldimethylsiloxy)-isobenzofuran-1(3H)-one: ^1H NMR (500 MHz, $CDCl_3$) δ = 0.23 (s, 6 H), 0.26 (s, 6 H), 0.98 (s, 9 H), 1.04 (s, 9 H), 5.09 (s, 2 H), 6.29 (s, 1 H), 6.45 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = -4.4, 18.2, 25.6, 68.1, 106.4, 109.7, 112.5, 150.5, 156.2, 162.5, 168.4; HRMS (EI) *m/z* 394.1990 [(M^+), calcd. for $C_{20}H_{34}O_4Si_2$ 394.1996].



Procedure for the Preparation of Biphenyldimethylsilyl Chloride (BDMSCl). To a solution of 4-bromobiphenyl (50 g, 215 mmol) in dry Et_2O (200 mL) at 0 °C was added *n*-BuLi (135 mL of a 1.6 M solution in hexanes, 215 mmol). After stirring at 0 °C for 20 min., the mixture was warmed to room temperature and stirred for another 30 min. The resulting 4-lithiobiphenyl was then added via cannula to a precooled (0 °C) solution of Me_2SiCl_2 (25.83 mL, 215 mmol) in dry Et_2O (300 mL). This mixture was then left stirring for ~14 h at 25 °C. The solution was then filtered and the filtrate was concentrated to afford biphenyldimethylsilyl chloride (46.30 g, 87%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.74 (s, 6 H), 7.34-7.42 (m, 1 H), 7.42-7.50 (m, 2 H), 7.57-7.69 (m, 4 H), 7.70-7.75 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 2.1, 126.8, 127.2, 127.7, 128.8, 133.6, 134.8, 140.6, 143.1

Physical and spectral data were consistent with those obtained from a commercial sample.

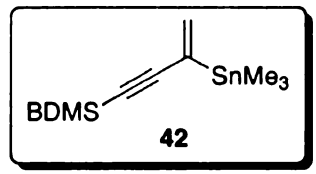


41

Preparation of (Buta-1,3-diynyl)dimethyl(4-biphenyl)-silane: Hexachlorobutadiene (1.9 mL, 12.16 mmol) was added dropwise to a solution of *n*-BuLi (30.5 mL of a 1.6 M solution in hexanes, 49 mmol) at –78 °C in THF (15 mL). After the addition was complete, the mixture was allowed to warm to room temperature and then was stirred for 2 h. The solution was then recooled to –78 °C and BDMSCl (3.0 g, 12.16 mmol) was added dropwise as a solution in THF (5 mL). After the addition, the reaction was allowed to warm to room temperature and the mixture was stirred for 5 h. The reaction was then washed with 1M HCl and extracted with Et_2O. The combined organics were washed with brine, dried ($MgSO_4$), filtered and concentrated to afford a dark oil. The resulting residue was purified by column chromatography [silica; Pentane] to afford (buta-1,3-diynyl)dimethyl(4-biphenyl)silane (1.84 g, 60%) as a white solid. mp 77 °C (lit. mp 77°C)[17]

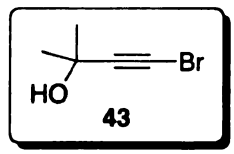
IR (neat) 3323 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.50 (s, 6 H), 2.16 (s, 1 H), 7.32-7.40 (m, 1 H), 7.42-7.50 (m, 2 H), 7.55-7.65 (m, 4 H), 7.66-7.72 (m, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = -1.3, 67.2, 68.3, 82.6, 88.9, 126.8, 127.2,

127.5, 128.8, 134.2, 140.9, 142.6; HRMS (EI) *m/z* 260.1029 [(M^+), calcd. for $C_{18}H_{16}Si$ 260.1021]



42

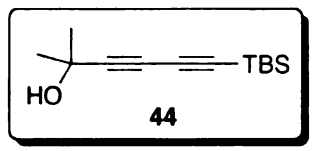
Procedure for the Hydrostannation of the Silyldiyne: (Buta-1,3-diynyl)dimethyl(4-biphenyl)silane (1.84 g, 7.07 mmol) was dissolved into THF (30 mL). Me_3SnCl (8.5 mL of a 1M solution in THF, 8.5 mmol), KF (1.23 g, 21.21 mmol), water (5-10 mL), PMHS (0.64 mL, 10.61 mmol) and $PdCl_2(PPh_3)_2$ (50 mg, 0.07 mmol) were all added. After 2 h of stirring at room temperature, the phases were separated and the organics were dried ($MgSO_4$), filtered and concentrated. ^1H NMR analysis of the crude reaction indicated only the formation of internal terminal vinylstannane. All attempts to isolate this compound failed.



43

Preparation of 4-Bromo-2-methyl-3-butyn-2-ol: A 1L 3-neck flask was charged with KOH (89.2 g, 1600 mmol) and water (350 mL). This mixture was cooled with an ice bath followed by the addition of Br_2 (110 mL, 200 mmol) dropwise. Once the dark red color discharged, the reaction was allowed to stir for 15 min. To this solution was added 2-methyl-3-butyn-2-ol (26.75 mL, 276 mmol) in hexanes (40 mL) via an addition funnel. Once the addition was complete, the reaction was allowed to stir for 15 min. A white solid could be seen floating on the surface of the colorless solution. The reaction was diluted with Et_2O, and washed with water. The

organics were dried ($MgSO_4$), filtered and concentrated. The resulting residue was purified by distillation [bp 68 °C @ 12 mmHg] to afford 4-bromo-2-methyl-3-butyn-2-ol (32.60 g, 100%) as a clear liquid.[18]

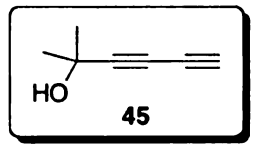


44

Preparation of 6-(*tert*-Butyldimethylsilyl)-2-methylhexa-3,5-diyn-2-ol.

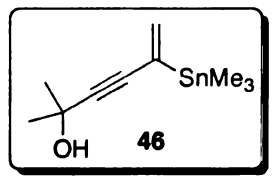
CuCl (120 mg, 1.2 mmol) was added to a 30% aq. *n*-$BuNH_2$ solution (50 mL) which turned blue. A few crystals of $NH_2OH{\cdot}HCl$ were added to discharge the color. TBS acetylene (13.37 mL, 71.3 mmol) was added to the solution in one portion. The now yellow mixture was cooled with an ice bath. At this point, 4-bromo-2-methyl-3-butyn-2-ol (9.68 g, 60 mmol) was added in one portion with vigorous stirring. If at any time during this addition the solution turned blue or green, a few crystals of $NH_2OH{\cdot}HCl$ were added immediately. The reaction turned from red to a rusty color that denotes the reaction was complete. The mixture was extracted with Et_2O (3x), dried ($MgSO_4$), filtered and concentrated to afford 6-(*tert*-butyldimethylsilyl)-2-methylhexa-3,5-diyn-2-ol (6.67 g, 50%) of a white solid. mp 75–76 °C (lit. 80–81 °C)[19]

IR (KBr) 3395 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 0.12 (s, 6 H), 0.94 (s, 9 H), 1.52 (s, 6 H), 2.08 (br s, 1 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = -4.9, 16.7, 25.9, 31.0, 65.5, 67.5, 81.4, 86.4, 87.8 ppm; HRMS (EI) *m/z* 222.1436, [(M^+), calcd. for $C_{13}H_{22}OSi$ 222.1440]



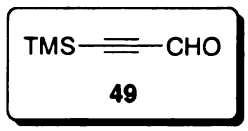
45

Preparation of 2-Methylhexa-3,5-diyn-2-ol: 6-(*tert*-Butyldimethylsilyl)-2-methylhexa-3,5-diyn-2-ol (6.67 g, 30 mmol) was dissolved into THF (50 mL) and this solution was cooled with an ice bath. TBAF (45 mL of a 1M solution in THF, 45 mmol) was added dropwise. After 5 h, the reaction was concentrated and the residue was purified by column chromatography [silica; 90:10 pentane/Et_2O] to afford 2-methylhexa-3,5-diyn-2-ol (3.24 g, 100%) as a clear liquid.[20]



46

Procedure for the Hydrostannation of the Diyne: 2-Methylhexa-3,5-diyn-2-ol (765 mg, 7.07 mmol) was dissolved into THF (30 mL). Me_3SnCl (8.5 mL of a 1M solution in THF, 8.5 mmol), KF (1.23 g, 21.21 mmol), water (5-10 mL), PMHS (0.64 mL, 10.61 mmol) and $PdCl_2(PPh_3)_2$ (50 mg, 0.07 mmol) were all added. After 2 h of stirring at room temperature, the phases were separated and the organics were dried ($MgSO_4$), filtered and concentrated. ^1H NMR analysis of the crude reaction indicated only the formation of internal terminal vinylstannane. All attempts to isolate this compound failed.



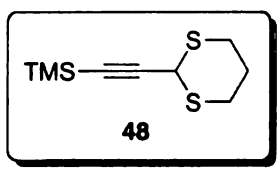
49

Preparation of 3-(Trimethylsilyl)propiolaldehyde from Ethynyltrimethylsilane: To prepare EtMgBr, syringe pump-dropwise (20 mL/h) bromoethane (10.9 g, 100 mmol) into 100 mL THF and 2.43 g Mg then stir an hour at rt. Cool the reaction to 0 °C then dropwise add

ethynyltrimethylsilane (14.2 mL, 100 mmol). The reaction mixture was heated for an hour at 50–60 °C, cooled and transferred to a dropwise funnel. A flask was charged with 21 g dimethylformamide in 20 mL absolute ether, then with cooling to -25–30 °C ((trimethylsilyl)ethynyl)-magnesium bromide was added dropwise. The temperature of the reaction mixture was gradually raised to rt and stirring continued for an hour. The content of the flask were cooled to -10 °C and poured into 5% H_2SO_4 solution. After cooling to -5 °C, the mixture was stirred for an hour and set aside overnight. The next day the aqueous layer was separated and extracted with ether. The ethereal extracts were combined, dried with $MgSO_4$, and purified through flash chromatography with pentane to afford product in 52–65% yield.

IR (KBr) 2963, 2165, 1723, 1252, 1211, 845 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 9.13 (s, 1 H), 0.23 (s, 9 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 176.7, 103.0, 102.1, -1.0 ppm

All spectroscopic data matched those of the literature.[21]

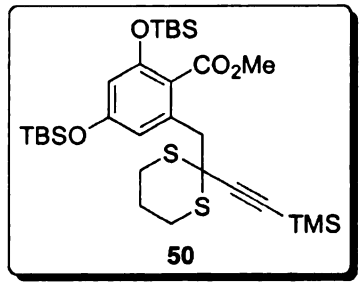


48

Preparation of ((1,3-Dithian-2-yl)ethynyl)trimethylsilane: $BF_3{\cdot}Et_2O$ (0.15 mL, 1.2 mmol), acetic acid (0.5 mL, 8.7 mmol) and 1,3-propanedithiol (0.12 mL, 1.2 mmol) were added to a stirring solution of 3-(trimethylsilyl)propiolaldehyde(130 mg, 1 mmol) in toluene (2 mL) in the ice bath. The progress of the reaction was followed by TLC. After completion, the reaction was quenched with water and

extracted with $NaHCO_3$ (X3), 2 M NaOH (X2) dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography with 5%EtOAc/hexane to afford product in 62% yield.

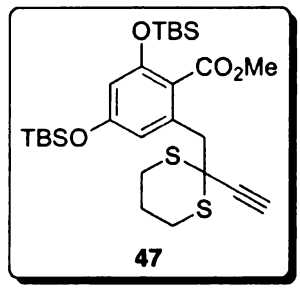
IR (KBr) 2957, 2164, 1423, 1248 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 0.18 (s, 9 H), 3.21 (m, 2 H), 2.73 (m, 2 H), 1.96–2.08 (m, 2 H), 4.52 (s, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 100.8, 90.9, 33.2, 27.5, 25.8 ppm.



50

Preparation of Methyl 2,4-Bis(*tert*-butyldimethyl silyloxy)-6-((2-((trimethylsilyl)ethynyl)-1,3-dithian-2-yl) methyl)benzoate: The ((1,3-dithian-2-yl)ethynyl)-trimethylsilane (0.342 g, 0.79 mmol) was added to a flame-dried flask equipped with a stir bar under Argone pressure. Anhydrous THF (8 mL) was added via cannula and the resulting solution was cooled to -20 °C. *n*-BuLi (1 mL, 1.6 mmol) was added in a steady stream and the resulting dark purple solution was stirred at -20 °C for an hour. The solution was cooled to -78 °C and cannulated into a solution of methyl 2-(bromomethyl)-4,6-di-(t-butyldimethylsiloxy)-benzoate (0.387 g, 0.79 mmol) in anhydrous THF (8 mL) at -78 °C. The resulting purple reaction was stirred 90 min at -78 °C before it was stored overnight in a -78 °C freezer. The reaction was then quenched by the addition of 1N HCl, extracted with CH_2Cl_2, and dried with Na_2SO_4. Evaporation of the solvents under reduced pressure followed by flash chromatography (silica gel, 10% EtOAc/hexane) afforded a product in 87% yield.

IR (KBr) 3021, 2953, 2928, 2856, 2155, 1733, 1597, 1472, 1430, 1252 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 6.80 (d, *J* = 2.2 Hz, 1 H), 6.22 (d, *J* = 2.2 Hz, 1 H), 3.82 (s, 3 H), 3.30 (s, 2 H), 3.26 (m, 2 H), 2.74 (m, 2 H), 2.06 (m, 1 H), 1.79 (m, 1 H), 0.94 (d, *J* = 4.2 Hz, 18 H), 0.17 (m, 21 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.7, 156.8, 154.0, 135.3, 121.0, 117.2, 110.3, 103.3, 93.8, 60.7, 52.3, 43.3, 29.1, 25.9, 25.7, 25.5, 18.5, 18.3, 0.4, -4.1(2) ppm; HRMS (EI) *m/z* 625.2693 [(M+H), calcd. for $C_{30}H_{53}O_4S_2Si_3$ 625.2734]

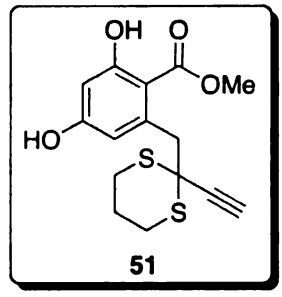


47

Preparation of Methyl 2,4-Bis(*tert*-butyldimethylsilyloxy)-6-((2-ethynyl-1,3-dithian-2-yl)methyl)benzoate: Water (4 mL) and $AgNO_3$ (0.35 g, 2.06 mmol) were added to a solution of methyl 2,4-bis(*tert*-butyldimethyl silyloxy)-6-((2-((trimethylsilyl)ethynyl)-1,3-dithian-2-yl) methyl)benzoate (2.06 mmol, 1.289 g) in acetone (20 mL) and the resulting mixture was stirred in the dark at the rt and for 7 h. The reaction was then poured into a saturated aqueous NaCl solution (20 mL) and extracted with Et_2O (3x10 mL). The organic extract was washed with brine (2x10 mL), dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel in 91% yield. mp 83–85 °C

IR (KBr) 3296, 2953, 2859, 2339, 1709, 1599, 1431, 1281, 1170 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 6.73 (d, *J* = 2.2 Hz, 1 H), 6.24 (d, *J* = 2.2 Hz, 1 H), 3.82 (s, 3 H), 3.38 (s, 2 H), 3.29 (td, *J* = 14.9, 2.5 Hz, 2 H), 2.86 (s, 1 H), 2.76 (dt, *J* =

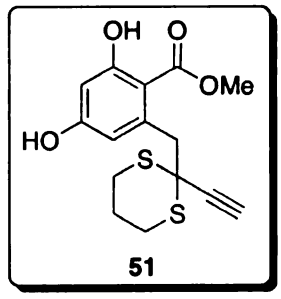
14.2, 3.7 Hz, 2 H), 2.11 (m, 1 H), 1.81 (m, 1 H), 1.55 (s, 1 H), 0.94 (d, J = 2.6 Hz, 18 H), 0.17 (d, J = 2.4 Hz, 12 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.4, 156.7, 154.3, 134.9, 120.6, 116.9, 110.7, 82.3, 76.3, 51.8, 45.9, 43.4, 28.7, 25.6, 25.2, 18.2, -4.3 ppm



51

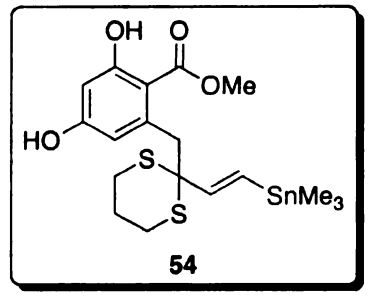
Preparation of Methyl 2-((2-Ethynyl-1,3-dithian-2-yl)methyl)-4,6-dihydroxybenzoate: Methyl 2,4-bis(*tert*-butyldimethyl silyloxy)-6-((2-((trimethylsilyl)ethynyl)-1,3-dithian-2-yl) methyl)benzoate (0.625 g, 1 mmol) was dissolved in THF (10 mL) and treated at -20 °C with a TBAF trihydrate solution (3 mL, 1M in THF, 3 mmol). The solution was allowed to warm up to 0 °C, stirred for 60 minutes and transferred into a cooled NH_4Cl-solution (10 mL, saturated). The organic layer was separated and the remaining aqueous phase extracted twice with ethyl acetate. The combined organic phases were washed with and purified by flash column chromatography (silica gel, hexanes/ethyl acetate 3:1) to afford the pure alkyne as a colorless oil (702 mg, 2.84 mmol, 88%). mp 137–138 °C

IR (KBr) 3365(br), 3276, 3039, 3001, 2949, 2914, 1651, 1579, 1432, 1322, 1262, 1199, 1171 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.45 (s, 1 H), 7.28 (s, 1 H), 6.48 (d, J = 2.8 Hz, 1 H), 6.42 (d, J = 2.8 Hz, 1 H), 3.94 (s, 3 H), 3.74 (s, 2 H), 3.33 (td, J = 2.8 Hz, 2 H), 2.88 (s, 1 H), 2.80 (m, 2 H) 2.18 (m, 1 H), 1.86 (m, 1 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0, 164.5, 159.5, 138.3, 113.6, 106.9, 103.4, 81.8, 76.3, 51.7, 46.0, 45.8, 28.7, 25.3 ppm



51

Preparation of Methyl 2-((2-Ethynyl-1,3-dithian-2-yl) methyl)-4,6-dihydroxybenzoate: Potassium carbonate was added to a stirred solution of TMS-alkyne in methanol at rt. After 10 min, the solution was filtered through a pad of celite, diluted with Et_2O and poured into water. The solution was extracted into Et_2O and the combined organic layers were further treated with saturated NH_4Cl, saturated $NaHCO_3$, and brine. The resulting ethereal solution was dried over Na_2SO_4, filtered through a plug of silica, and concentrated in vacuum to afford the product in 60% yield.

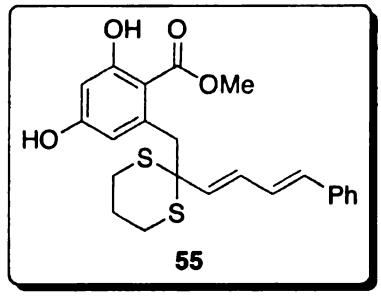


54

Preparation of (E)-Methyl 2,4-Dihydroxy-6-((2-(2-(trimethylstannyl)vinyl)-1,3-dithian-2-yl)methyl) benzoate: Pd_2dba_3 (0.02 mmol, 18.4 mg) and TFP (0.08 mmol, 18.6 mg) were added to THF (5 mL) and the resulting mixture was stirred at rt for 15 min. At that time, methyl 2-((2-ethynyl-1,3-dithian-2-yl)methyl)-4,6-dihydroxybenzoate (1 mmol, 0.324 g), Me_3SnF (1.5 mmol, 274 mg), PMHS (2.5 mmol, 0.15 mL), and TBAF (1 drop of a 1 M solution in THF (~0.008 mmol)) were added successively. The reaction was then allowed to stir at rt for 2 h, at which time the hydrostannation was complete by GC. At that time, the reaction was extracted with Et_2O and H_2O and the aqueous phase was back extracted with Et_2O. The combined organics were

dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by short silica gel chromatography (30%EtOAc/hexane) to afford the corresponding vinylstannane in 96% yield.

IR (KBr) 3365 (br), 2952, 2913, 2852, 1653, 1616, 1272, 1117 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 11.30 (s, 1 H), 6.22 (d, J = 18.8 Hz, 1 H), 5.59 (d, J = 18.8 Hz, 1 H), 3.85 (s, 3 H), 3.55 (s, 2 H), 2.73 (m, 2 H), 2.57 (m, 2 H), 1.96 (m, 1H), 1.81 (m, 1H), 0.09 (s, 9H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 171.7, 164.1, 160.1, 146.3, 139.0, 133.3, 114.0, 106.7, 102.8, 58.6, 51.5, 46.9, 27.5, 25.3, -9.6 ppm

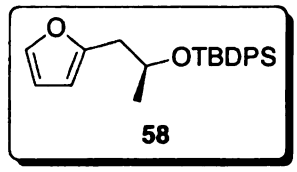


55

Preparation of Methyl 2,4-Dihydroxy-6-((2-((1E,3E)-4-phenylbuta-1,3-dienyl)-1,3-dithian-2-yl)methyl)benzoate: Pd_2dba_3 (0.002 mmol, 3.7 mg) and TFP (0.008 mmol, 9.3 mg) were added to THF (2 mL) and the resulting mixture was stirred at rt for 15 min. At that time, methyl 2-((2-ethynyl-1,3-dithian-2-yl)methyl)-4,6-dihydroxybenzoate (0.2 mmol, 65 mg), Me_3SnF (0.3 mmol, 55 mg), PMHS (0.5 mmol, 0.03 mL), and TBAF (1 drop of a 1 M solution in THF (~0.008 mmol)) were added successively. The reaction was then allowed to stir at rt for 2 h, at which time the hydrostannation was complete by TLC. The (E)-β-bromo styrene (0.04 mL, 0.3 mmol) and $Pd(PPh_3)_4$ (0.05 mmol, 7 mg) was then added and the mixture was allowed to reflux (~65 °C) until the cross-coupling was judged complete by TLC (8 h). At

that time, the reaction was diluted with saturated aq. KF (2 mL) and stirred for 0.5 h. The reaction was extracted with Et_2O and H_2O and the aqueous phase was back extracted with Et_2O. The combined organics were dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by silica gel chromatography to afford the product in 48% yield.

IR (KBr) 3363(br), 3023, 2163, 1656, 1249 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 11.20 (s, 1 H), 7.38 (d, J = 7.1 Hz, 2 H), 7.32 (t, J = 7.8 Hz, 2 H), 7.23 (m, 1 H), 6.78 (dd, J = 15.1, 10.5 Hz, 1 H), 6.56 (d, J = 15.6 Hz, 1 H), 6.47 (dd, J = 14.9, 10.5 Hz, 1 H), 6.38 (d, J = 2.5 Hz, 2 H), 5.61 (d, J = 15.3 Hz, 1 H), 3.85 (s, 3 H), 3.64 (s, 2 H), 2.90 (m, 2 H), 2.62 (m, 2 H), 2.01 (m, 1 H), 1.83 (m, 1 H) ppm.



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Preparation of (*S*)-*tert*-Butyl(1-(furan-2-yl)propan-2-yloxy)diphenylsilane: In a seal-tube were placed *tert*-butyl((S)-1-((2R,3R)-3-((Z)-2-iodovinyl)oxiran-2-yl)propan-2-yloxy)diphenylsilane (0.2 mmol, 99 mg), $Pd(PPh_3)_4$ (0.02 mmol, 23 mg) and *N,N*-diisopropylethylamine (0.4 mmol, 0.07 mL), and benzene (1 mL) were added. The reaction was stirred at 80 °C for 8 h. After TLC monitoring, the reaction was quenched with water. Extracted with EtOAc, then the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. Crude mixture was purified by column chromatography (10% EtOAc/hexane) to afford product in 62% yield.

IR (neat) 3070, 3048, 2957, 2929, 2857, 1427, 1111, 725 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.65 (m, 4 H), 7.39 (m, 6 H), 6.24 (s, 1 H), 5.94 (s, 1 H), 4.13 (m, 1 H), 2.82 (m, 1 H), 2.71 (m, 1 H), 1.02 (s, 9 H) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 153.2, 140.9, 135.9, 135.8, 134.6, 134.2, 129.5(2), 127.5(2), 110.1, 106.7, 68.7, 38.2, 26.9, 23.2, 19.1 ppm.

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