TITANIUM-CATALYZED ONE-POT MULTICOMPONENT COUPLING REACTIONS FOR DIRECT ACCESS TO HETEROCYCLES

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ABSTRACT

TITANIUM-CATALYZED ONE-POT MULTICOMPONENT COUPLING REACTIONS FOR DIRECT ACCESS TO HETEROCYCLES

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Titanium-catalyzed multicomponent reactions have been utilized in the synthesis of various heterocycles and natural products. In this research further applications of titanium-catalyzed multicomponent reactions towards the synthesis of nitrogen containing heterocycles are investigated.

The first part of the thesis discusses the development of novel titanium complexes bearing the 2-(2`-pyridyl)-3,5-dimethylpyrrole ancillary ligands. This novel titanium catalyst demonstrates the single step synthesis of 1,3-disubstituted pyrazoles can be prepared in a one-pot fashion from terminal alkyne, isonitrile, and monosubstituted hydrazines (Chapter 2).

Titanium-catalyzed 3-component coupling of an alkyne, isonitrile, and amine can be used to generate tautomers of 1,3-diimines. These diimines produced in situ undergo cyclization with hydroxylamine hydrochloride, glycine ethyl ester hydrochloride and malononitrile in a one-pot procedure to provide isoxazoles (Chapter 3), pyrrole-2-carboxylates (Chapter 4) and aminopyridines (Chapter 5) respectively. Finally substituted quinolines from the acid mediated cyclizations of diimines have also been synthesized. For their biological activity and inhibitions of the 20S proteasome of these substituted quinolines are currently under investigation (Chapter 6).

I dedicate this dissertation to my loving parents, Mrs. Anoma Dissanayake and Mr. Lionel Dissanayake for their continuous love and encouragement, and my dearly wife Dr. Hashini Galhena Dissanayake for her patience, sacrifice and the support

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KEY OF ABBREVIATIONS

dpma	*N*,*N*-di(pyrrolyl-α-methyl)-*N*-methylamine
dpm	5,5-dimethyldipyrrolylmethane
GC/FID	Gas Chromotography Flame Ionization Detector
TFA	trifluoroacetic acid
THF	tetrahydrofuran
RT	room temperature
EtOAc	ethyl acetate
3CC	three-component coupling
Bn	benzyl
DMF	*N*,*N*-dimethyl formamide
NMR	nuclear magnetic resonance
DMSO	dimethyl sulfoxide
M.p.	melting point

CHAPTER 1. INTRODUCTION TO MULTICOMPONENT COUPLING REACTIONS

1.1 Introduction to multicomponent coupling reactions

In organic synthesis, individual bonds are formed in a stepwise process. This process often involves isolation, purification of synthetic intermediates and modification of reaction conditions for the next synthetic steps. However, in ideal cases, synthetic target molecules are prepared from readily available materials in one simple, safe, resource-efficient and environmentally friendly operation, which proceeds quickly, and in quantitative yields (**Figure 1.1**).[1]

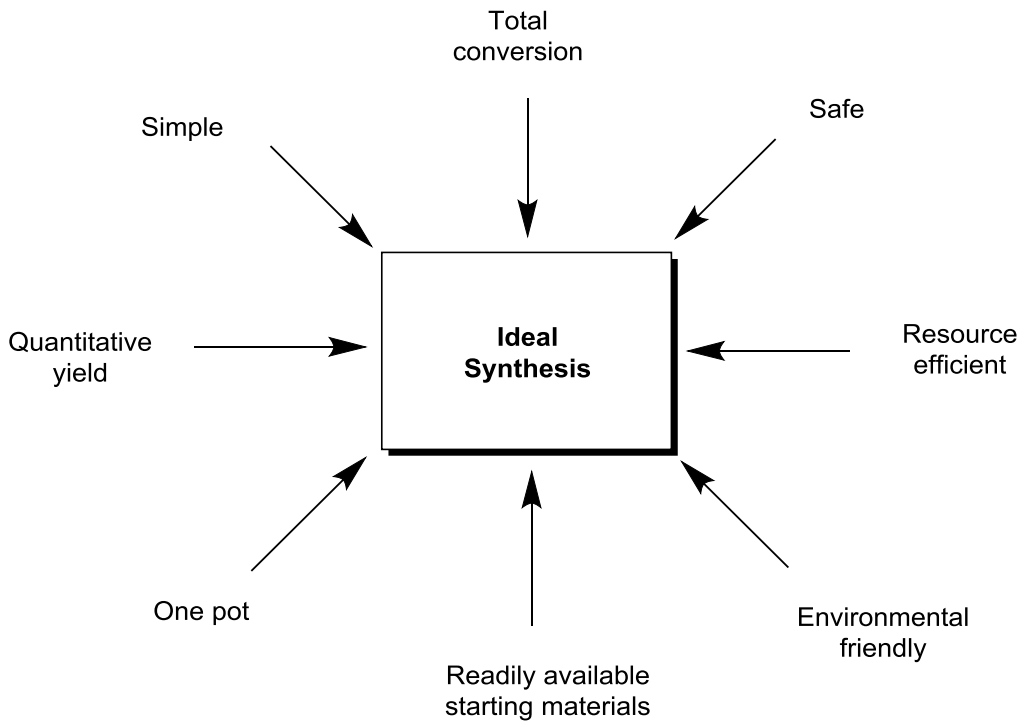


Figure 1.1 General aspects of the ideal synthesis

Over the past decades, it has been the aim of many groups to fulfill the requirements of the ideal synthesis by discovery and development of multistep, single operation processes for the construction of complex molecular scaffolds in simple manner. Multicomponent coupling reactions, are defined as "reactions in which more than two starting compounds react to form a product in such a way that the majority of the atoms of the starting material can be found in the product".[2]

Multicomponent coupling reactions are classified in to three main categories,

- **Type I :** In this category starting material, intermediates and products are always in a mobile equilibrium, in most cases the products occur as mixtures with the intermediates or starting materials (yields can vary from 0 to 100%).

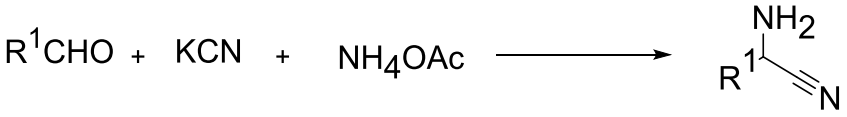
- **Type II :** In this category, elementary reactions are in equilibrium, and the last step is an irreversible reaction. An advantage of this type of reaction is the irreversible step shifts the reaction to the products side. Isocyanide-based MCRs often fall into this category due to irreversible oxidation of C^{II} to C^{IV}.

- **Type III :** When all the elementary sequences of the MCR are irreversible they fall in to type III category. Major driving forces of the irreversibility of the elementary reactions are attributed to the thermodynamic factors. Many biochemical pathways in living cells fall into the type III category.

Multicomponent reactions can also subcategorized in to two major classes based in starting materials used in the reaction.[3]

1. isocyanide-based multicomponent coupling reactions
2. nonisocyanide-based multicomponent coupling reactions

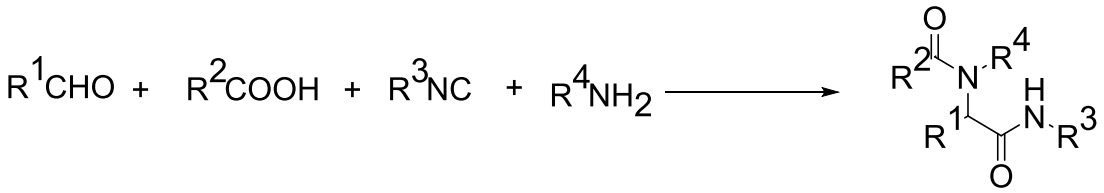
The first multicomponent coupling reaction was reported by Strecker in 1850 by the reaction of aldehydes with ammonia and cyanides to generate α-aminonitriles (**Scheme 1.1**).[4] After this report several name multicomponent reaction were developed by Biginelli (1891),[5] Hantzsch (1881),[6] Asinger (1958),[7] and Mannich (1912).[8] These new reactions led to easy access to a variety of heterocycles in very few steps for medicinal and pharmaceutical research.[9]



Scheme 1.1 Strecker reaction

The first isocyanide-based multicomponent coupling reaction was reported by Passerini in 1921 by the reaction of carbonyl, acid and an isonitrile to generate α-hydroxy carboxamides.[10] In 1959, Ivar Ugi further improved the Passerini reaction by replacement of the carbonyl functionality with an aldehyde (or ketone) and primary amine (**Scheme 1.2**).[11] Due to the high

exploratorary power of the Ugi 4CC reaction, currently it's the most famous and widely used multicomponent coupling reaction in the drug discovery and other applications.[12]



Scheme 1.2 Ugi 4-component reaction

1.2 Transition metal-catalyzed multicomponent coupling reactions

Transition-metal catalyzed reactions provide unique and potentially useful reaction types such as ligand substitution, oxidative addition/reductive elimination, migratory insertion, cycloaddition, and nucleophilic/electrophilic attack on ligands which cannot be accessed via traditional organic methodologies (**Figure 1.2**).[13] Therefore, the diverse reactivity of transition metal-catalyzed reactions results in unique and predictable reaction methodologies for organic and organometallic chemistry.

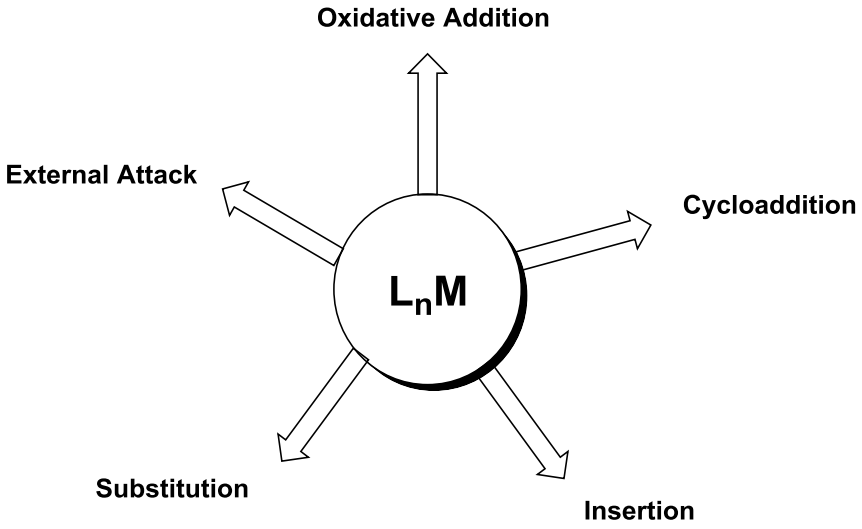
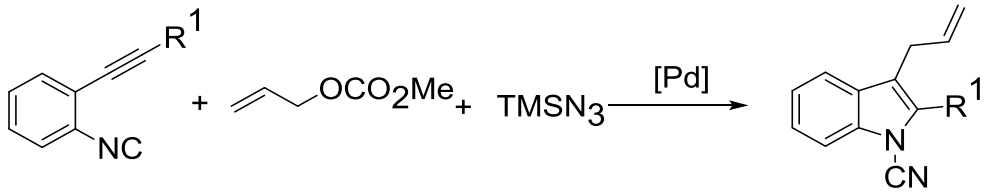


Figure 1.2 Diversity of transition-metal based reactions

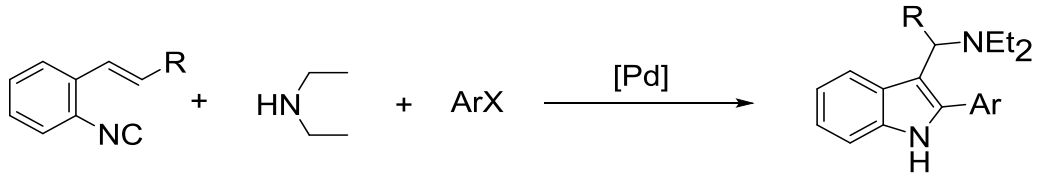
Over the past decade numerous transition metal-catalyzed reactions were developed using of palladium,[14] rhodium,[15] copper,[16] titanium,[17] nickel,[18] cobalt,[19] zirconium,[20] scandium,[21] hafnium,[22] bismith,[23] samarium,[24] silver[25] and other precious metals.[26] The other major advantage of transition metal-catalyzed reactions is the control of substitution pattern,

stereochemistry and skeleton of the expected product by varying the transition metal or the ligands around the metal. [27,28]



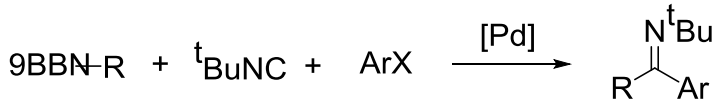
Scheme 1.3 Palladium-catalyzed 3-component syntheses of N-cyanoindoles

In 2001, Yamamoto and co-worker developed a palladium-mediated cyclization of 2-alkynylisocyanobenzenes with allyl methyl carbonate and trimethylsilylazide to generate N-cyanoindoles in good yields.[29] According to the authors, the reaction proceeds via a π-allylpalladium carbodiimide complex followed by isomerization to π-allylpalladium cyanamide complex (**Scheme 1.3)**.



Scheme 1.4 Palladium catalyzed 3-component syntheses of indoles

In 2002, Takahashi and co-workers reported the synthesis of substituted indoles via palladium-catalyzed multicomponent coupling from o-alkenylphenylisonitriles, aryl iodides, and secondary amines in poor to moderate yields (**Scheme 1.4**).[30]



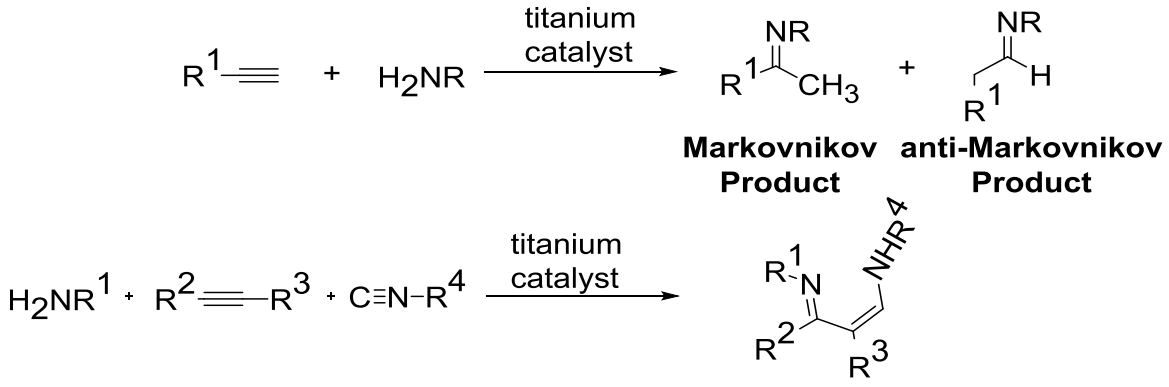
Scheme 1.5 Palladium-catalyzed 3-component syntheses of ketimines

Migita and co-workers (1986) also reporetd palladium-catalyzed iminocarbonylative cross-coupling reaction between 9-alkyl-9-BBN derivatives, *tert*-butylisocyanide, and arylhalides gives access to ketimine intermediates (**Scheme 1.5)**.[31] Upon hydrolysis of these intermediates, alkyl and aryl ketones can be generated. This observation was further developed by Whitby and co-workers to generate aromatic and heteroaromatic amidines.[32]

Apart from the above palladium-catalyzed isocyanide-based multicomponent coupling examples, our research group is engaged in titanium-catalyzed isocyanide-based multicomponent coupling reactions.

1.3 Odom group chemistry and diversity oriented synthesis (DOS)

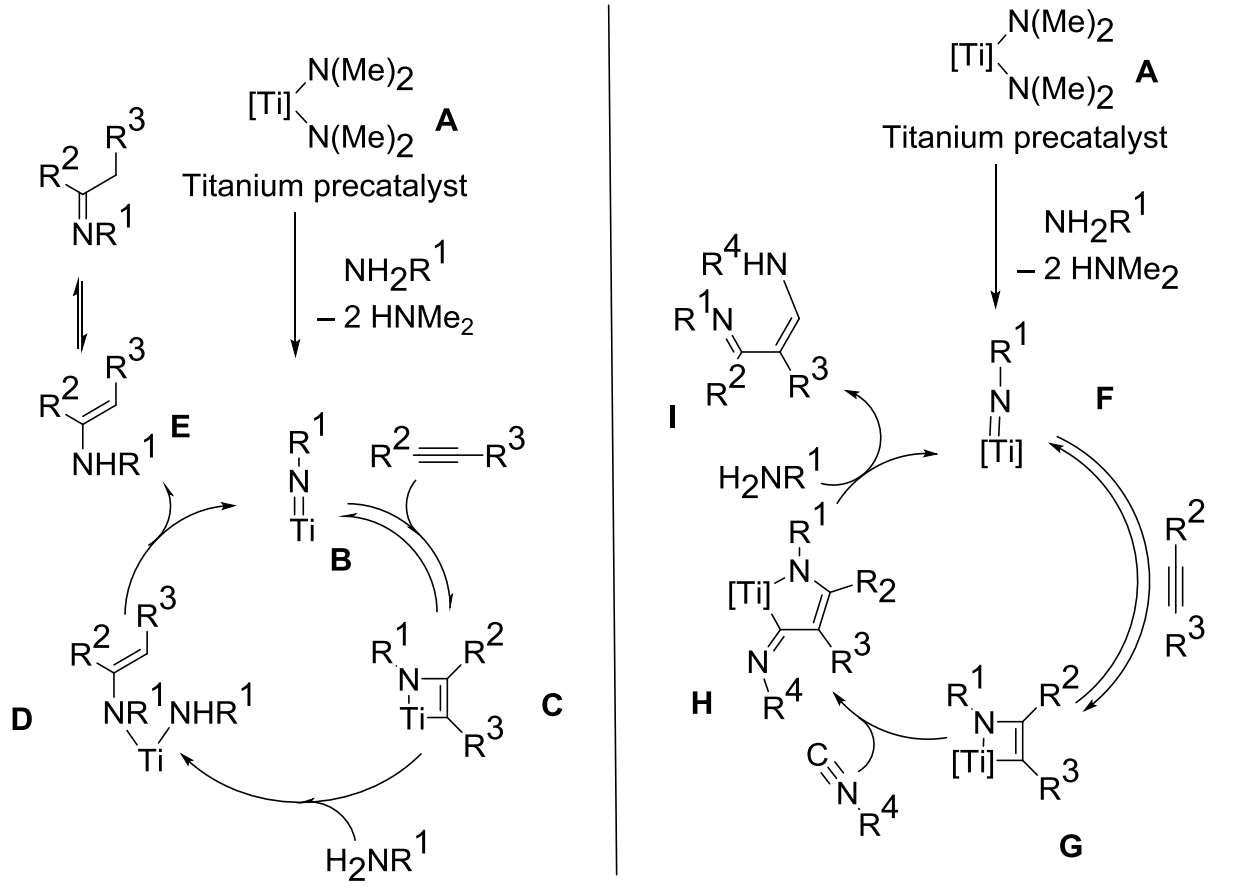
Hydroamination is the addition of amine N-H functional group to an unsaturated carbon-carbon bond in either an intramolecular or intermolecular fashion.[34] This process is 100% atom economical and generates imines from alkynes or amines from alkenes respectively. Our research group is the first to demonstrate the catalytic hydroamination of alkynes with primary amines from commercially available $Ti(NMe_2)_4$ (**Scheme 1.6)**. Even though the reaction was surprisingly fast, many substrates result in mixtures of Markovnikov and anti-Markovnikov products. This was overcome by incorporation of pyrrolyl-based ancillary ligands such as H_2dpma (*N*,*N*-di(pyrrolyl-α-methyl)-*N*-methylamine) and H_2dpm (5,5-dimethyl-dipyrrolylmethane) (more details in Chapter 3). [35]



Scheme 1.6 Titanium-catalyzed hydroamonation (top) and iminoamination (bottom)

The proposed mechanism for the above catalytic hydroamination is shown in **Scheme 1.7** (left). The dimethylamido ligands in the titanium precatalyst (**A**) are protolytically removed by

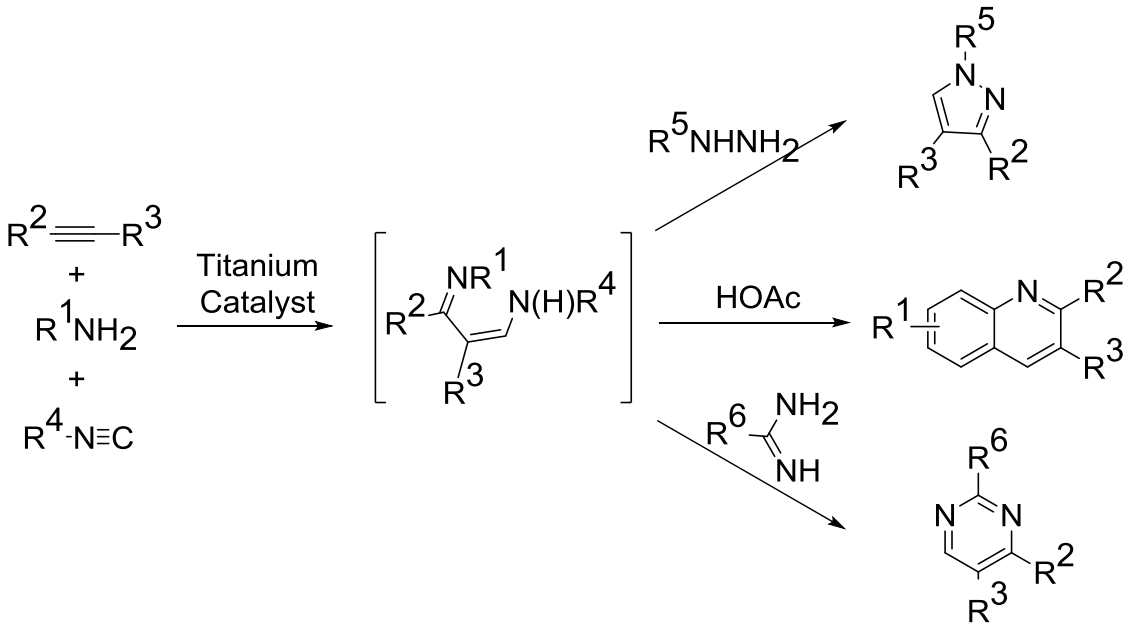
the primary amine substrate to generate titanium imido complexes (**B**) which can undergo [2 + 2]-cycloaddition with alkynes resulting an azatitanacyclobutene intermediate (**C**). Protonolysis of the metallacycle (**C**) is believed to form the intermediate (**D**), which is converted back to the titanium imido (**B**) with release of the hydroamination product (**E**).[36] Later on, catalytic hydroamination was extended to a multicomponent coupling reaction by incorporation of isonitriles to generate tautomers of 1,3-diimines (α,β-unsaturated-β-iminoamines).[37]



Scheme 1.7 Proposed mechanism for the titanium catalyzed hydroamination (left) and iminoamination (right) of alkynes

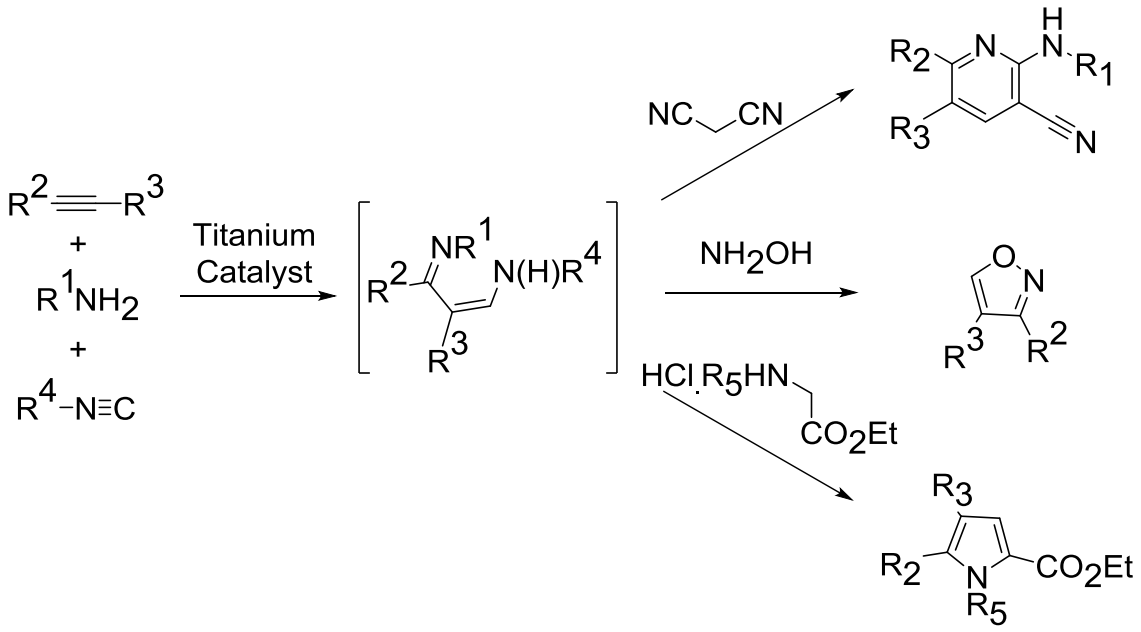
The multicomponent reaction used in this study is a formal alkyne iminoamination, addition of an iminyl and amine across the triple bond (**Scheme 1.7**). The proposed mechanism for the reaction is shown in **Scheme 1.7**. The titanium was introduced as a dimethylamido-containing precatalyst (**A**), the dimethylamido ligands are protolytically removed by the primary amine substrate to generate titanium imido complexes (**F**) which can undergo [2 + 2]-cycloaddition with alkynes. The resulting azatitanacyclobutenes (**G**) undergo 1,1-insertion of isonitriles to generate 5-membered metallacycles (**G**). The 5-membered metallacycles are protolytically converted back to titanium imido complex by primary amines with concomitant release of the iminoamination products (**I**).

Our group has reported utilization of 1,3-diimines from titanium-catalyzed 3-component coupling to generate various heterocycles. These diimines produced in situ undergo cyclization with hydrazine and amidine derivatives in a one-pot procedure to provide pyrazoles[38] and pyrimidines[39] respectively. The acid-mediated cyclizations of diimines have also been investigated and a variety of quinolines, benzoquinolines and other heterocyclic compounds were prepared in one-pot procedures (**Scheme 1.8)**.[40] These new one-pot multicomponent coupling methodologies have been applied to the synthesis of natural products such as withasomnine and angustureine.



Scheme 1.8 Heterocycles from titanium-catalyzed multicomponent reactions

In this work tautomers of 1,3-diimines generated via titanium-catalyzed 3-component coupling of an alkyne, isonitrile, and primary amine were converted to various heterocycles. These diimines produced in situ undergo cyclization with hydroxylamine hydrochloride, glycine ethyl ester hydrochloride and malononitrile in a one-pot procedure to provide isoxazoles (Chapter 3),[41] pyrrole-2-carboxylates (Chapter 4) and 2-amino-3-cyanopyridines (Chapter 5), respectively (**Scheme 1.9)**.



Scheme 1.9 Applications of titanium-catalyzed multicomponent reactions in this work

1.4 Diversity oriented synthesis (DOS) via multicomponent coupling reactions

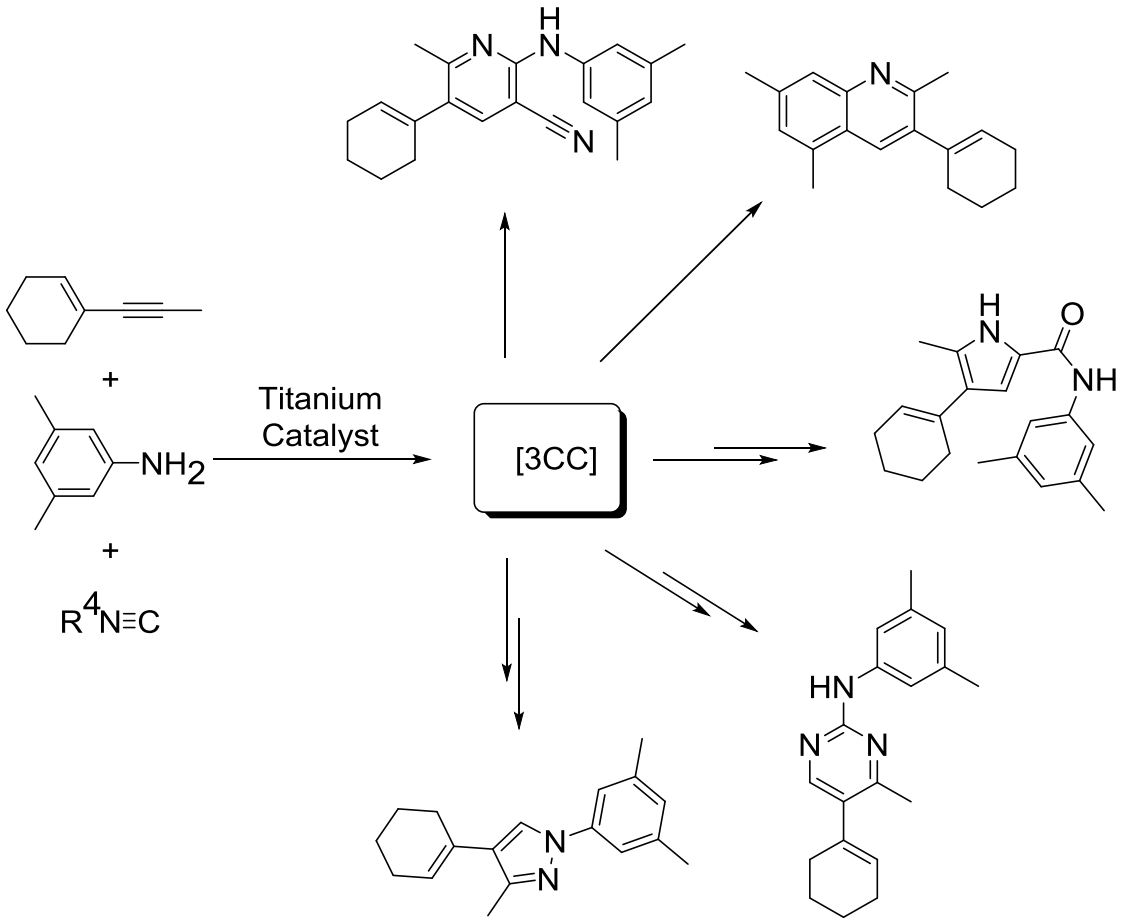
Diversity oriented synthesis continues to grow as an important aspect in synthetic organic chemistry and biological chemistry towards discovery of biologically active molecules.[42] The major aim of the DOS is to prepare a very large number of small molecules with different substitution patterns, stereochemistry and skeletons simultaneously from common substrates in as few steps as possible. Molecular diversity can be distinguished by three fundamental levels of diversity,

1) Appendage diversity

2) Stereochemical diversity

3) Scaffold diversity

Appendage diversity involves introduction of different appendages (functional groups) to a common molecular skeleton. Since all the compounds have the same molecular skeleton, this limits the broader aspects of diversity. Secondly, stereochemical diversity involves the generation of as many stereoisomers as possible of the same molecule. This can be achieved by chiral starting materials or changing the stereochemistry of the catalysis.[43]



Scheme 1.10 Scaffold diversity via titanium-catalyzed multicomponent reactions

Finally scaffold diversity is the most important approach in diversity oriented synthesis. This can be easily achieved by the generation of a collection of compounds with different molecular skeletons (scaffolds). Diverse molecular scaffolds can be generated by changing the reagents added to a common substrate (reagent-based approach)[44] or by use of different starting materials containing suitable pre-encoded skeletal information under similar reaction conditions to obtain different skeletal outcomes (substrate-based approach).[45]

Research from this work and previous work demonstrates that diverse molecular scaffold such as quinolines, pyrazoles, pyramidines, aminopyridines and pyrroles bearing similar appendages can be synthesized via our chemistry (**Scheme 1.10**). This can be easily achieved by post condensation of titanium-catalyzed multicomponent coupling product with appropriate reaction conditions. This elaborates the versatility of the titanium-catalyzed multicomponent coupling reactions towards synthesis of various heterocyclic scaffolds in simple one-pot procedures.

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CHAPTER 2. SINGLE-STEP SYNTHESIS OF PYRAZOLES USING TITANIUM CATALYSIS

2.1 Introduction

Pyrazoles are five-membered heterocycles consisting of a doubly unsaturated ring containing two adjacent nitrogen atoms.[1] These pyrazole core structures have attracted considerable attention in numerous applications over the past decade. A wide range of bioactivities such as anti-microbial,[2] anti-cancer,[3] anti-inflammatory,[4] anti-depressant,[5] anti-convulsant,[6] anti-hyperglycemic,[7] anti-pyretic,[8] anti-bacterial,[9] anti-fungal activities,[10] CNS regulants,[11] sedative-hypnotic activity,[12] and selective enzyme inhibitory activities[13] are found in pyrazole core structures (**Figure 2.1**). Furthermore pyrazoles are also found as ligands for transition metal-catalyzed reactions,[14] building blocks in heterocyclic synthesis,[15] optical brighteners,[16] UV stabilizers,[17] photoinduced electron-transfer systems,[18] and units in supramolecular entities.[19]

Classical methods for the synthesis of substituted pyrazole involve construction of two C-N bonds by cyclocondensation of hydrazines with 1,3-dicarbonyl compounds, or their 1,3-dielectrophile equivalent reagents or construction of one C-N and C-C bond by intermolecular [3+2] cycloaddition of 1,3-dipoles to dipolarophiles.[20] The disadvantage of these methods are the lack of availability of the 1,3-dielectrophilic and 1,3-dipole building blocks and that unsymmetrical starting materials often result in a mixture of regioisomeric pyrazoles in poor yields.

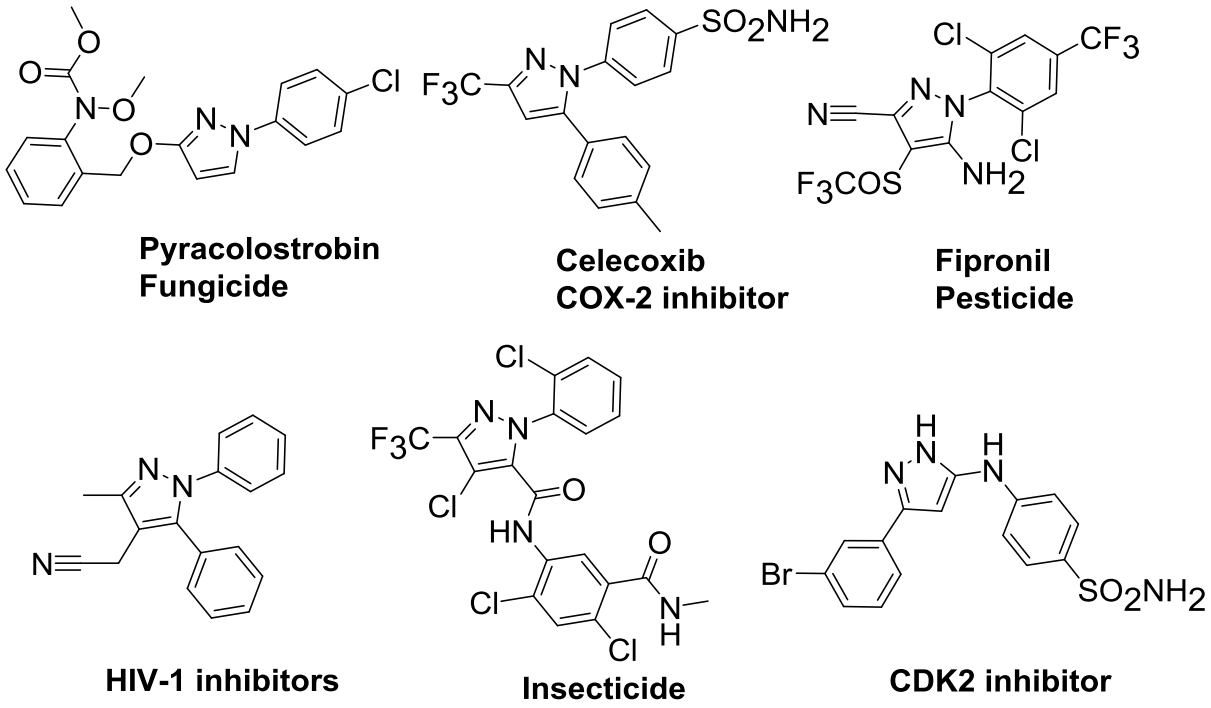
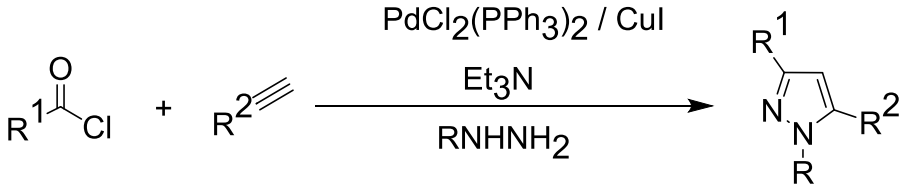


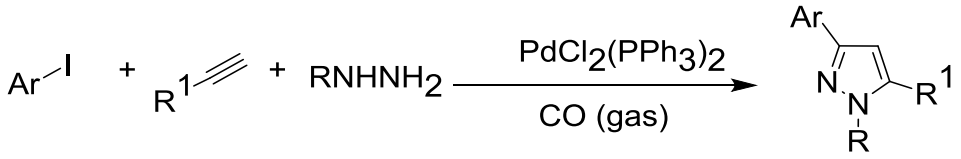
Figure 2.1 Bioactive substituted pyrazoles

In recent years, transition metal-catalyzed multicomponent one-pot reactions have attracted great interest in the synthesis of heterocyclic scaffolds in a small number of steps. This is a powerful tool for the construction of diverse chemical libraries of "drug-like' molecules in a short period of time by simply varying the reacting components.[21] In 2008, Jiang and co-workers[22] as well as Muller and co-workers[23] independently reported palladium-catalyzed 3-component coupling of acid chloride, terminal alkyne, and hydrazine to afford 1,3,5-trisubstituted pyrazoles in good yields (**Scheme 2.1**).



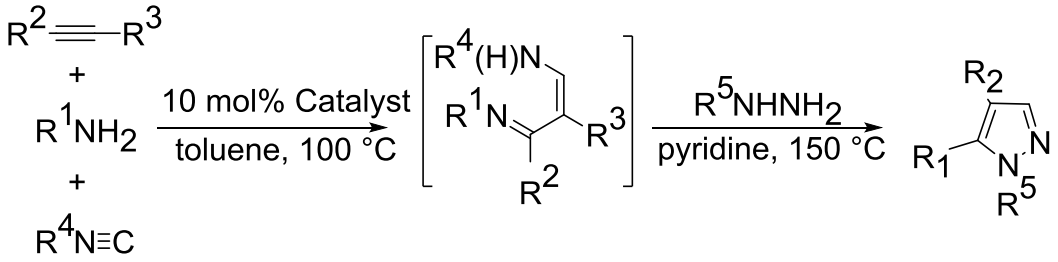
Scheme 2.1 Palladium-catalyzed 3-component coupling for pyrazole synthesis

A novel synthesis of 1,3,5-trisubstituted pyrazoles using palladium-catalyzed 4-component coupling of terminal alkyne, monosubstituted hydrazine, and aryl halide in presence of carbon monoxide was recently independently reported by the Mori group[24] and the Stonehouse group[25] (**Scheme 2.2**).



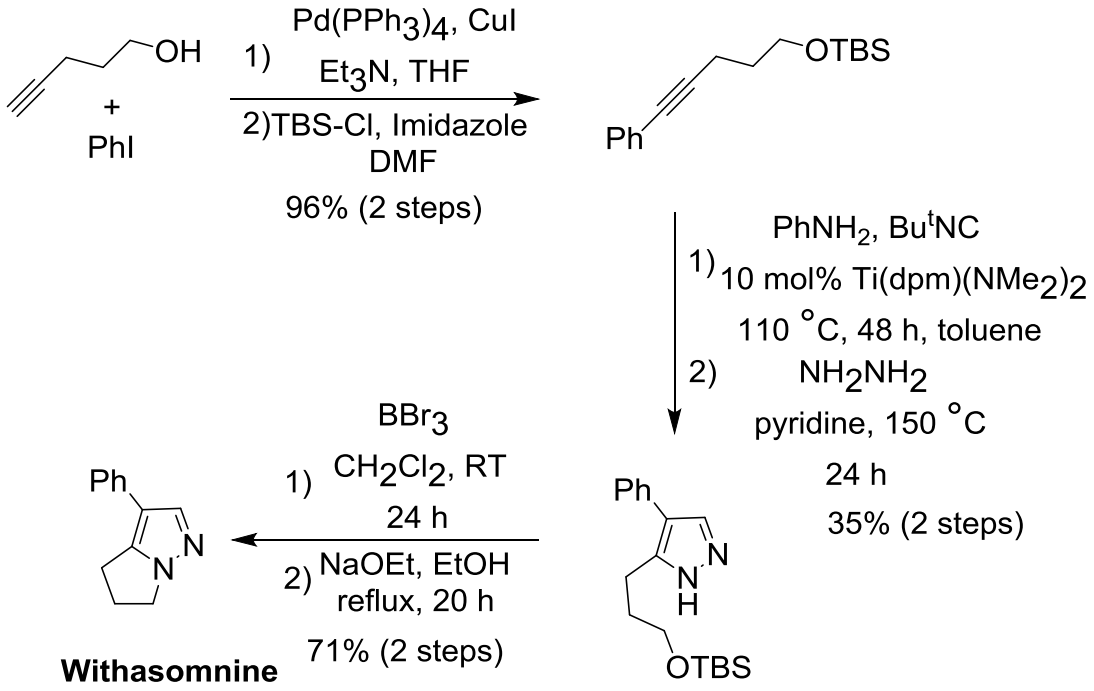
Scheme 2.2 One-pot palladium catalyzed 4-component synthesis of pyrazoles

In 2009 our group demonstrated that a variety of different pyrazoles can be prepared in a one-pot, 4-component fashion (**Scheme 2.3**).[26] This methodology uses a titanium-catalyzed catalyzed 3-component coupling of an alkyne, isonitrile, and primary amine to generate unsymmetrical 1,3-diimine tautomers followed by cyclo-condensation with commercially available hydrazines to afford 1,4,5-trisubstituted pyrazoles in moderate yields. This 4-component one-pot methodology was applied in the synthesis of natural product withasomnine in 24% overall yield from commercially available 4-pentyn-1-ol (**Scheme 2.4**).



Scheme 2.3 Titanium-catalyzed one-pot synthesis of pyrazoles

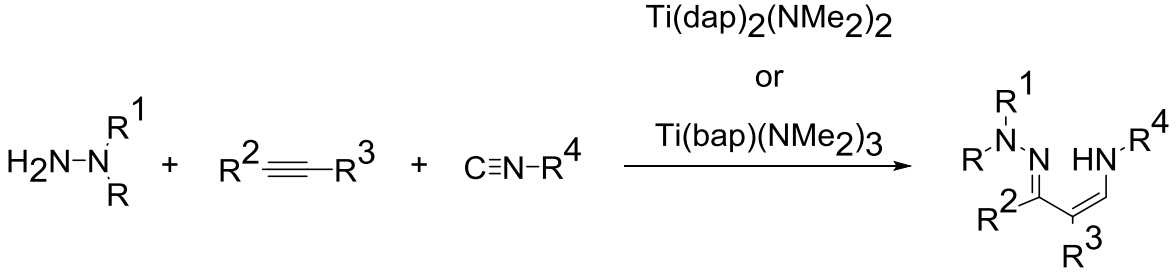
In this study reported in this thesis, we demonstrate that 1,3-disubstituted pyrazoles can be prepared in a one-pot fashion in a single step. The methodology uses a novel titanium-catalyzed 3-component coupling of terminal alkynes, isonitriles, and monosubstituted hydrazines to generate unsymmetrical 1,3-diimines, α,β-unsaturated β-iminoamines, which undergoes intermolecular cyclization, which results in substituted pyrazole products upon loss of a primary amine.[27]



Scheme 2.4 Synthesis of withasomnine

2.2 Results and Discussion

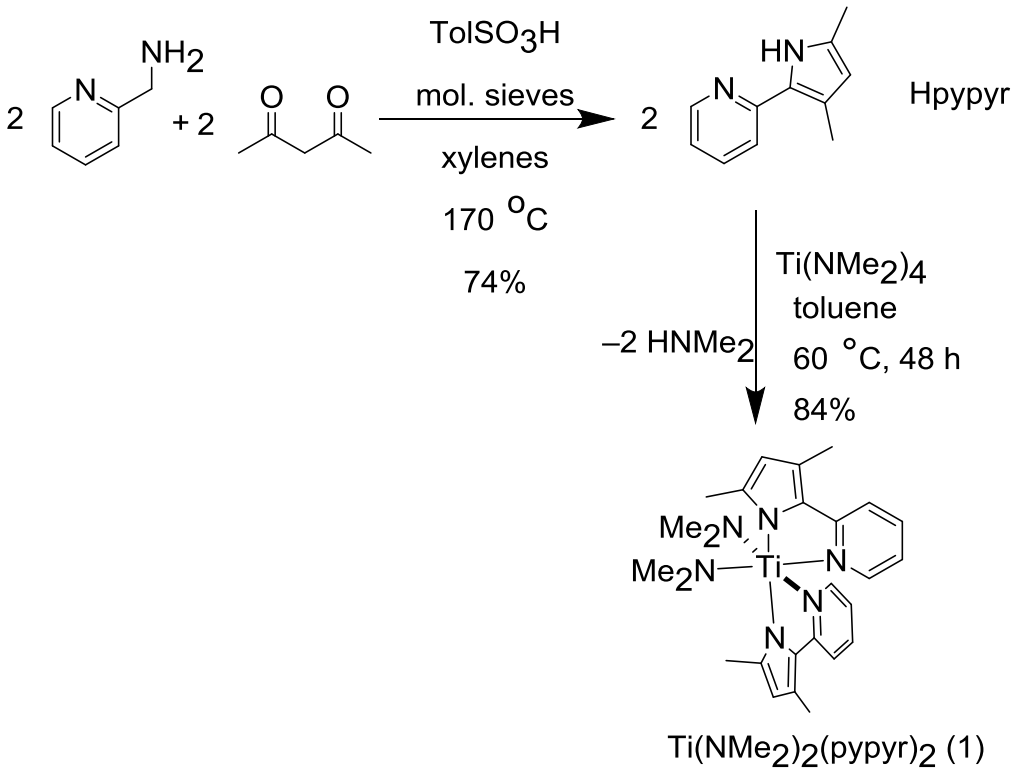
Our group demonstrated iminohydrazination of alkynes, isonitriles, and hydrazines to genate 1,3-iminohydrazones via titanium-catalysts in 2005.[26(b)] Unfortunately, that catalysis was limited to 1,1-disubstituted hydrazines as starting materials. The cause of the inactivity in some of the previous catalytic systems was the protolytic removal of all the ancillary ligands by more aggressive monsubstituted hydrazines (**Scheme 2.5**). The loss of the ancillaries likely leads to inactive bridged hydrazido complexes. These observations interest us to design and development of novel catalytic architecture for iminohydrazination of alkynes using monosubstitured hydrazines.



Scheme 2.5 Titanium-catalyzed iminohydrazination

For this study, we employed pyridylpyrrole-based catalysts.[27] These catalysts use ligand architectures synthesized in a single step from commercially available acetylacetone and 2-aminomethylpyridine. The 2-(2'-pyridyl)-3,5-dimethylpyrrole[29] (Hpypyr) ligands can be introduced on the titanium in good yields by reaction with commercially available $Ti(NMe_2)_4$ (**Scheme 2.6**). The catalyst described for this novel 3-component coupling reaction was

$Ti(NMe_2)_2(pypyr)_2$ (**1**) (**Figure 2.2**), which efficiently catalyzes the multicomponent coupling of terminal alkynes, isonitriles, and monosubstituted hydrazine to generate 1,3-iminohydrazones, which subsequently undergoes cyclization to provide pyrazoles in a single step.



Scheme 2.6 Synthesis of Hpypyr and $Ti(NMe_2)_2(pypyr)_2$ (**1**)[27]

The structure of this catalyst (**Figure 2.2**) was obtained from X-ray diffraction of the pseudo-octahedral complex **1**. The more strongly donating dimethylamido ligands are *trans* to the neutral pyridine donors, placing the pyrrolyl ligands mutually *trans*. As is typical, the Ti–

N(pyrrolyl) distances average 2.111(1) Å, significantly longer than the Ti–NMe_2 bonds, 1.910(2) Å. The Ti–N(pyridyl) distances average 2.260(2) Å.

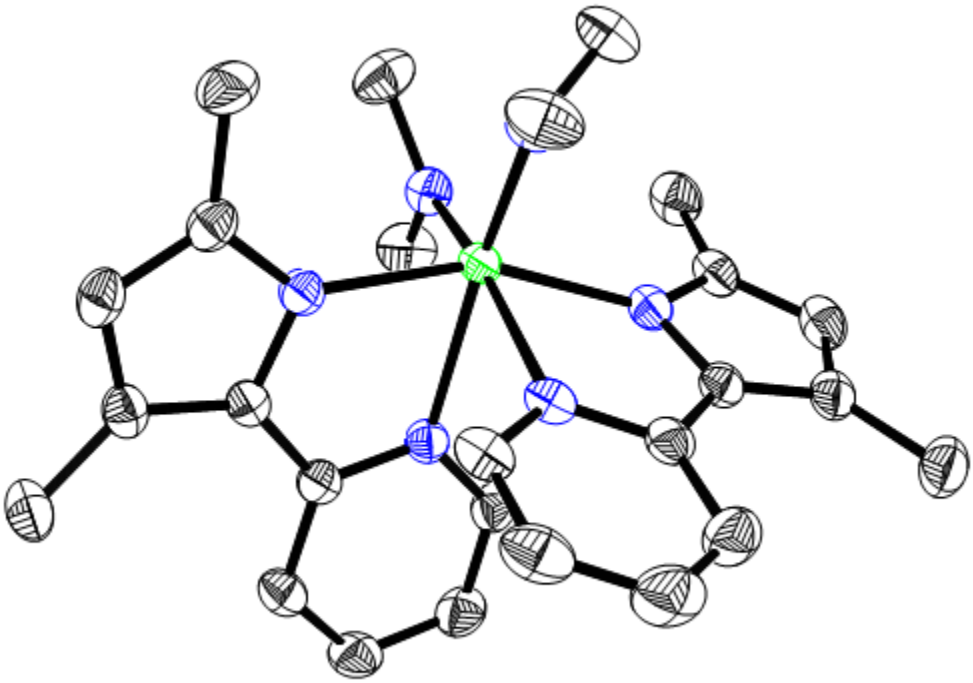
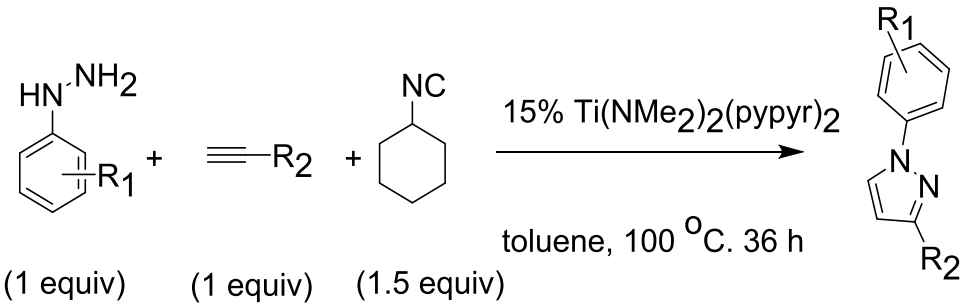


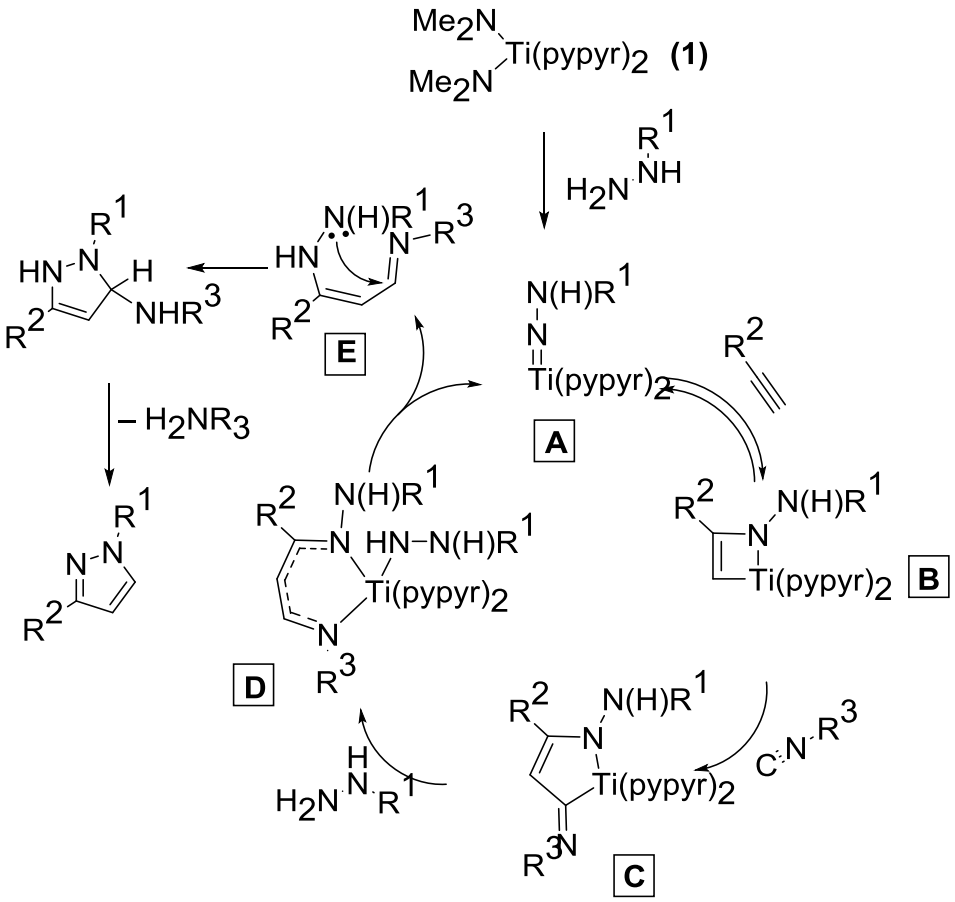
Figure 2.2 Structure of $Ti(NMe_2)_2(pypyr)_2$ (**1**) by X-ray diffraction[27] For interpretation of the references to color in this and all other figures, the reader is referred to the electronic version of this dissertation

Selected distances (Å) Ti(1)-N(5) 1.9081(15), Ti(1)-N(6) 1.9111(15), Ti(1)-N(3) 2.1025(14), Ti(1)-N(2) 2.1195(14), Ti(1)-N(1) 2.2559(14), Ti(1)-N(4) 2.2634(15). Selected angles (°) N(5)-Ti(1)-N(6) 104.45(6), N(5)-Ti(1)-N(3) 94.75(6), N(6)-Ti(1)-N(3) 98.76(6), N(5)-Ti(1)-N(2) 98.96(6), N(6)-Ti(1)-N(2) 95.51(6), N(3)-Ti(1)-N(2) 157.07(6), N(5)-Ti(1)-N(1)162.73(6)



Scheme 2.7. Optimized titanium-catalyzed one step synthesis of pyrazoles

In screening isonitriles, we used the coupling between phenylacetylene, phenylhydrazine, and CNR^3 catalyzed by **1**. The isonitriles investigated had R^3 = *tert*-butyl,2,6-dimethylphenyl, cyclohexyl, and *n*-butyl. While cyclohexylisonitrile gave relatively clean reactions, reactions employing 2,6-dimethylphenylisonitrile and *n*-butylisonitrile resulted in a myriad of unidentified products. On the other hand, the reaction with *tert*-butylisonitrile was relatively clean but did not proceed with as good conversions as the slightly smaller cyclohexyl derivative. Thus cyclohexyl isonitrile was used in all subsequent reactions.



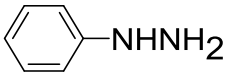
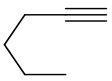
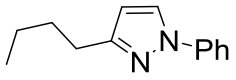
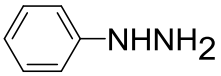
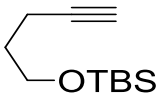
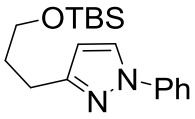
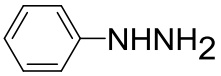
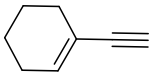
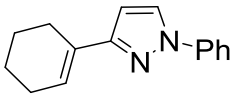
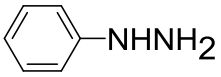
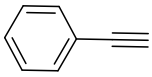
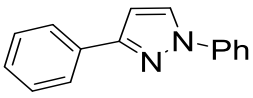
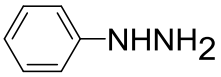
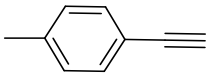
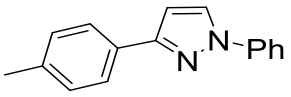
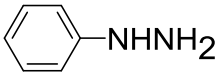
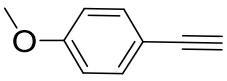
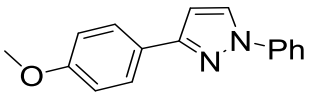
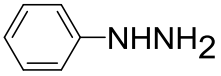
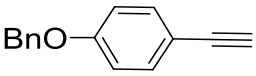
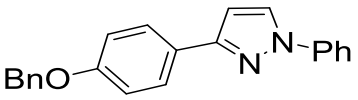
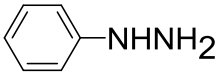
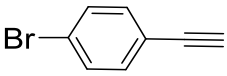
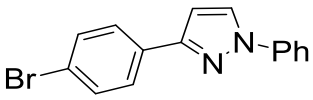
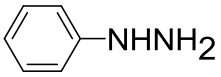
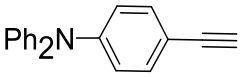
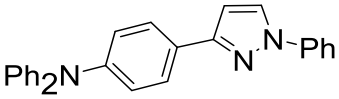
Scheme 2.8 Proposed catalytic cycle for the synthesis of pyrazoles

The proposed catalytic cycle for the titanium-catalyzed multicomponent coupling reaction is shown in **Scheme 2.8**. The dimethylamido ligands are protolytically removed by the monosubstituted hydrazine to generate titanium hydrazido(2–) complex **A**. The hydrazido(2–) complex **A** could then undergo [2 + 2]-cycloaddition with the alkyne to give intermediate **B**, Isonitrile can under go 1,1-insertion into the Ti–C bond in **B** to give the 5-membered metallacycle **C**. Hydrazine protonolysis of metallacycle **C** would give **D**; Proton migration from the hydrazido in **D** could liberate imine **E (**1,3-diimines or α,β-unsaturated-β-iminoamines) which would undergo intermolecular cyclization to afford the pyrazole product with loss of H_2NR^3.

The regioselectivity of the reactions are such that a single observable isomer is generated. For the substrates examined in this study, 1,3-disubstituted pyrazoles were the products. In other words, the favored product isomer is derived from [2 + 2]-cycloaddition to place the larger group on the alkyne (R^2) away from the metal center in metallacyclobutene **B** (**Scheme 2.8**).

The general procedure involves the addition of hydrazine (1 mmol), alkyne (1 mmol), isonitrile (1.5 mmol), to a 40 mL pressure tube containing catalyst **1** (15 mol%), in 2 mL of toluene to a under nitrogen, which was sealed and heated at 100 °C for 36 h with stirring. Once the multicomponent coupling reaction was complete, The products were purified by column chromatography on neutral alumina.

Table 2.1 Examples of pyrazoles syntheses using phenylhydrazine and a variety of alkynes *(***Scheme 2.7)** [27]

Entry	Hydrazene	Alkyne	Product	Isolated yieds
a				66%[a]
b				71%[a]
c				55%[a]
d				48%[a]
e				46%[a]
f				60%[a]
g				49%[a]
h				60%[a]
i				47%[a]

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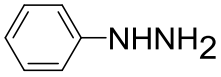
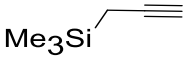
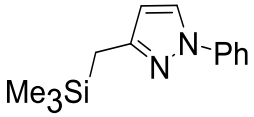
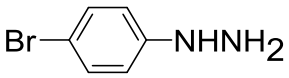
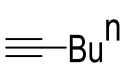
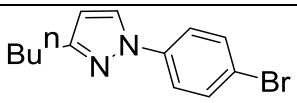
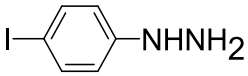
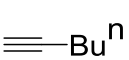
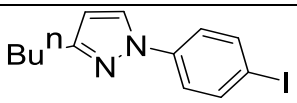
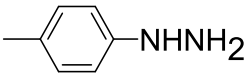
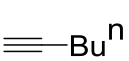
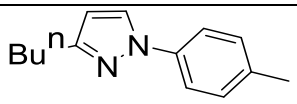
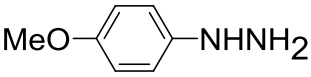
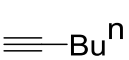
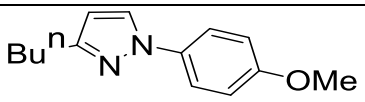
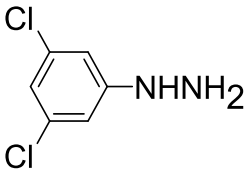
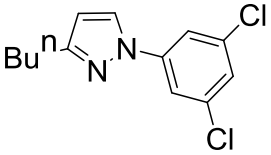
j				75% [a]

[a] Reactions carried out with phenylhydrazine, alkyne, and cyclohexylisonitrile in a 1:1:1.5 ratio with 15 mol % catalyst (**1)** at 100 °C for 36 h.

Some applications of the methodology are shown in Tables 2.1 and 2.2. For this initial study, we chose to look at the multicomponent coupling product of various terminal alkynes, phenylhydrazine**,** and cyclohexylisonitrile, which generated 1,3-disubstituted pyrazoles 2a-j in one-pot. In the second stage of the study (**Table 2.2**), a selection of different monosubstituted phenylhydrazines with hex-1-yne and cyclohexylisonitrile were examined, which generated 1,3-disubstituted pyrazoles 2k-o.

Table 2.2 Examples of pyrazoles syntheses using hex-1-yne and a variety of hydrazines (**Scheme 2.7**) [27]

Entry	Hydrazene	Alkyne	Product	Isolated yieds
k				52% [a]
l				62% [a]
m				57% [a]
n				70% [a]
o				45% [a]

[a] Reactions carried out with hydrazine, hex-1-yne, and cyclohexylisonitrile in a 1:1:1.5 ratio with 15 mol % catalyst (**1**) at 100 °C for 36 h.

2.3 Conclusion

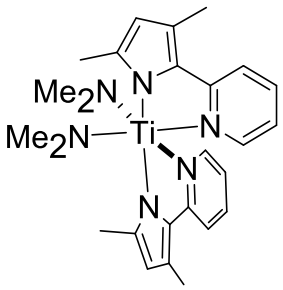
A novel titanium-catalyzed 3-component coupling of a monosubstuted hydrazine, a terminal alkyne, and cyclohexylisonitrile provides 1,3-disubstituted pyrazoles in a one-pot procedure. This new procedure has significant flexibility in the types of pyrazoles that can be accessed. The yields are generally modest, but the products are readily isolated by column chromatography in moderate yields.

The reaction has several points to allow optimization for a specific target of interest. For example, the catalyst architectures themselves are also quite flexible and could be optimized for specific products. In fact, it was found that multicomponent coupling reaction is very much slower for internal alkynes due to steric bulk of the methyl groups in the pyridylpyrrole ligands. Further Improvements in ligand design to expand the substrate scope and reduce heating times are currently under investigation.

2.4 Experimental

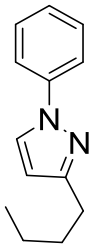
General procedure for Pyrazole Synthesis*:* All manipulations of air sensitive compounds were carried out in an MBraun drybox under a purified nitrogen atmosphere. Toluene was purified by sparging with dry N_2 and removing water by running through activated alumina systems purchased from Solv-Tek. ^{1}H and ^{13}C spectra were recorded on Varian VXR-500 spectrometers. Melting points were measured on a Mel-Temp II apparatus with a mercury thermometer and are uncalibrated. 2-(3,5-dimethyl-1H-pyrrol-2-yl)pyridine[29] and cyclohexylisonitrile[30] were made according to the literature procedures. Alkynes were purchased either from Aldrich or from GFS chemicals and were distilled from CaO under dry nitrogen. Phenylhydrazine was purchased from Aldrich, dried over KOH, and distilled under dry nitrogen. (4-bromophenyl)hydrazine, (4-iodophenyl)hydrazine, (4-methoxyphenyl)hydrazine, *p*-tolylhydrazine, and (3,5-dichlorophenyl)hydrazine were made using the typical literature procedure.[31] Neutral alumina was purchased from Sigma-Aldrich Co. and used as received. Hexanes and EtOAc was purchased from Mallinckrodt chemicals and used as received. Anhydrous NH_2NH_2 was prepared using the literature procedure.[32]

Preparation and characterization of titanium-catalyst (1)



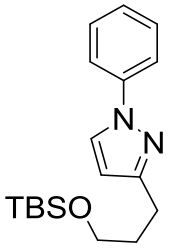
$Ti(NMe_2)_2(pypyr)_2$ (1):[27] A schlink flask (250 mL) loaded with $Ti(NMe_2)_4$ in toluene (6 mL) (2.11 g, 9.4 mmol) and cooled inside the cold-well in a dry box. To this solution was added a cold solution of 2-(3,5-dimethyl-1H-pyrrol-2-yl)pyridine (3.23 g, 18.8 mmol) in 8 mL of toluene. The resulting solution allowed to warm up to room temperature and stirred at 60 °C for 48 h. The reaction mixture was cooled to room temperature and volatiles were removed under reduced pressure. The resulting red solid was crystallized from ether/pentane solution mixture (3.92 g, 7.8 mmol) to give catalyst (**1**) in 84% yield. M.p.: 199-201 °C. ^1H NMR ($CDCl_3$, 500 MHz): 2.36 (6 H, s, CH_3), 2.57 (6 H, s, CH_3), 3.19 (12 H, s, $N(CH_3)_2$), 6.0 (2 H, s, 4-CH pyrrole), 6.43-6.46 (2 H, m, Ar-H), 6.99-7.01 (2 H, m, Ar-H), 7.19-7.21 (2 H, m, Ar-H), 7.27-7.31 (2 H, m, Ar-H), $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 14.65, 16.04, 47.66, 113.37, 116.01,116.50, 122.03, 132.53, 136.78, 140.92, 146.79, 154.06. Elemental Analysis: found: %C, 65.42; % H, 7.23; %N, 17.42; expected: %C, 65.27; %H, 7.16; %N, 17.56. Further characterized by X-ray diffraction studies.

Preparation and Characterization of Compounds in Table 2.1



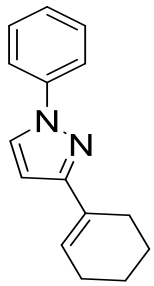
3-butyl-1-phenyl-pyrazole (Table 2.1, entry a):[27] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing $Ti(NMe_2)_2(pypyr)_2$ (71.7 mg, 0.15 mmol) in dry toluene (2 mL) was loaded with phenylhydrazine (108 mg, 1 mmol), hex-1-yne (82 mg, 1 mmol), and cyclohexylisonitrile (186 μL, 1.5 mmol), The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 36 h at 100 °C in a silicone oil bath**.** After completion of the reaction, the pressure tube was cooled to room temperature, and volatiles were removed under reduced pressure. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (132 mg, 66%) as a yellow oil.[33] ^{1}H NMR ($CDCl_3$, 500 MHz): 0.94 (3 H, t, *J* = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 1.39-1.43 (2 H, m, $CH_2CH_2CH_2CH_3$), 1.64-1.69 (2 H, m, $CH_2CH_2CH_2CH_3$), 2.71 (2 H, t, *J* = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 6.23-6.24 (1 H, d, *J* = 2 Hz, 4-C*H*-pyrazole), 7.18-7.23 (1 H, m, Ar-H), 7.38-7.41 (2 H, m, Ar-H), 7.62-7.64 (2 H, m, Ar-H), 7.79-7.78 (1 H, d, *J* = 2 Hz, 5-C*H*-pyrazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 13.89, 22.49, 28.10, 31.78, 106.39, 118.86, 125.82, 127.11, 129.29, 140.28, 155.37. MS(EI): *m/z* 200 (M^+).

Elemental Analysis: found: %C, 78.01; % H, 8.13; %N, 13.86; expected: %C, 77.96; %H, 8.05; %N, 13.99.



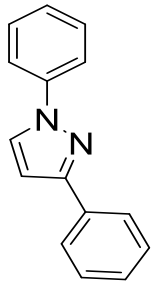
3-(3-(tert-butyldimethylsilyloxy)propyl)-1-phenyl-pyrazole (Table 2.1, entry b):[27] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing $Ti(NMe_2)_2(pypyr)_2$ (71.7 mg, 0.15 mmol) in dry toluene (2 mL) was loaded with phenylhydrazine (108 mg, 1 mmol), *tert*-butyldimethyl(pent-4-ynyloxy)silane (198 mg, 1 mmol), and cyclohexylisonitrile (186 μL, 1.5 mmol), The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 36 h at 100 °C in a silicone oil bath**.** After completion of the reaction, the pressure tube was cooled to room temperature, and volatiles were removed under reduced pressure. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (224 mg, 71%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 0.04 (6 H, s, Si-CH_3), 0.88 (9 H, s, Si-CMe_2CH_3), 1.90-1.93 (2 H, m, $CH_2CH_2CH_2OTBS$), 2.75-2.78 (2 H, t, J = 7.5 Hz, $CH_2CH_2CH_2OTBS$), 3.68-3.71 (2 H, t, J = 6 Hz, $CH_2CH_2CH_2OTBS$), 6.24-6.25 (1 H, d, J = 2 Hz, 4-C*H* pyrazole), 7.22-7.24 (1 H, m, Ar-*H*), 7.38-7.42 (2 H, m, Ar-*H*), 7.62-7.64 (2 H, m, Ar-*H*), 7.79-7.80 (1 H, d, J = 2 Hz, 5-C*H* pyrazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 1.01, 18.36, 24.73, 25.27, 25.94, 32.56, 62.64, 106.54, 118.86, 125.88, 127.18, 127.44, 129.32, 154.81.

MS(EI): *m/z* 316 (M^+). Elemental Analysis: found: %C, 68.41; % H, 8.86; %N, 8.48; expected: %C, 68.30; %H, 8.92; %N, 8.55.



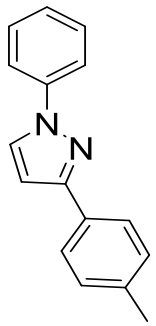
3-cyclohexenyl-1-phenyl-pyrazole (Table 2.1, entry b):[27] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing $Ti(NMe_2)_2(pypyr)_2$ (71.7 mg, 0.15 mmol) in dry toluene (2 mL) was loaded with phenylhydrazine (108 mg, 1 mmol), 1-ethynylcyclohex-1-ene (106 mg, 1 mmol), and cyclohexylisonitrile (186 μL, 1.5 mmol), The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 36 h at 100 °C in a silicone oil bath**.** After completion of the reaction, the pressure tube was cooled to room temperature, and volatiles were removed under reduced pressure. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (123 mg, 55%) as a yellow oil.[34] ^{1}H NMR ($CDCl_3$, 500 MHz): 1.63-1.67 (2 H, m, C*H*$_2$), 1.72-1.77 (2 H, m, C*H*$_2$), 2.17-2.21 (2 H, m, C*H*$_2$), 2.49-2.53 (2 H, m, C*H*$_2$), 6.35-6.37 (1 H, m, C*H*), 6.46-6.47 (1 H, d, *J* = 2 Hz, 4-C*H*-pyrazole), 7.18-7.36 (1 H, m, Ar-H), 7.37-7.41 (2 H, m, Ar-H), 7.64-7.66 (2 H, m, Ar-H), 7.79-7.80 (1 H, d, *J* = 2 Hz, 5-C*H*-pyrazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 22.32, 22.60, 25.54, 25.85, 103.79, 118.78, 125.33, 125.85, 127.19, 129.29, 130.56, 140.33, 154.97. MS(EI): *m/z* 224 (M^+).

Elemental Analysis: found: %C, 80.44; % H, 7.11; %N, 12.57; expected: %C, 80.32; %H, 7.17; %N, 12.49.



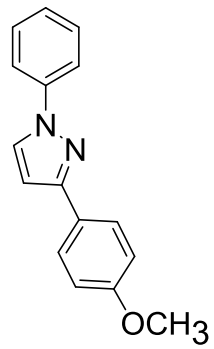
1,3-diphenyl-pyrazole (Table 2.1, entry d): [27] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing $Ti(NMe_2)_2(pypyr)_2$ (71.7 mg, 0.15 mmol) in dry toluene (2 mL) was loaded with phenylhydrazine (108 mg, 1 mmol), phenylacetylene (102 mg, 1 mmol), and cyclohexylisonitrile (186 μL, 1.5 mmol), The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 36 h at 100 °C in a silicone oil bath**.** After completion of the reaction, the pressure tube was cooled to room temperature, and volatiles were removed under reduced pressure. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (105 mg, 48%) as a yellow solid. M.p.: 83-84 °C (Lit M.p.: 84-86 °C).[35] ^{1}H NMR ($CDCl_3$, 500 MHz): 6.76-6.77 (1 H, d, *J* = 2 Hz, 4-C*H*-pyrazole), 7.26-7.29 (2 H, m, Ar-H), 7.31-7.34 (2 H, m, Ar-H), 7.40-7.47 (4 H, m, Ar-H), 7.75-7.77 (2 H, m, Ar-H), 7.90-7.92 (2 H, m, Ar-H), 7.93-7.94 (1 H, d, *J* = 2, Hz, 5-C*H*-pyrazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 104.97, 105.04, 119.03, 125.84, 126.31, 127.92, 128.41, 128.63, 133.13, 140.24, 152.92. MS(EI): *m/z* 220 (M^+).

Elemental Analysis: found: %C, 81.70; % H, 5.54; %N, 12.76; expected: %C, 81.79; %H, 5.49; %N, 12.72.



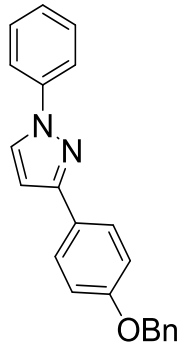
1-phenyl-3-p-tolyl-pyrazole (Table 2.1, entry e): [27] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing $Ti(NMe_2)_2(pypyr)_2$ (71.7 mg, 0.15 mmol) in dry toluene (2 mL) was loaded with phenylhydrazine (108 mg, 1 mmol), 1-ethynyl-4-methylbenzene (116 mg, 1 mmol), and cyclohexylisonitrile (186 μL, 1.5 mmol), The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 36 h at 100 °C in a silicone oil bath**.** After completion of the reaction, the pressure tube was cooled to room temperature, and volatiles were removed under reduced pressure. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (107 mg, 46%) as a yellow solid. M.p.: 92-94 °C (Lit M.p.: 95.5-96 °C).[36] ^{1}H NMR ($CDCl_3$, 500 MHz): 2.43 (3 H, s, CH_3), 6.78-6.79 (1 H, d, J = 4 Hz, 4-C*H* pyrazole), 7.27-7.32 (3 H, m, Ar-*H*), 7.47-7.52 (2 H, m, Ar-*H*), 7.79-7.87 (4 H, m, Ar-*H*), 7.97-7.98 (1 H, d, J = 4 Hz, 5-C*H* pyrazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 21.29, 104.82,

118.97, 125.51, 125.70, 126.18, 127.85, 129.32, 129.37, 130.30, 137.78, 152.96. MS(EI): *m/z* 234 (M^+). Elemental Analysis: found: %C, 81.96; % H, 6.05; %N, 11.99; expected: %C, 82.02; %H, 6.02; %N, 11.96.



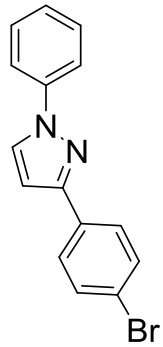
1-phenyl-4-(4-methoxyphenyl)pyrazole (Table 2.1, entry f): [27] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing $Ti(NMe_2)_2(pypyr)_2$ (71.7 mg, 0.15 mmol) in dry toluene (2 mL) was loaded with phenylhydrazine (108 mg, 1 mmol), 4-methoxyphenylacetylene (132 mg, 1 mmol), and cyclohexylisonitrile (186 μL, 1.5 mmol), The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 36 h at 100 °C in a silicone oil bath**.** After completion of the reaction, the pressure tube was cooled to room temperature, and volatiles were removed under reduced pressure. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (150 mg, 60%) as a yellow solid. M.p.: 100-102 °C (Lit M.p.: 103-104 °C).[37] ^{1}H NMR ($CDCl_3$, 500 MHz): 3.84 (3 H, s, OCH_3), 6.68-6.69 (1 H, d, J = 2.5 Hz, 4-C*H* pyrazole), 6.94-6.96 (2 H, d, J = 12 Hz, Ar-*H*), 7.24-7.27 (1 H, m, Ar-

H), 7.42-7.46 (2 H, m, Ar-*H*), 7.74-7.75 (2 H, d, J = 8.5 Hz, Ar-*H*), 7.82-7.85 (2 H, d, *J* = 12 Hz, Ar-*H*), 7.91-7.92 (1 H, d, J = 2.5 Hz, 5-C*H* pyrazole). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 55.32, 104.57, 114.03, 118.95, 125.89, 126.16, 127.09, 127.88, 129.38, 140.24, 152.75, 159.59. MS(EI): *m/z* 250 (M^+). Elemental Analysis: found: %C, 76.72; % H, 5.58; %N, 11.23; expected: %C, 76.78; %H, 5.54; %N, 11.19.



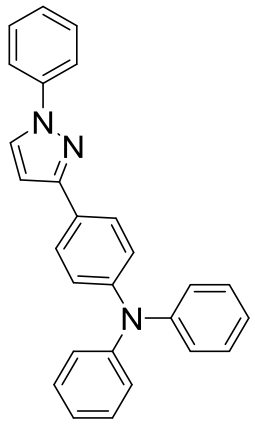
3-(4-(benzyloxy)phenyl)-1-phenyl-pyrazole (Table 2.1, entry g): [27] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing $Ti(NMe_2)_2(pypyr)_2$ (71.7 mg, 0.15 mmol) in dry toluene (2 mL) was loaded with phenylhydrazine (108 mg, 1 mmol), 1-(benzyloxy)-4-ethynylbenzene (208 mg, 1 mmol), and cyclohexylisonitrile (186 µL, 1.5 mmol), The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 36 h at 100 °C in a silicone oil bath**.** After completion of the reaction, the pressure tube was cooled to room temperature, and volatiles were removed under reduced pressure. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (122 mg, 49%) as a brown solid. M.p.: 116-118 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 5.13 (2 H, s, CH_2), 6.68-6.69 (1 H, d, J = 2.5 Hz, 4-C*H*

pyrazole), 7.03-7.04 (2 H, m, Ar-*H*), 7.26-7.28 (1 H, m, Ar-*H*), 7.33-7.37 (1 H, m, Ar-*H*), 7.37-7.43 (2 H, m, Ar-*H*), 7.43-7.46 (4 H, m, Ar-*H*), 7.74-7.76 (2 H, m, Ar-*H*), 7.82-7.85 (2 H, m, Ar-*H*), 7.91-7.92 (1 H, d, J = 2.5 Hz, 5-C*H* pyrazole). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 70.02, 104.58, 114.99, 118.92, 126.15, 127.10, 127.49, 127.88, 127.96, 128.57, 129.37, 136.92, 140.20, 152.69, 158.79. MS(EI): *m/z* 326 (M^+). Elemental Analysis: Found (Expected): %C, (80.96) 80.82; %H, (5.56) 5.72; %N, (8.58) 8.66. Elemental Analysis: found: %C, 80.89; % H, 5.59; %N, 8.62; expected: %C, 80.96; %H, 5.56; %N, 8.58.



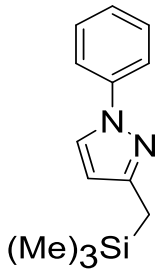
3-(4-bromophenyl)-1-phenyl-pyrazole (Table 2.1, entry h): [27] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing $Ti(NMe_2)_2(pypyr)_2$ (71.7 mg, 0.15 mmol) in dry toluene (2 mL) was loaded with phenylhydrazine (108 mg, 1 mmol), 1-bromo-4-ethynylbenzene (181 mg, 1 mmol), and cyclohexylisonitrile (186 μL, 1.5 mmol), The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 36 h at 100 °C in a silicone oil bath**.** After completion of the reaction, the pressure tube was cooled to room temperature, and volatiles were removed under reduced pressure. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which

afforded the desired compound (179 mg, 60%) as a brown solid. M.p.: 124-126 °C (Lit M.p.: 128 °C).[38] ^{1}H NMR ($CDCl_3$, 500 MHz): 6.73-6.74 (1 H, d, J = 2.5 Hz, 4-C*H* pyrazole), 7.24-7.27 (1 H, m, Ar-*H*), 7.44-7.47 (2 H, m, Ar-*H*), 7.53-7.54 (2 H, m, Ar-*H*), 7.73-7.78 (4 H, m, Ar-*H*), 7.93-7.94 (1 H, d, J = 2.5 Hz, 5-C*H* pyrazole). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 104.95, 114.06, 119.08, 125.96, 126.52, 127.35, 127.91, 128.18, 129.13, 129.45, 131.75. MS(EI): *m/z* 299 (M^+). Elemental Analysis: found: %C, 59.84; % H, 3.62; %N, 9.51; expected: %C, 60.22; %H, 3.71; %N, 9.36.



N,N-diphenyl-4-(1-phenyl-pyrazol-3-yl)aniline (Table 2.1, entry i):[27] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing $Ti(NMe_2)_2(pypyr)_2$ (71.7 mg, 0.15 mmol) in dry toluene (2 mL) was loaded with phenylhydrazine (108 mg, 1 mmol), 4-ethynyl-N,N-diphenylaniline (269 mg, 1 mmol), and cyclohexylisonitrile (186 µL, 1.5 mmol), The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 36 h at 100 °C in a silicone oil bath**.** After completion of the reaction, the pressure tube was cooled to room temperature, and volatiles were removed under reduced pressure. Purification was accomplished by column chromatography on neutral alumina. The eluent was

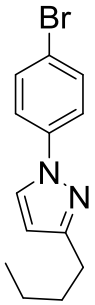
hexanes:ethyl acetate 9:1, which afforded the desired compound (182 mg, 47%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 6.63-6.64 (1 H, d, J = 2.5 Hz, 4-C*H* pyrazole), 6.94-6.97 (2 H, m, Ar-*H*), 7.05-7.07 (6 H, m, Ar-*H*), 7.17-7.21 (7 H, m, Ar-*H*), 7.37-7.39 (2 H, m, Ar-*H*), 7.67-7.71 (4 H, m, Ar-*H*), 7.86-7.87 (1 H, d, J = 2.5 Hz, 5-C*H* pyrazole). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 104.74, 114.07, 118.90, 122.87, 123.88, 124.35, 125.97, 127.38, 127.92, 129.24, 129.39, 139.27, 140.22, 147.64, 152.70. MS(EI): *m/z* 387 (M^+). Elemental Analysis: found: %C, 83.74; % H, 5.32; %N, 10.94; expected: %C, 83.69; %H, 5.46; %N, 10.85.



1-phenyl-3-((trimethylsilyl)methyl)-pyrazole (Table 2.1, entry j): [27] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing $Ti(NMe_2)_2(pypyr)_2$ (71.7 mg, 0.15 mmol) in dry toluene (2 mL) was loaded with phenylhydrazine (108 mg, 1 mmol), trimethyl(prop-2-ynyl)silane (112 mg, 1 mmol), and cyclohexylisonitrile (186 μL, 1.5 mmol), The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 36 h at 100 °C in a silicone oil bath**.** After completion of the reaction, the pressure tube was cooled to room temperature, and volatiles were removed under reduced pressure. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (172 mg, 75%) as a yellow oil. ^{1}H NMR

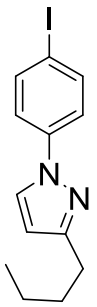
($CDCl_3$, 500 MHz): 0.07 (9H, s, Si-CH_3), 2.15 (2 H, 2, CH_2), 6.09-6.10 (1 H, d, J = 2 Hz, 4-C*H* pyrazole), 7.18-7.23 (1 H, m, Ar-*H*), 7.37-7.41 (2 H, m, Ar-*H*), 7.61-7.64 (2 H, m, Ar-*H*), 7.75-7.76 (1 H, d, J = 2 Hz, 5-C*H* pyrazole). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): -1.65, 18.44, 106.84, 118.52, 125.48, 126.92, 129.24, 129.45, 140.29, 152.63. MS(EI): *m/z* 230 (M^+). Elemental Analysis: found: %C, 67.54; % H, 7.79; %N, 12.33; expected: %C, 67.77; %H, 7.88; %N, 12.16.

Preparation and Characterization of Compounds in Table 2.2



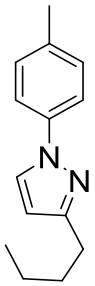
1-(4-bromophenyl)-3-butyl-pyrazole (Table 2.2, entry k): [27] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing $Ti(NMe_2)_2(pypyr)_2$ (71.7 mg, 0.15 mmol) in dry toluene (2 mL) was loaded with (4-bromophenyl)hydrazine (187 mg, 1 mmol), hex-1-yne (82 mg, 1 mmol), and cyclohexylisonitrile (186 μL, 1.5 mmol), The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 36 h at 100 °C in a silicone oil bath**.** After completion of the reaction, the pressure tube was cooled to room temperature, and volatiles were removed under reduced pressure. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (145 mg, 52%) as a brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 0.94 (3 H, t, *J* = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 1.38-1.42 (2 H, m, $CH_2CH_2CH_2CH_3$), 1.64-1.69 (2 H, m, $CH_2CH_2CH_2CH_3$), 2.68 (2 H, t, *J* = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 6.24-6.25 (1 H, d, *J* = 2 Hz, 4-C*H*-pyrazole), 7.51-7.53 (4 H, m, Ar-H), 7.75-7.76 (1 H, d, *J* = 2 Hz, 5-C*H*-pyrazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz):13.90, 22.49, 28.07, 29.69, 31.69, 106.92, 11.87, 120.20,

127.03, 132.32, 139.26, 155.78. MS(EI): *m/z* 279 (M^+). Elemental Analysis: found: %C, 56.04; % H, 5.63; %N, 10.18; expected: %C, 55.93; %H, 5.72; %N, 10.03.



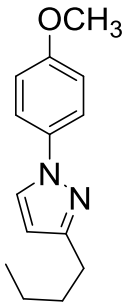
3-butyl-1-(4-iodophenyl)-pyrazole (Table 2.2, entry l):[27] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing $Ti(NMe_2)_2(pypyr)_2$ (71.7 mg, 0.15 mmol) in dry toluene (2 mL) was loaded with (4-iodophenyl)hydrazine (234 mg, 1 mmol), hex-1-yne (82 mg, 1 mmol), and cyclohexylisonitrile (186 μL, 1.5 mmol), The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 36 h at 100 °C in a silicone oil bath**.** After completion of the reaction, the pressure tube was cooled to room temperature, and volatiles were removed under reduced pressure. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (202 mg, 62%) as a brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 0.93 (3 H, t, *J* = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 1.36-1.43 (2 H, m, $CH_2CH_2CH_2CH_3$), 1.62-1.69 (2 H, m, $CH_2CH_2CH_2CH_3$), 2.68 (2 H, t, *J* = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 6.24-6.25 (1 H, d, *J* = 2.5 Hz, 4-C*H*-pyrazole), 7.39-7.42 (2 H, m, Ar-H), 7.69-7.71 (2 H, m, Ar-H), 7.76-7.77 (1 H, d, *J* = 2.5 Hz, 5-C*H*-pyrazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 13.90, 22.49, 28.07, 29.69, 89.62,

106.96, 120.45, 126.95, 138.26, 139.92, 155.82. MS(EI): *m/z* 326 (M^+). Elemental Analysis: found: %C, 47.58; % H, 4.73; %N, 8.72; expected: %C, 47.87; %H, 4.64; %N, 8.59.



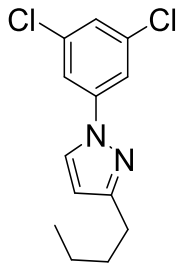
3-butyl-1-p-tolyl-pyrazole (Table 2.2, entry m): [27] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing $Ti(NMe_2)_2(pypyr)_2$ (71.7 mg, 0.15 mmol) in dry toluene (2 mL) was loaded with *p*-tolylhydrazine (122 mg, 1 mmol), hex-1-yne (82 mg, 1 mmol), and cyclohexylisonitrile (186 μL, 1.5 mmol), The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 36 h at 100 °C in a silicone oil bath**.** After completion of the reaction, the pressure tube was cooled to room temperature, and volatiles were removed under reduced pressure. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (122 mg, 57%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 0.93 (3 H, t, *J* = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 1.36-1.43 (2 H, m, $CH_2CH_2CH_2CH_3$), 1.62-1.69 (2 H, m, $CH_2CH_2CH_2CH_3$), 2.35 (3 H, s, CH_3), 2.70 (2 H, t, *J* = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 6.21-6.22 (1 H, d, *J* = 2.5 Hz, 4-C*H*-pyrazole), 7.18-7.20 (2 H, d, J = 8.5 Hz, Ar-H), 7.50-7.52 (2 H, d, J = 8.5 Hz, Ar-H), 7.74-7.75 (1 H, d, *J* = 2.5 Hz, 5-C*H*-pyrazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125

MHz): 13.19, 20.86, 22.52, 28.10, 31.85, 106.05, 118.86, 127.08, 129.80, 135.56, 138.05, 155.06. MS(EI): *m/z* 214 (M^+). Elemental Analysis: found: %C, 78.23; % H, 8.64; %N, 13.13; expected: %C, 76.46; %H, 8.47; %N, 13.07.



3-butyl-1-(4-methoxyphenyl)-pyrazole (Table 2.2, entry n): [27] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing $Ti(NMe_2)_2(pypyr)_2$ (71.7 mg, 0.15 mmol) in dry toluene (2 mL) was loaded with (4-methoxyphenyl)hydrazine (138 mg, 1 mmol), hex-1-yne (82 mg, 1 mmol), and cyclohexylisonitrile (186 μL, 1.5 mmol), The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 36 h at 100 °C in a silicone oil bath**.** After completion of the reaction, the pressure tube was cooled to room temperature, and volatiles were removed under reduced pressure. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (161 mg, 70%) as a brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 0.93 (3 H, t, *J* = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 1.39-1.41 (2 H, m, $CH_2CH_2CH_2CH_3$), 1.62-1.69 (2 H, m, $CH_2CH_2CH_2CH_3$), 2.69 (2 H, t, *J* = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 3.81 (3 H, s, OCH_3), 6.20-6.21 (1 H, d, *J* = 2.5 Hz, 4-C*H*-pyrazole), 6.91-6.93 (2 H, d, J = 9 Hz, Ar-H), 7.51-7.53 (2

H, d, J = 9 Hz, Ar-H), 7.74-7.75 (1 H, d, *J* = 2.5 Hz, 5-C*H*-pyrazole). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 13.93, 22.53, 28.07, 31.89, 55.54, 105.88, 114.41, 120.63, 127.26, 154.92, 157.84. MS(EI): *m/z* 230 (M^+). Elemental Analysis: found: %C, 73.19; % H, 7.62; %N, 12.30; expected: %C, 73.01; %H, 7.88; %N, 12.16.



3-butyl-1-(3,5-dichlorophenyl)-pyrazole (Table 2.2, entry o):[27] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing $Ti(NMe_2)_2(pypyr)_2$ (71.7 mg, 0.15 mmol) in dry toluene (2 mL) was loaded with (3,5-dichlorophenyl)hydrazine (177 mg, 1 mmol), hex-1-yne (82 mg, 1 mmol), and cyclohexylisonitrile (186 μL, 1.5 mmol), The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 36 h at 100 °C in a silicone oil bath**.** After completion of the reaction, The pressure tube was cooled to room temperature, and volatiles were removed under reduced pressure. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (121 mg, 45%) as a brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 0.93 (3 H, t, *J* = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 1.36-1.41 (2 H, m, $CH_2CH_2CH_2CH_3$), 1.62-1.66 (2 H, m, $CH_2CH_2CH_2CH_3$), 2.69 (2 H, t, *J* = 7.5 Hz, $CH_2CH_2CH_2CH_3$), 6.24-6.25 (1 H, d, *J* = 2 Hz, 4-C*H*-pyrazole), 7.15-7.16 (1 H, m, Ar-H), 7.54-7.55 (2 H, m, Ar-H), 7.72-7.73 (1 H, d, *J* =

2 Hz, 5-C*H*-pyrazole). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 13.84, 22.41, 27.98, 31.48, 107.56, 116.82, 125.36, 127.06, 135.65, 141.51, 156.29. MS(EI): *m/z* 269 (M^+). Elemental Analysis: found: %C, 58.19; % H, 5.11; %N, 10.69; expected: %C, 58.01; %H, 5.24; %N, 10.41.

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CHAPTER 3. REGIOSELECTIVE CONVERSION OF ALKYNES TO 4-SUBSTITUTED AND 3,4-DISUBSTITUTED ISOXAZOLES USING TITANIUM-CATALYZED MULTICOMPONENT COUPLING REACTIONS

3.1 Introduction

Isoxazoles (1,2-oxazoles) are five-membered aromatic heterocycles containing adjacent oxygen and nitrogen atoms in the ring.[1] The isoxazole core structure is found in many natural products such as ibotenic acid, muscimol, cloxacillin and medicinally useful compounds (**Figure 3.1)**.[2] Typical biological uses of these compounds includes selective agonists of human cloned dopamine D4 receptors,[3] $GABA_A$ antagonist (Broxaterol),[4] analgesic,[5] antiinflammatory (Valdecoxid),[5] ulcerogenic,[5] antimicrobial (Sulfamethoxazole),[6] antifungal,[6] COX-2 inhibitory,[7] antithrombotic,[8] antinociceptive,[9] and anticancer activity.[10]

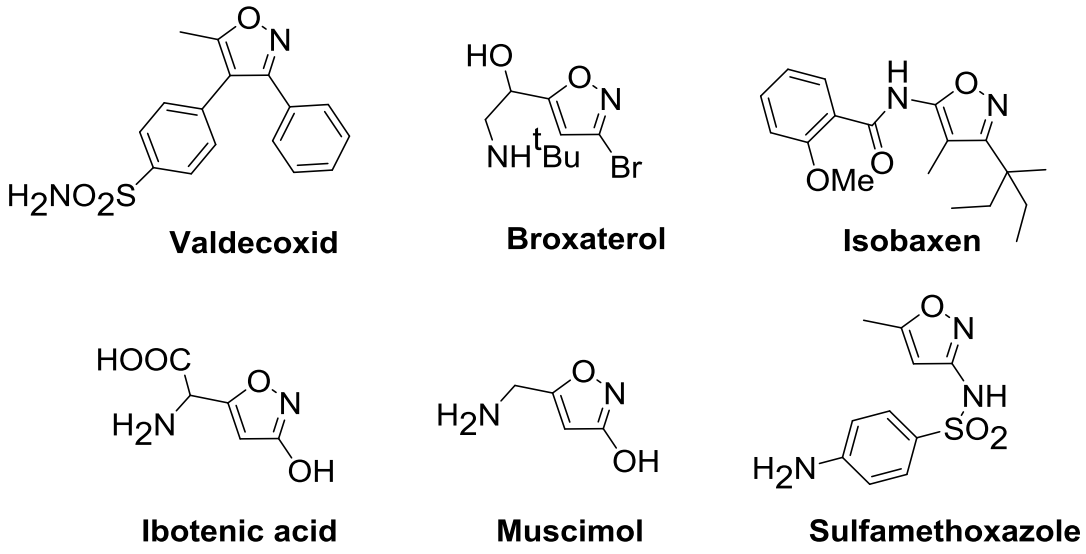
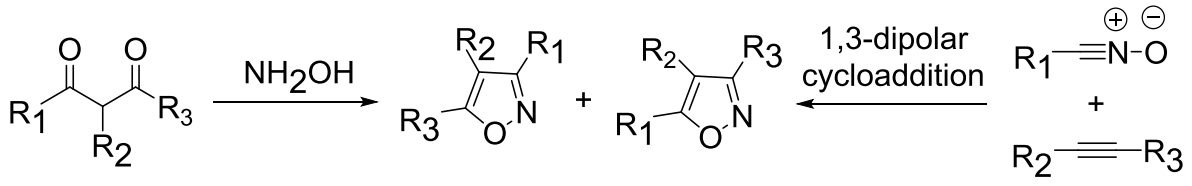


Figure 3.1 Structures of bioactive isoxazoles

Isoxazoles are less than stable their oxazole counterparts due to the relatively weak N-O bond energy (55 Kcal/mol).[11] Therefore substituted isoxazoles can be easily converted under thermal or photochemical reaction conditions to functionally complex derivatives such as β-hydroxyketones, γ-aminoalcohols, α,β-unsaturated oximes, β-hydroxynitriles and aziridine esters which can be useful as synthetic intermediates.[12]

Isoxazoles are generally prepared by (i) the reaction of 1,3-dicarbonyls or their 1,3-dielectrophile equivalent reagents such as β-keto aldehydes, β-keto esters, α-acetylenic ketones/aldehydes, α,β–unsaturated ketones, β-imino nitriles and β-keto nitriles with hydroxylamines[13] (ii) 1,3-dipolar cycloaddition of nitrile oxides with alkynes.[14] The disadvantage of these methods are the lack of availability of the 1,3-dielectrophilic and 1,3-dipole building blocks and that unsymmetrical starting materials often results in a mixture of regioisomeric isoxazoles in poor yields (**Scheme 3.1**).

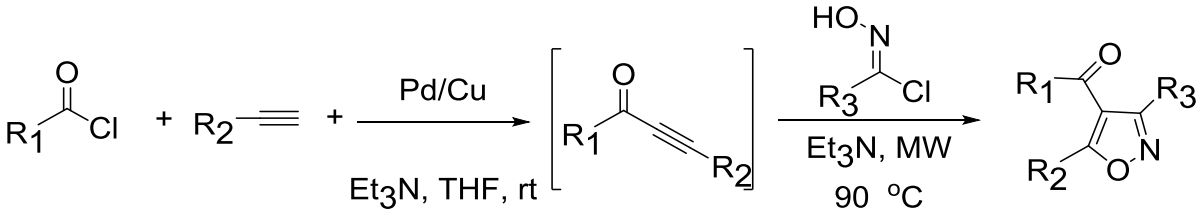


Scheme 3.1 Typical synthesis of isoxazoles

Multicomponent coupling reactions (**MCRs**) are defined as a one-pot process which involves the reaction of at least three components to form a single product that incorporates

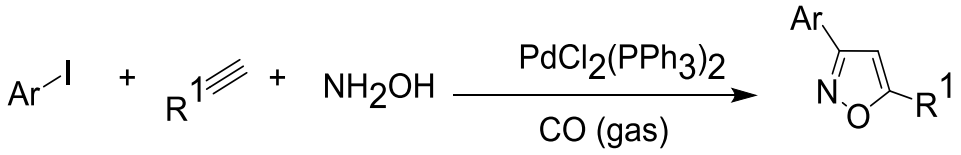
essentially all the atoms of the starting materials. These multicomponent reactions are atom economic, step efficient, convergent and flexible. Therefore, transition metal catalyzed MCRs have attracted considerable attention from academia and industry over the last decade for synthesis of heterocyclic core structures.[15]

Microwave-assisted multicomponent coupling reactions in organic synthesis have received much interest in recent years. Rate enhancement, increased yield, improved purity and greater reproducibility are amoung the major advantages in using microwave reactors in organic synthesis.[16] In 2008 the Muller group reported the synthesis of substituted isoxazoles by employing a one-pot three-component reaction, including a Sonogashira coupling of acid chlorides with terminal alkynes followed by 1,3-dipolar cycloaddition of the resulting alkynones with nitrile oxides under microwave irradiation to generate trisubstituted isoxazoles in good yields (**Scheme 3.2**).[17]



Scheme 3.2 Microwave-assisted multicomponent synthesis of isoxazoles

A novel synthesis of 3,5-trisubstituted isoxazoles in moderate yields using a palladium-catalyzed 4-component coupling of terminal alkynes, hydroxylamine, and aryl halides in the presence of carbon monoxide was recently reported by the Mori group (**Scheme 3.3**).[18]

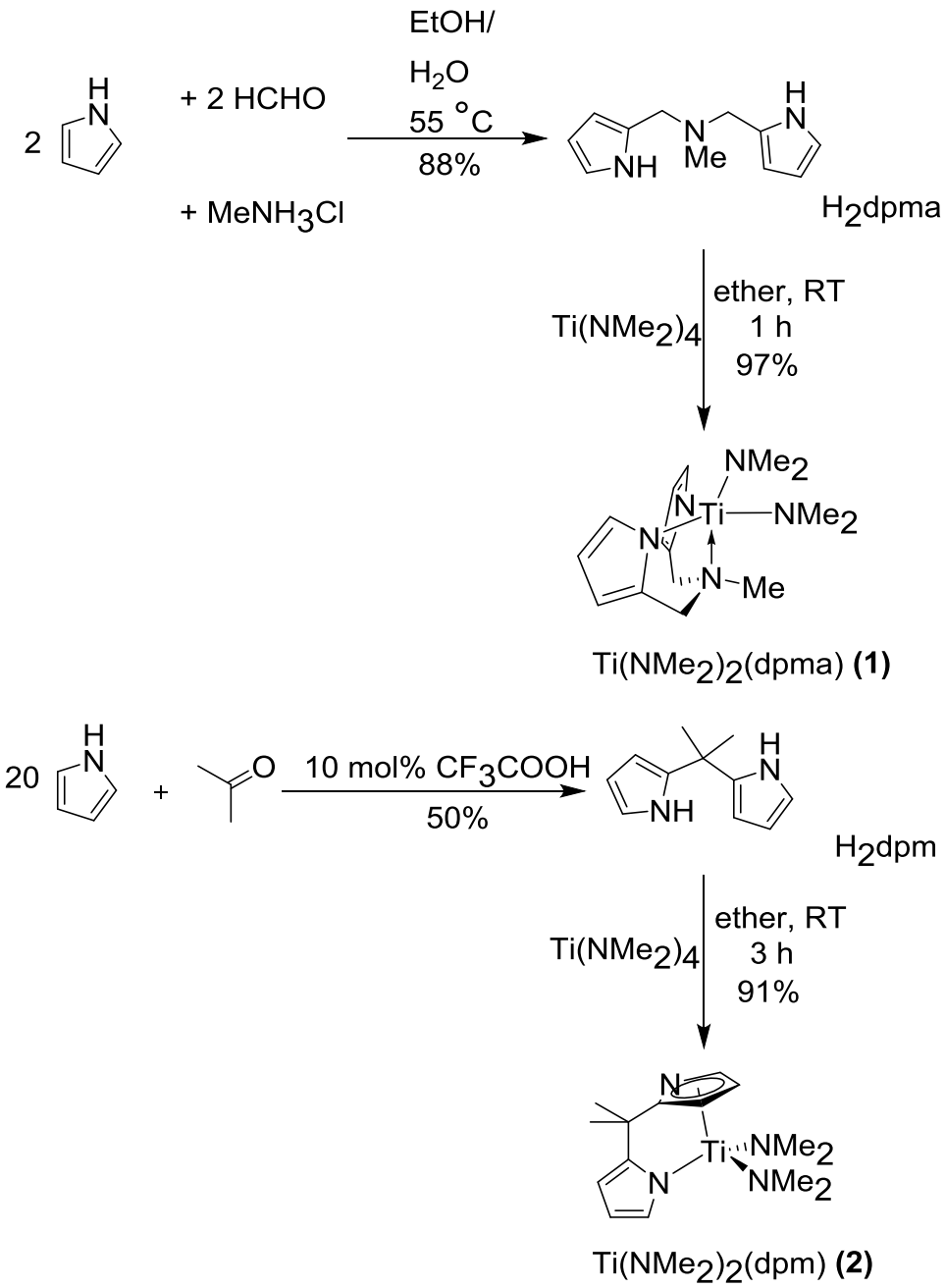


Scheme 3.3 One-pot palladium catalyzed 4-component synthesis of isoxazoles

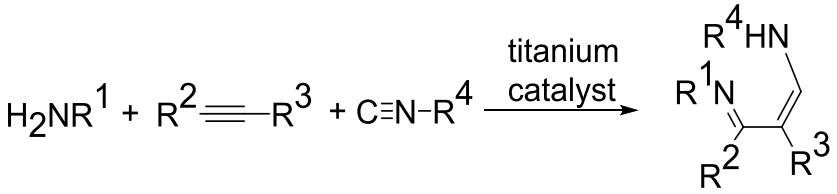
In this study, we demonstrate that a variety of substituted isoxazoles can be prepared in a one-pot 4-component fashion (**Scheme 3.8)**. The methodology uses a titanium-catalyzed 3-component coupling of an alkyne, isonitrile, and primary amine to generate unsymmetrical 1,3-diimine tautomers. Isoxazoles can be generated by simply removing the volatiles from the multicomponent coupling reaction and treating the crude product with commercially available hydroxylamine hydrochloride.[19]

3.2 Results and Discussion

The titanium catalysts for these reactions use pyrrolyl-based ancillary ligands prepared in a single step (**Scheme 3.4**). A double Mannich reaction between methylamine hydrochloride, formaldehyde, and pyrrole generates N,N-di(methyl-α-pyrrolyl)-N-methylamine (H_2dpma).[20] The other ancillary commonly employed, 5,5-dimethyldipyrrolylmethane (H_2dpm), is prepared from trifluoroacetic acid-catalyzed condensation of pyrrole and acetone.[21] Addition of the NH-pyrrole compounds H_2dpm and H_2dpma to commercially available $Ti(NMe_2)_4$ generates the catalysts in high yield. For this work, two different catalysts were employed. For most of the reactions, the milder catalyst with the tridentate ancillary, $Ti(NMe_2)_2$(dpma) (**1**),[22] was found to be optimal. In a few cases, the more reactive $Ti(NMe_2)_2$(dpm) (**2**)[23] gave higher conversions, especially with more sterically hindered (internal) alkynes.

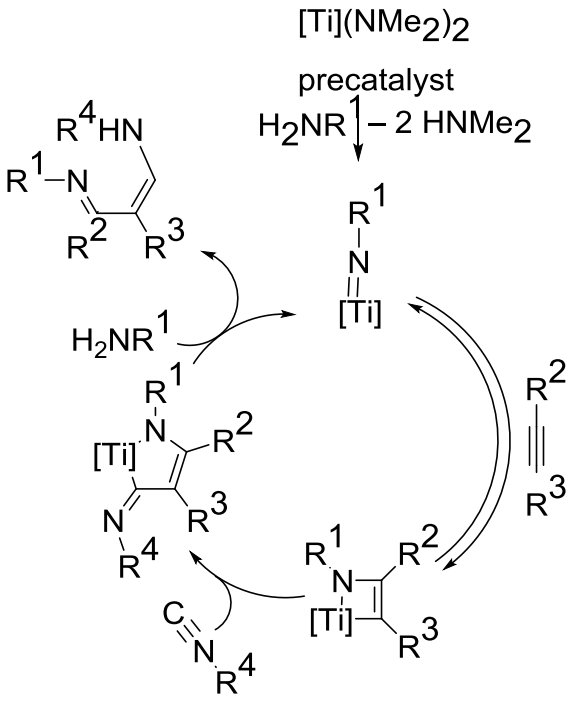


Scheme 3.4 Synthesis of H_2dpma, H_2dpm, Ti(NMe$_2$)$_2$(dpma) (**1**), and Ti(NMe$_2$)$_2$(dpm) (**2**)



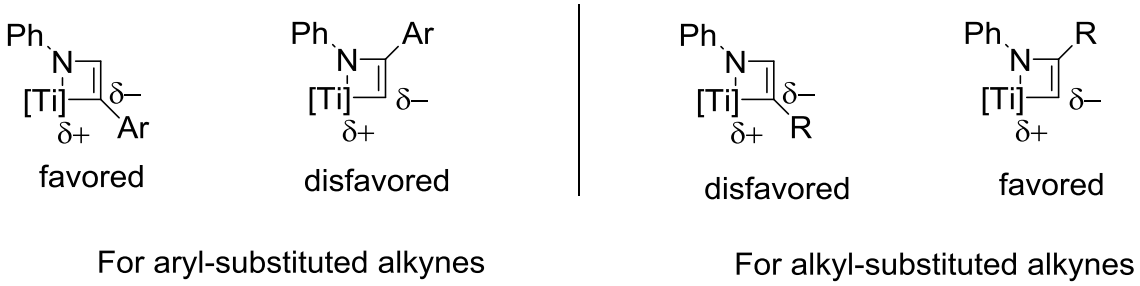
Scheme 3.5 Titanium catalyzed 3-component iminoamination of alkynes

The multicomponent reaction used in this study is a formal alkyne iminoamination, addition of an iminyl and amine across the triple bond (**Scheme 3.5**).[24] The proposed mechanism for the reaction is shown in **Scheme 3.6**. The titanium was introduced as a dimethylamido-containing precatalyst, the dimethylamido ligands are protolytically removed by the primary amine substrate to generate titanium imido complexes which can undergo [2 + 2]-cycloaddition with alkynes. The resulting azatitanacyclobutenes undergo 1,1-insertion of isonitriles to generate 5-membered metallacycles. The 5-membered metallacycles are protolytically converted back to titanium imido complex by primary amines with concomitant release of the iminoamination products.[25]



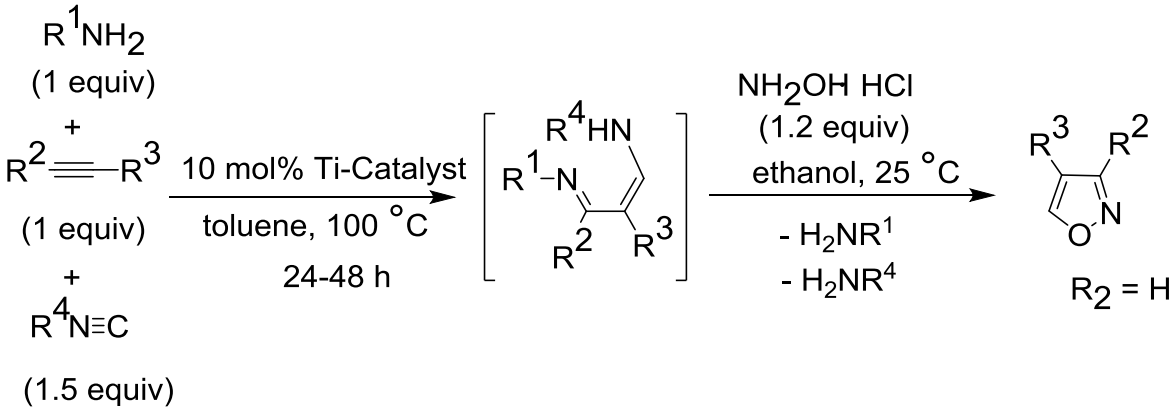
Scheme 3.6 Proposed mechanism for titanium-catalyzed iminoamination of alkynes

The regioselectivity of the multicomponent reaction is set by the [2+2]-cycloaddition reaction in conjunction with the relative trapping rates by isonitrile. The regioselectivity of the addition is electronically controlled when an arene is found on the alkyne triple bond through stabilization of a partial anionic charge adjacent to the metal in the azametallacyclobutene intermediate (**Scheme 3.7**).



Scheme 3.7 Regioselectivity in alkyne addition

The general procedure for the one-pot synthesis of 4-substituted isoxazoles used here is shown in **Scheme 3.8**. The 3CC reaction is commonly done at 100 °C in toluene. The products of iminoamination can be converted to substituted isoxazoles via cyclo-condensation by addition of hydroxylamine hydrochloride (1.2 equiv) in a more polar solvent (ethanol).



Scheme 3.8 General scheme for one-pot synthesis of 4-substituted isoxazoles

During the first part of the study, the reaction was limited to vinyl-, heterocyclic-, and aryl-substituted terminal alkynes, which results exclusively in 4-substituted isoxazoles in moderate yields (**Table 3.1**, entries a-h). The reactions of alkyl-containing terminal alkynes such as 1-hexyne and *tert*-butyldimethyl(pent-4-yn-1-yloxy)silane, result in the production of the 3CC product in good yields using either catalyst; however, for reasons currently unknown, the addition of hydroxylamine hydrochloride under any reaction conditions we investigated did not result in formation of the alkyl-substituted isoxazoles.

Table 3.1 Examples of isoxazoles syntheses using hydroxylamine hydrochloride with different terminal alkynes (**Scheme 3.8**)

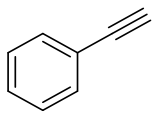
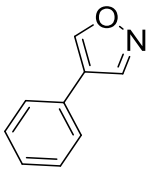
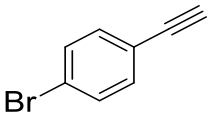
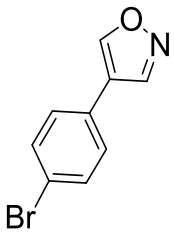
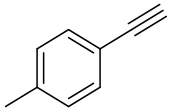
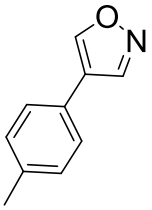
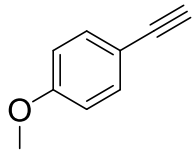
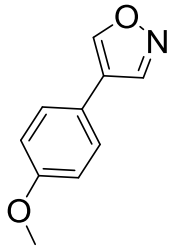
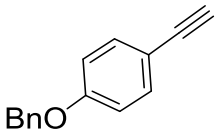
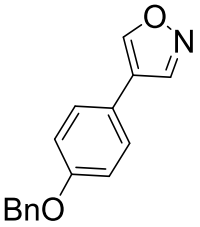
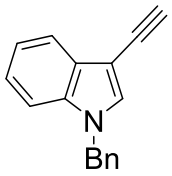
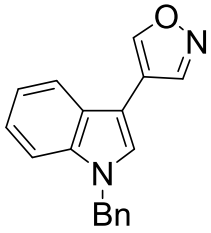
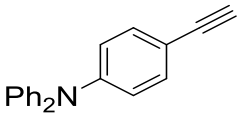
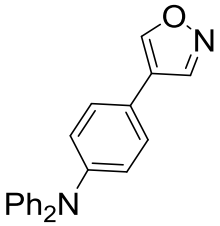
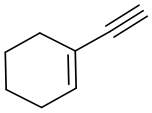
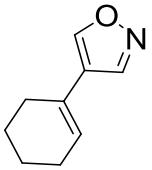
Entry	Alkyne	Catalyst	Product	Isolated yield
a		**1**		35% [a]
b		**1**		55% [a]
c		**1**		51% [a]
d		**1**		48% [a]
e		**1**		57% [a]

Table 3.1 (cont'd)

f		**2**		50% [a]
g		**1**		48% [a]
h		**1**		60% [a]

[a] Reactions carried out with cyclohexylamine, alkyne, and *tert*-butylisonitrile in a 1:1:1.5 ratio with 10 mol % catalyst (**1)** at 100 °C for 24 h. Once the 3CC is complete, product was stirred at 25 °C in ethanol with hydroxylamine hydrochloride (1.2 eqviv).

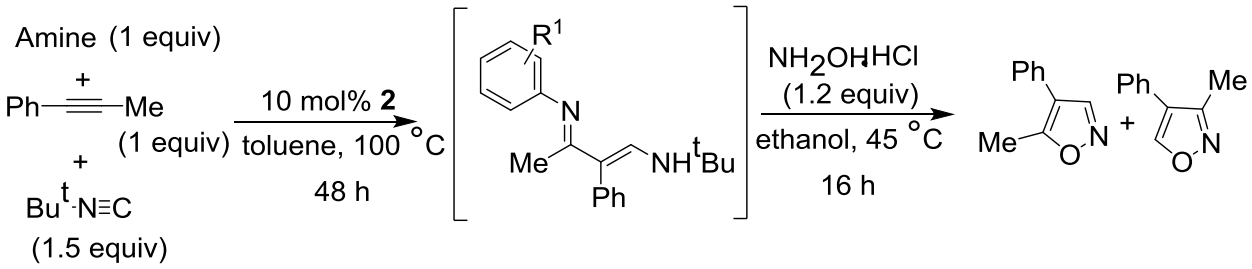
[b] Aniline was used in place of cyclohexylamine with 10 mol % of catalyst (**2**).

For the second part of the study iminoamination of internal aliphatic and aromatic alkynes were investigated. These reactions typically give a single 3CC product in the form of the iminoamine, however the subsequent reaction with hydroxylamine hydrochloride is not

regioselective for these substrates. Initially, the multicomponent coupling of aniline, 1-phenylpropyne and *tert*-butylisonitrile followed by cyclo-condensation with hydroxylamine hydrochloride in ethanol at 45 °C was investigated. The reactions were heated slightly as the cyclizations were somewhat slower than with terminal alkynes. The regioselectivity of the hydroxylamine hydrochloride-mediated cyclization results in a 1.0 : 1.8 ratio of 4,5- to 3,4-isomers of the substituted isoxazole products (**Table 3.2**, entry 1).

This observation was further explored by varying the amine (R^1) substituent in the 3CC product in an affort to improve the isomer ratio of the cyclization step. The results of those studies are shown in **Table 3.2**. While most substitutions on the aniline ring had little consequence on the isomer ratios with no clear electronic or steric effect, one of the aniline derivatives did significantly improve the regioselectivity, 3,5-dichloroaniline (**Table 3.2**, entry 5). Noticeably naphthalen-1-amine results in more of the of 4,5 regioisomer than observed from substituted anilines and this may result from the fact that an ortho position is substituted (**Table 3.2**, entry 10). Further, multicomponent coupling reactions with varius substituted anilines gave poor yields of 3CC products due to steric bulkyness around the catalytically active metal site.

Table 3.2 Effect of R^1 on the isomer ratio in the synthesis of 4-phenyl-3-methylisoxazole



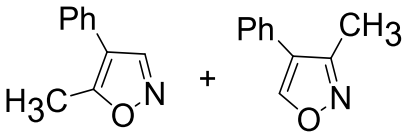
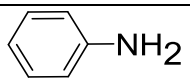
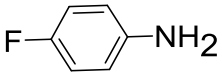
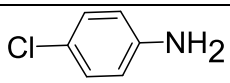
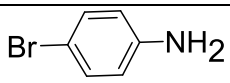
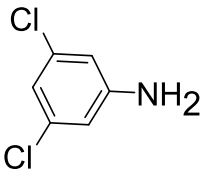
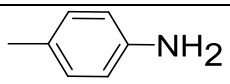
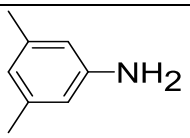
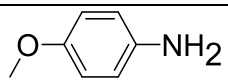
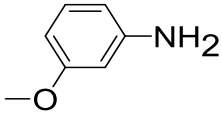
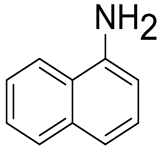
Entry	Amine (R^1)	Isomer ratio 
1		1.00 : 1.75 [a]
2		1.00 : 1.10 [a]
3		1.00 : 2.32 [a]
4		1.00 : 1.80 [a]
5		1.00 : 8.00 [a]
6		1.00 : 1.50 [a]
7		1.00 : 1.10 [a]

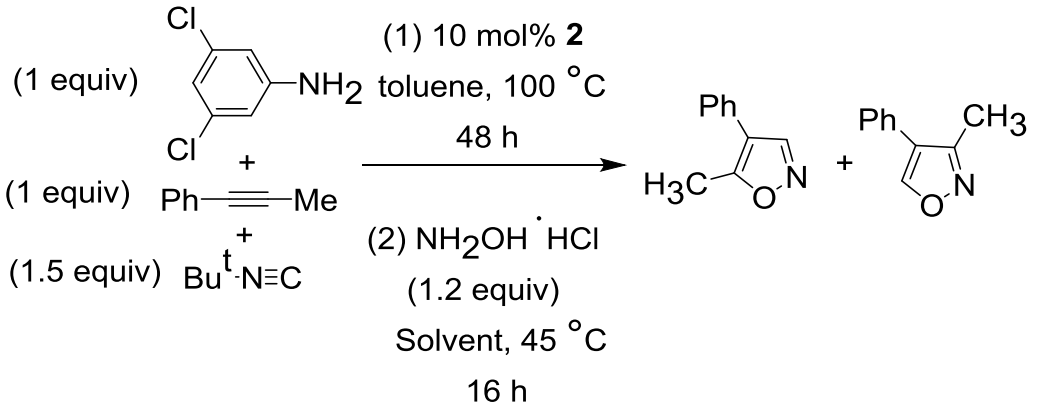
Table 3.2 (cont'd)

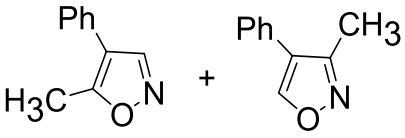
8		1.00 : 1.53 [a]
9		1.00 : 1.41 [a]
10		1.00 : 0.75 [a]

[a] Isomer ratios were determined by NMR integrations of the crude reaction mixture.

Further optimization of the reaction was carried out by examining solvent effects on the observed isomer ratio. the results are summarized in **Table 3.3**; As shown use of THF along with 3,5-dichloroaniline as the aromatic amine substrate provided a single regioisomer, the 3,4-disubstituted isoxazoles.

Table 3.3 Solvent effects on the isomer ratio in the synthesis of 4-phenyl-3-methylisoxazole

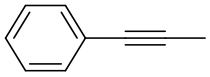
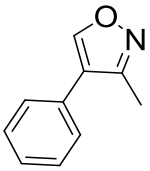
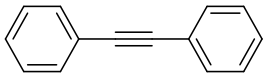
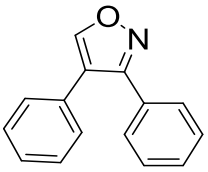
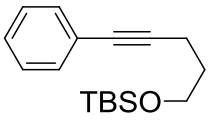
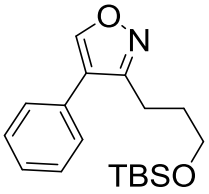


Entry	Solvent	Isomer ratio 
1	ethanol	1.00 : 8.00 [a]
2	ethyacetate	1.00 : 5.23 [a]
3	N,N-dimethylformamide	1.00 : 4.56 [a]
4	tetrahydrofuran	single isomer
5	1,4-dioxane	1.00 : 3.06 [a]
6	N,N-dimethylacetamide	1.00 : 4.03 [a]
7	dimethyl sulfoxide	1.00 : 5.28 [a]

[a] Isomer ratios were determined by NMR integrations of the crude reaction mixture

Substituted isoxazoles synthesized from internal alkynes are summarized in table 3.4. This methodology results in poor yields of substituted isoxazoles (**Table 3.4**, entry i-k). For reasons currently unknown, substituted isoxazoles from aliphatic internal alkynes such as hex-3-yne, 2-methylhex-1-en-3-yne and 1-(prop-1-yn-1-yl)cyclohex-1-ene were not isolated under any reaction conditions we investigated.

Table 3.4 Examples of isoxazoles syntheses using hydroxylamine hydrochloride with different internal alkynes[a]

Entry	Alkyne	Catalyst	Product	Isolated yield
i		**2**		35%
j		**2**		25%[a]
k		**2**		30%[a]

[a] Reactions carried out with aniline, alkyne, and *tert*-butylisonitrile in a 1:1:1.5 ratio with 10 mol % catalyst (**2)** at 100 °C for 48 h. Once the 3CC is complete, product was stirred at 45 °C in THF with hydroxylamine hydrochloride (1.2 eqviv).

3.3 Conclusion

Titanium-catalyzed 3-component coupling of a primary amine, an alkyne, and an isonitrile followed by treatment with hydroxylamine hydrochloride provides substituted isoxazoles in a one-pot procedure. This new procedure has significant flexibility in the types of substituted isoxazoles that can be accessed. The yields are generally modest, but the products are readily isolated in pure form using column chromatography. Reactions with terminal alkynes are more facile and can be accomplished with the milder $Ti(NMe_2)_2$(dpma) (**1**) as catalyst. The more active dipyrrolylmethane catalyst $Ti(NMe_2)_2$(dpm) (**2**) was used for internal alkynes.

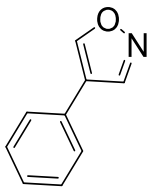
The reaction has several points to allow for future optimization of a specific target of interest. For example, the type of substituent on the isonitrile can be varied in this reaction and hopefully this could improve the regioselectivities or yields. This methodology allows access to a large number of 4-substituted and 3,4-disubstituted isoxazoles in a regioselective manner from internal and terminal alkynes respectively. The products are easily isolated in pure form after the one-pot syntheses.

3.4 Experimental

General considerations

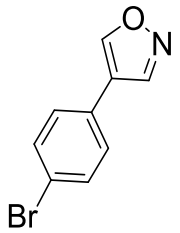
All manipulations of air sensitive compounds were carried out in an MBraun dry box under a purified nitrogen atmosphere. Toluene was purified by sparging with dry N_2 and removing water by running through activated alumina systems purchased from Solv-Tek. ^{1}H and ^{13}C spectra were recorded on VXR-500 spectrometers. Melting points were measured on a Mel-Temp II apparatus with a mercury thermometer and are uncalibrated. $Ti(NMe_2)_2$(dpma) (**1**) and $Ti(NMe_2)_2$(dpm) (**2**) were made following the literature procedures. Alkynes were purchased either from Aldrich or from GFS chemicals and were distilled from BaO under dry nitrogen. Amines were purchased from Aldrich, dried over KOH, and distilled under dry nitrogen. tert-Butylisonitrile was made according to the literature procedure and purified by distillation under nitrogen.[27] Hydroxylamine hydrochloride was purchased from Columbus Chemical Industries, and neutral alumina was purchased Sigma-Aldrich Co and used as received. EtOH, CH_2Cl_2, hexanes, tetrahydrofuran (THF) and EtOAc were purchased from Mallinckrodt chemicals and used as received.

Preparation and Characterization of Compounds in Table 3.1



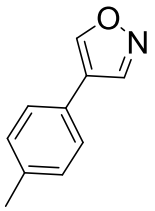
4-Phenylisoxazole (Table 3.1, entry a)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **1** (32.4 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (95 mg, 1 mmol), phenylacetylene (102 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and absolute ethanol (2 mL). The reaction was stirred at room temperature (25 °C) for 16 h. After completion of the reaction, solvents were removed in vacuo, The crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9:1, which afforded the desired compound (51 mg, 35%) as a white solid. Mp: 44-45 °C (lit. mp: 44-46 °C).[28] ^{1}H NMR ($CDCl_3$, 500 MHz): 7.27-7.34 (1H, m, Ar-H), 7.39-7.42 (2H, m, Ar-H), 7.46-7.48 (2H, m, Ar-H), 8.55 (1H, s, 3-CH isoxazole), 8.66 (1H, s, 5-CH isoxazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125

MHz): 121.3, 126.3, 128.0, 128.4, 129.1, 147.9, 153.3. MS(EI): *m/z* 145. Elemental Analysis: found: %C, 74.85; %H, 4.52; %N, 9.71; expected: %C, 74.47; %H, 4.86; %N, 9.65.



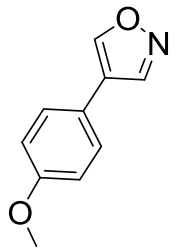
4-(4-Bromophenyl)isoxazole (Table 3.1, entry b)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **1** (32.4 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (95 mg, 1 mmol), 1-bromo-4-ethynylbenzene (181 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and absolute ethanol (2 mL). The reaction was stirred at room temperature (25 °C) for 16 h. After completion of the reaction, solvents were removed in vacuo, The crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9:1, which afforded the desired compound (123 mg, 55%) as a yellow solid. Mp: 111-113 °C (lit. mp: 113 °C).[29] ^{1}H NMR

($CDCl_3$, 500 MHz): 7.32-7.34 (2H, d, 11 Hz, Ar-H), 7.51-7.53 (2H, d, 11 Hz, Ar-H), 8.51 (1H, s, 3-CH isoxazole), 8.65 (1H, s, 5-CH isoxazole). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 120.4, 121.9, 127.4, 127.9, 132.3, 147.7, 153.5. MS(EI): *m/z* 224. Elemental Analysis: found: %C, 47.93; % H, 2.59; %N, 6.34; expected: %C, 48.25; %H, 2.70; %N, 6.25.



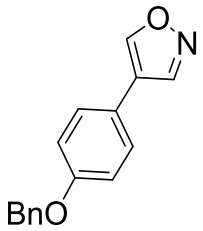
4-p-Tolylisoxazole (Table 3.1, entry c)**:**[19] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **1** (32.4 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (95 mg, 1 mmol), 1-ethynyl-4- methylbenzene (116 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and absolute ethanol (2 mL). The reaction was stirred at room temperature (25 °C) for 16 h. After completion of the reaction, solvents were removed in vacuo, The crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9:1, which afforded the desired

compound (81 mg, 51%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 2.36 (3H, s, CH_3), 7.20-7.22 (2H, d, 8 Hz, Ar-H), 7.34-7.36 (2H, d, 8 Hz, Ar-H), 8.52 (1H, s, 3-CH isoxazole), 8.62 (1H, s, 5-CH isoxazole). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 21.2, 121.3, 125.5, 126.3, 129.8, 138.0, 148.0, 153.0. MS(EI): *m/z* 159. Elemental Analysis: found: %C, 74.98; %H, 5.88; %N, 8.66; expected: %C, 75.45; %H, 5.70; %N, 8.80.



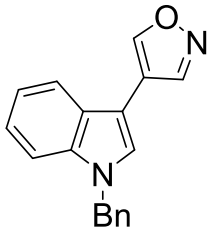
4-(4-Methoxyphenyl)isoxazole (Table 3.1, entry d)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **1** (32.4 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (95 mg, 1 mmol), 1-ethynyl-4-methoxybenzene (132 mg, 1 mmol), and *tert*-butylisonitrile (171 µL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and absolute ethanol (2 mL). The reaction was stirred at room temperature (25 °C) for 16 h. After completion of the reaction, solvents were removed in vacuo, The crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). The organic layer was dried over anhydrous

Na_2SO_4 and concentrated by rotary evaporation. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9:1, which afforded the desired compound (81 mg, 51%) as a yellow solid. Mp: 40-42 °C (lit. mp: 40 °C).[30] ^{1}H NMR ($CDCl_3$, 500 MHz): 3.82 (3H, s, OCH_3), 6.93-6.94 (2H, d, 8.5 Hz, Ar-H), 7.37-7.39 (2H, d, 8.5 Hz, Ar-H), 8.49 (1H, s, 3-CH isoxazole), 8.57 (1H, s, 5-CH isoxazole). ^{13}C {^{1}H} NMR ($CDCl_3$, 125 MHz): 55.4, 114.6, 127.7, 128.4, 129.6, 148.0, 152.5, 159.5. MS(EI): *m/z* 175. Elemental Analysis: found: %C, 67.98; %H, 5.33; %N, 8.13; expected: %C, 68.56, %H, 5.18, %N, 8.00.



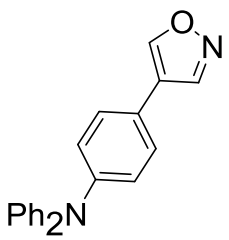
4-(4-(Benzyloxy)phenyl)isoxazole (Table 3.1, entry e)**:**[19] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **1** (32.4 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (95 mg, 1 mmol), 1-(benzyloxy)-4-ethynylbenzene (208 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (83

mg, 1.2 mmol) and absolute ethanol (2 mL). The reaction was stirred at room temperature (25 °C) for 16 h. After completion of the reaction, solvents were removed in vacuo, The crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9:1, which afforded the desired compound (143 mg, 57%) as a light brown solid. Mp: 110-112 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 5.09 (2H, s, CH_2), 7.00-7.01 (2H, d, 6.5 Hz, Ar-H), 7.32-7.34 (1H, d, 6.5 Hz, Ar-H), 7.37-7.44 (6H, m, Ar-H) 8.45 (1H, s, 3-CH isoxazole), 8.57 (1H, s, 5-CH isoxazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 70.1, 115.5, 121.0, 121.2, 127.4, 127.7, 128.1, 128.6, 136.6, 148.0, 152.6, 158.6. MS(EI): *m/z* 251. Elemental Analysis: found: %C, 76.12; %H, 5.01; %N, 5.72; expected: %C, 76.48; %H, 5.21; %N, 5.57.

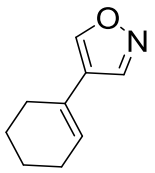


4-(1-Benzyl-1H-indol-3-yl)isoxazole (Table 3.1, entry f)**:** [19] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), 1-benzyl-3-ethynyl-1H-indole (231 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a

Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and absolute ethanol (2 mL). The reaction was stirred at room temperature (25 °C) for 16 h. After completion of the reaction, solvents were removed in vacuo, The crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9:1, which afforded the desired compound (137 mg, 50%) as a light brown solid. Mp: 128-130 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 5.28 (2H, s, CH_2) 7.08-7.10 (2H, d, 7 Hz, Ar-H), 7.14-7.29 (8H, m, Ar-H), 7.63-7.65 (2H, d, 9.5 Hz, Ar-H) 8.49 (1H, s, 3-CH isoxazole), 8.65 (1H, s, 5-CH isoxazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 50.2, 100.2, 119.4, 120.5, 122.7, 125.9, 126.9, 127.9, 128.9, 136.8, 148.8, 152.1. MS(EI): *m/z* 274. Elemental Analysis: found: %C, 78.64; %H, 5.22; %N, 10.32; expected: %C, 78.81; %H, 5.14; %N, 10.21.

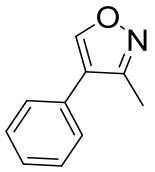


4-(Isoxazol-4-yl)-N,N-diphenylaniline (Table 3.1, entry g)**:**[19] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **1** (32.4 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (95 mg, 1 mmol), 4-ethynyl-N,N-diphenylaniline (269 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and absolute ethanol (2 mL). The reaction was stirred at room temperature (25 °C) for 16 h. After completion of the reaction, solvents were removed in vacuo, The crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9.5:0.5, which afforded the desired compound (143 mg, 48%) as a white solid. Mp: 144-146 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) 6.97-6.99 (2H, t, 7 Hz, Ar-H), 7.02-7.05 (6H, m, Ar-H), 7.18-7.22 (4H, m, Ar-H), 7.25-7.27 (2H. d, 9 Hz, Ar-H) 8.44 (1H, s, 3-CH isoxazole), 8.54 (1H, s, 5-CH isoxazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 121.1, 122.1, 123.3, 123.7, 124.6, 127.2, 129.4, 147.4, 147.8, 147.9, 152.7. MS(EI): *m/z* 312. Elemental Analysis: found: %C, 80.82; %H, 5.24; %N, 8.82; expected: %C, 80.75; %H, 5.16; %N, 8.97.



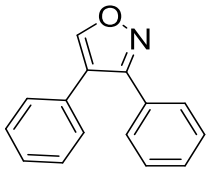
4-(Cyclohex-1-enyl)isoxazole (Table 3.1, entry h)**:** [19] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **1** (32.4 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (95 mg, 1 mmol), 1-ethynylcyclohex-1-ene (106 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and absolute ethanol (2 mL). The reaction was stirred at room temperature (25 °C) for 16 h. After completion of the reaction, solvents were removed in vacuo, The crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9.5:0.5, which afforded the desired compound (143 mg, 57%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.60-1.64 (2H, m, CH_2), 1.68-1.73 (2H, m, CH_2), 2.12-2.15 (2H, m, CH_2), 2.20-2.23 (2H, m, CH_2), 6.02-6.04 (1H, m, CH), 8.24 (1H, s, 3-CH isoxazole), 8.33 (1H, s, 5-CH isoxazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 22.0, 22.3, 25.2, 27.3, 122.9, 125.2, 125.3, 146.8, 151.4. MS(EI): *m/z* 149. Elemental Analysis: found: %C, 72.33; %H, 7.29; %N, 9.24; expected: %C, 72.46; %H, 7.43; %N, 9.39.

Preparation and Characterization of Compounds in Table 3.4



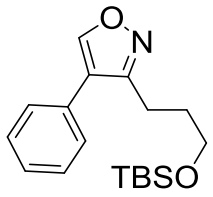
3-Methyl-4-phenylisoxazole (Table 3.4, entry i)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 3,5-dichloroaniline (162 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and THF (2 mL). The reaction was stirred at 45 °C for 16 h. After completion of the reaction, solvents were removed in vacuo, The crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9:1, which afforded the desired compound (55 mg, 35%) as a yellow oil.[30] ^{1}H NMR ($CDCl_3$, 500 MHz): 2.56 (3H, s, CH_3), 7.32-7.34 (1H, d, Ar-H), 7.35-7.37 (2H, m, Ar-H), 7.40-7.44 (2H, m, Ar-H), 8.34 (1H, s, 5-CH isoxazole). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 31.0, 126.0, 126.7, 127.4, 127.9, 129.1, 130.1, 150.2. MS(EI): *m/z* 159.

Elemental Analysis: found: %C, 75.28; %H, 5.59; %N, 8.92; expected: %C, 75.45; %H, 5.70; %N, 8.80.



3,4-Diphenylisoxazole (Table 3.4, entry j)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 3,5-dichloroaniline (162 mg, 1 mmol), diphenylacetylene (178 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and THF (2 mL). The reaction was stirred at 45 °C for 16 h. After completion of the reaction, solvents were removed in vacuo, The crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 9:1, which afforded the desired compound (55 mg, 25%) as a yellow solid. Mp: 90-92 °C (lit. mp: 91 °C).[31] ^{1}H NMR ($CDCl_3$, 500 MHz): 7.35-7.40 (8H, m, Ar-H), 7.61-7.62 (1H, m, Ar-H), 7.62-7.64 (1H, m, Ar-H), 8.35 (1H, s, 5-CH isoxazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 116.2, 127.2, 127.6, 128.0, 128.3, 128.6, 128.7, 129.0,

130.0, 131.6, 151.9, 164.0. MS(EI): *m/z* 221. Elemental Analysis: found: %C, 81.29; %H, 5.13; %N, 6.42; expected: %C, 81.43; %H, 5.01; %N, 6.33.



3-(3-(tert-Butyldimethylsilyloxy)propyl)-4-phenylisoxazole (Table 3.4, entry k)**:** [19] In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 3,5-dichloroaniline (162 mg, 1 mmol), *tert*-butyldimethyl(5-phenylpent-4-ynyloxy)silane (274 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then the same pressure tube was charged with hydroxylamine hydrochloride (83 mg, 1.2 mmol) and THF (2 mL). The reaction was stirred at 45 °C for 16 h. After completion of the reaction, solvents were removed in vacuo, The crude product was dissolved in CH_2Cl_2 (20 mL) and washed with water (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated by rotary evaporation. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes/ethyl acetate 19:1, which afforded the desired compound (95 mg, 30%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 0.059 (6H, s, Si-CH_3), 0.85 (9H, s, Si-C(CH_3)$_3$, 1.94-1.98 (2H, m, $CH_2CH_2CH_2$OTBS), 2.99-3.02 (2H, m, $CH_2CH_2CH_2$OTBS), 3.64-3.66 (2H, m,

$CH_2CH_2CH_2OTBS$), 7.31-7.32 (1H, m, Ar-H), 7.32-7.42 (4H, m, Ar-H), 8.33 (1H, s, 5-CH isoxazole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 1.0, 22.4, 25.9, 30.6, 35.7, 61.7, 127.4, 127.6, 128.2, 128.9, 131.5, 150.3, 167.8. Elemental Analysis: found: %C, 67.94; %H, 8.42; %N, 4.52; expected: %C, 68.09; %H, 8.57; %N, 4.41.

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CHAPTER 4. ONE-POT TITANIUM-CATALYZED MULTICOMPONENT COUPLING APPROACH TOWARDS SYNTHESIS OF 4,5-DISUBSTITUTED AND 4-SUBSTITUTED PYRROLE-2-CARBOXYLATES

4.1 Introduction

Substituted pyrroles represents an important class of nitrogen containing five-membered aromatic heterocycles, which are present in a wide range of natural products and drug molecules.[1] These pyrrole core structural units are abundantly found in porphyrins, such as porphyrins (heme) chlorine (chlorophyll) and corrins (vitamin B12). Also substituted pyrrole ring occur in porphobilinogen (intermediate in biosynthesis of porphyrins and vitamin B12) and biliverdin and bilirubin (pyrrole-based bile pigments)(**Figure 4.1)**.[2]

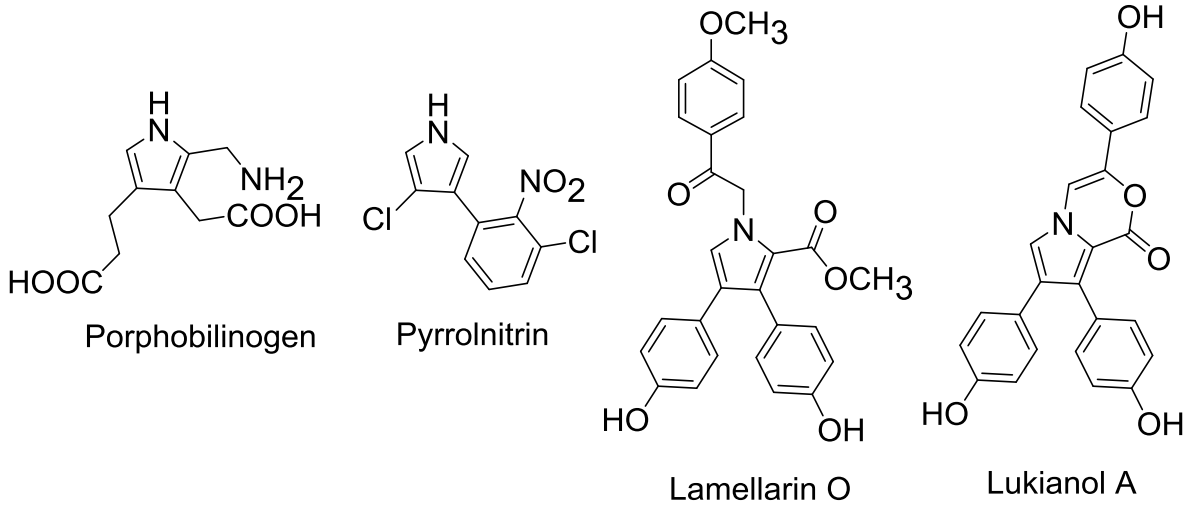


Figure 4.1 Pyrrole containing natural products

Substituted pyrroles also exhibit biological activities such as anti-tubercular,[3] anti-proliferative,[4] anti-inflammatory activity,[5] HIV-1 intigrase inhibitors,[6] glycogen synthase kinase-3(GSK-3) inhibitors,[7] analgesic and bactericidal activities,[8] fungicides and plant growth regulators, [6] action on the cardiovascular system,[9] antitumor agents.[10] Similarly substituted pyrroles are an important part of supramolecular chemistry as molecular sensors[11] and devices,[12] and nonlinear optics.[13]

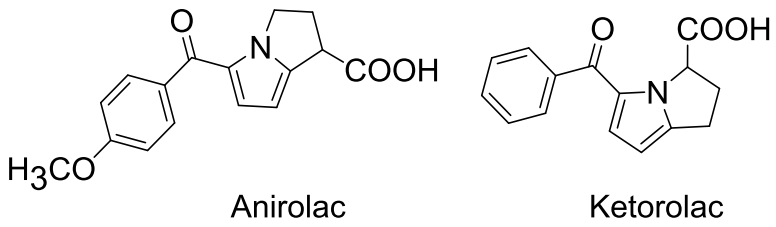
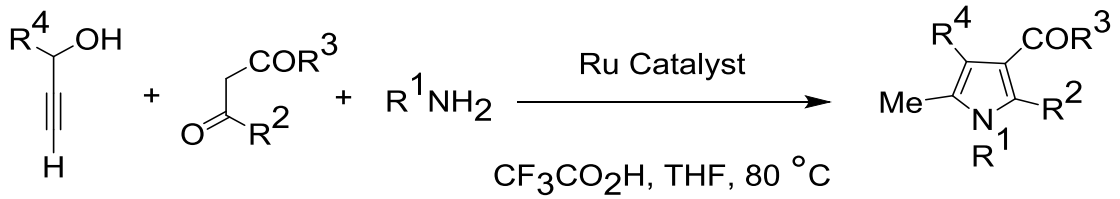


Figure 4.2 Substituted pyrrole containing drugs

Previous approaches for the synthesis of substituted pyroles include methods developed by as Knorr (1884),[14] Paal-Knorr (1884),[15] Hantzsch (1890),[16] Barton-Zard (1990)[17] and Piloty (1910).[18] Pyrrole synthesis involving classical cyclo-condensation reactions have limitations in terms of efficiency, substituent diversity, functional group compatibility, and regiospecificity.

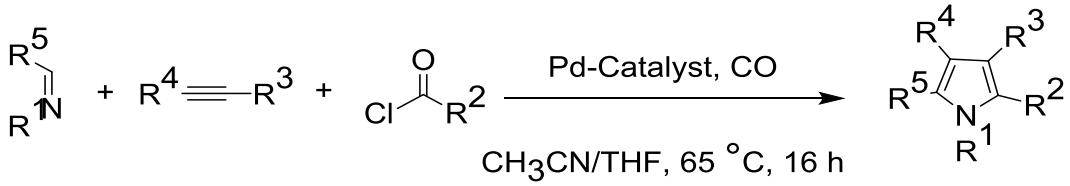
In recent years, several research groups have pursued transition metal-catalyzed multicomponent coupling reactions[19] for direct access to substituted pyrrole compounds due to bond-forming efficiency and high atom-economy provided by these complexes which allow for

the introduction of complexity in a fast and experimentally simple fashion.[20,21] In 2007 Gimeno and coworkers reported a one-pot, three-component reaction between primary amines, β-ketoesters or β-diketones and propargyl alcohols that provided substituted pyrroles in good to excellent yields (**Scheme 4.1**). This transformation is catalyzed by a ruthenium catalyst and afforded fully substituted pyrrole derivatives.[22]



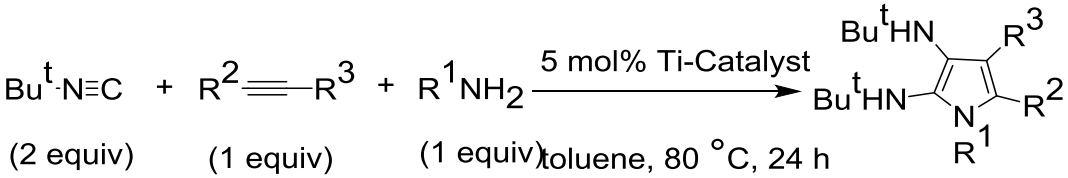
Scheme 4.1 Ruthenium-catalyzed, 3-component synthesis of substituted pyrroles

In 2004 Arndtsen and Dhawan reported a pyrrole synthesis based on the preparation of Munchnones in one step by a palladium-catalyzed coupling between imines, acid chlorides and carbon monoxide, and then the corresponding pyrroles by the [3+2] cyclo-addition of alkyne with the munchinone (**Scheme 4.2)**.[23]



Scheme 4.2 Pd-catalyzed synthesis of substituted pyrroles by 3-component synthesis

In 2009 our group demonstrated that a variety of differently substituted 2,3-diaminopyrroles can be prepared in a one step 4-component fashion (**Scheme 4.3**). This methodology uses a titanium- catalyzed 4-component synthesis from 2 equiv of an isonitrile, 1 equiv of an arylamine, and 1 equiv of an alkyne in an atom-efficient process (**Scheme 4.3**). The titanium catalyst used in this study was $Ti(NMe_2)_2(IndMe_2)_2$, which can be easily prepared from commercially available reagents, $Ti(NMe_2)_4$ and 2,3-dimethylindole. This reaction works well only with anilines not bearing an *ortho*-substituent and *tert*-butylisonitrile. Internal alkynes require higher reaction temperatures and longer reaction times than their terminal counterparts.[24]



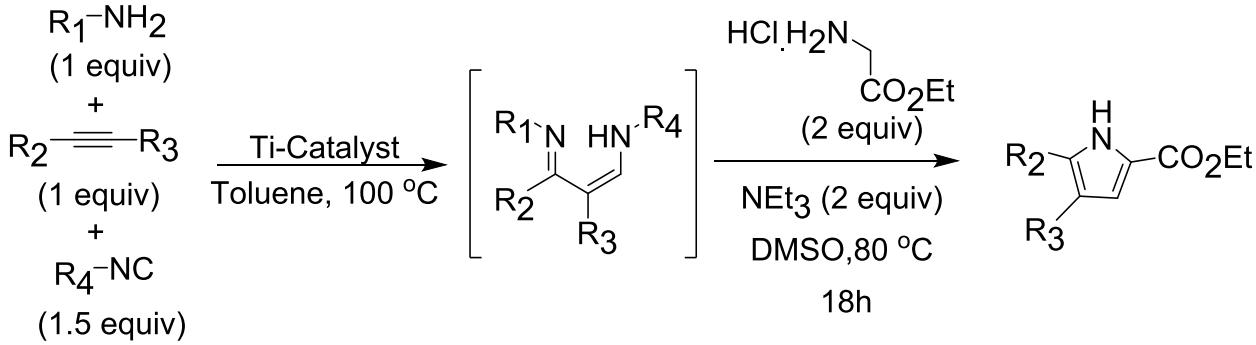
Scheme 4.3 One-pot titanium-catalyzed 4-component synthesis of 2,3-diaminopyrroles

In this study, we demonstrate that a variety of substituted pyrrole-2-carboxylates can be prepared in a one-pot 4-component fashion (**Scheme 4.4**). The methodology uses a titanium-catalyzed 3-component coupling of an alkyne, isonitrile, and primary amine to generate unsymmetrical 1,3-diimine tautomers. Substituted pyrrole-2-carboxylates result from simply removing the volatiles from the multicomponent coupling reaction and treating the crude product with commercially available glycine ethyl ester hydrochloride.

4.2 Results and Discussion

Our group has been investigating a titanium-catalyzed 3-component coupling (3CC) reaction that generates tautomers of 1,3-diimines.[25] In this work we report that these 3CC products, can be used as direct precursors for the synthesis of substituted pyrrole-2-carboxylates which result from simply removing the volatiles from the multicomponent coupling reaction and treating the crude product with commercially available glycine ethyl ester hydrochloride.

Two titanium catalysts Ti(dpma)(NMe_2)$_2$ (**1**), and Ti(dpm)(NMe_2)$_2$ (**2**) were employed for this study. They can be prepared (refer to chapter 3) in a single step by reacting the ancillary ligands with commertially available Ti(NMe_2)$_4$. The proposed catalytic cycle involved in the synthesis of the 3CC product (discussed in chapter 3) is based on the mechanism for catalytic hydroamination. For most of the reactions, the milder catalyst with the tridentate ancillary, Ti(dpma)(NMe_2)$_2$ (**1**), was found to be optimal. In a few cases, the more reactive Ti(dpm)(NMe_2)$_2$ (**2**) gave higher conversions, especially with more sterically hindered (internal) alkynes.[26.27]



Scheme 4.4 General scheme for one-pot synthesis of pyrrole-2-carboxylates

The general strategy for the one-pot synthesis of 4-substituted pyrrole-2-carboxylates used here is shown in Scheme 4.4. The 3CC reaction is commonly done at 100 °C in toluene. The products of iminoamination can be converted to substituted pyrroles via cyclo-condensation by addition of glycine ethyl ester hydrochloride in a more polar solvent (DMSO) under basic reaction conditions.

Table 4.1 Examples of pyrrole-2-carboxylates syntheses using glycine ethyl ester hydrochloride with different terminal alkynes (**Scheme 4.4**)

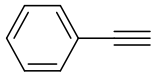
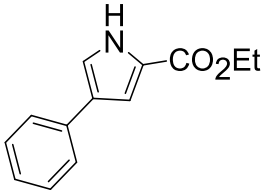
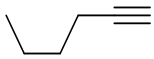
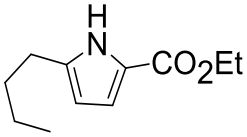
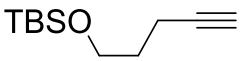
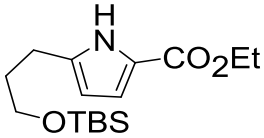
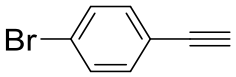
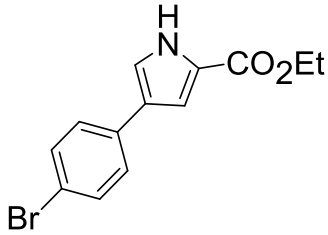
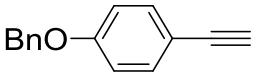
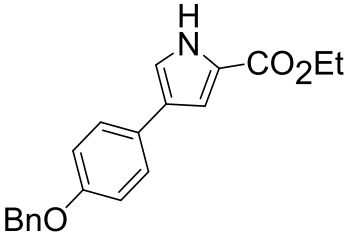
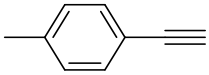
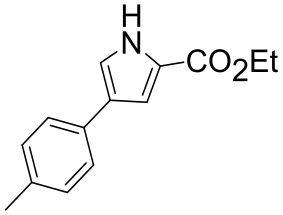
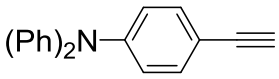
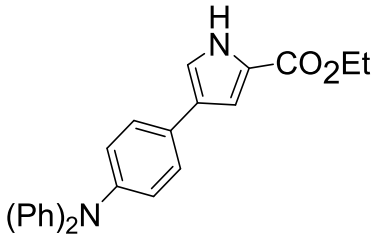
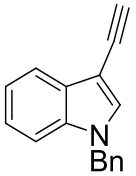
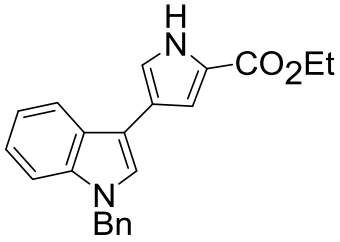
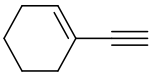
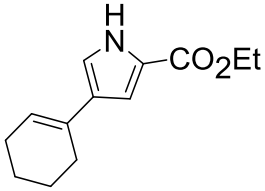
Entry	Alkyne	Catalyst	Product	Isolated yield
a		**1**		65% [a]
b		**2**		42% [b]
c		**2**		38% [b]
d		**1**		35% [a]
e		**1**		44% [a]
f		**1**		45% [a]

Table 4.1 (cont'd)

g		**1**		40% [a]
h		**2**		37% [b]
i		**1**		48% [a]

[a] Reactions carried out with cyclohexylamine, alkyne, and *tert*-butylisonitrile in a 1:1:1.5 ratio with 10 mol % catalyst (**1**) at 100 °C for 24 h. Once the 3CC is complete, product was heated at 80 °C in DMSO with glycine ethyl ester hydrochloride (2.0 equiv) and triethyl amine (2.0 equiv) for 18 h.

[b] Aniline was used in place of cyclohexylamine.

During the first part of the study, titanium catalyzed multicomponent coupling of various terminal alkynes (heterocycle-, alkyl-, and aryl-substituted) were condensed with glycine ethyl ester hydrochloride, which results exclusively in 4-substituted pyrrole-2-carboxylates in moderate yields (**Table 4.1**, entries a-i).

In the second part of the study substituted pyrrole-2-carboxylates were synthesized from internal alkynes as summarized in Table 4.2. This methodology results exclusively in 4,5-disubstituted pyrrole-2-carboxylates in modest yields (**Table 4.2**, entry a-d). Alkyl-containing internal alkynes such as hex-3-yne and 2-methylhex-1-en-3-yne results in production of the 3CC product in good yields using either catalyst; however, for reasons currently unknown the addition of glycine ethyl ester hydrochloride under any reaction conditions we investigated did not result in formation of the alkyl-substituted pyrrole-2-carboxylates. The regiochemistry was determined by an X-ray structure of the product with prop-1-yn-1-ylbenzene (**Figure 4.3**). The regio-chemistry with the other unsymmetrical alkynes were assumed to occure with the incorporation of the largest group in the 4-position.

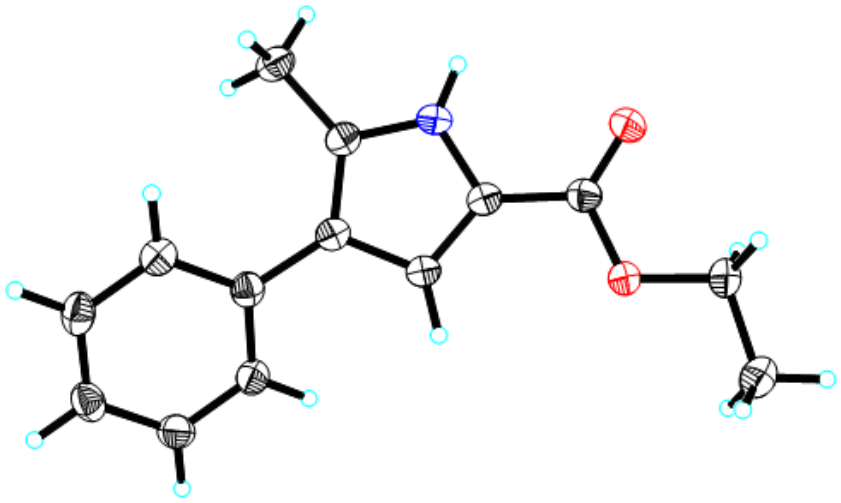
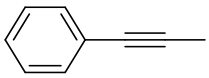
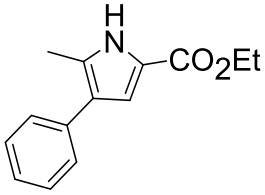
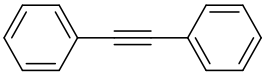
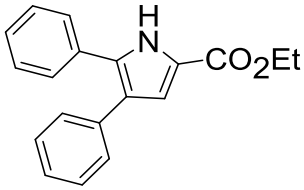
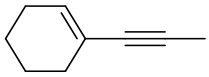
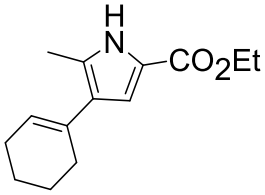
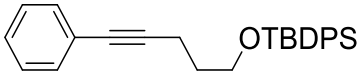
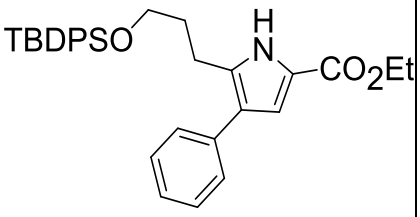


Figure 4.3 Structure of by ethyl 5-methyl-4-phenyl-1H-pyrrole-2-carboxylate X-ray diffraction

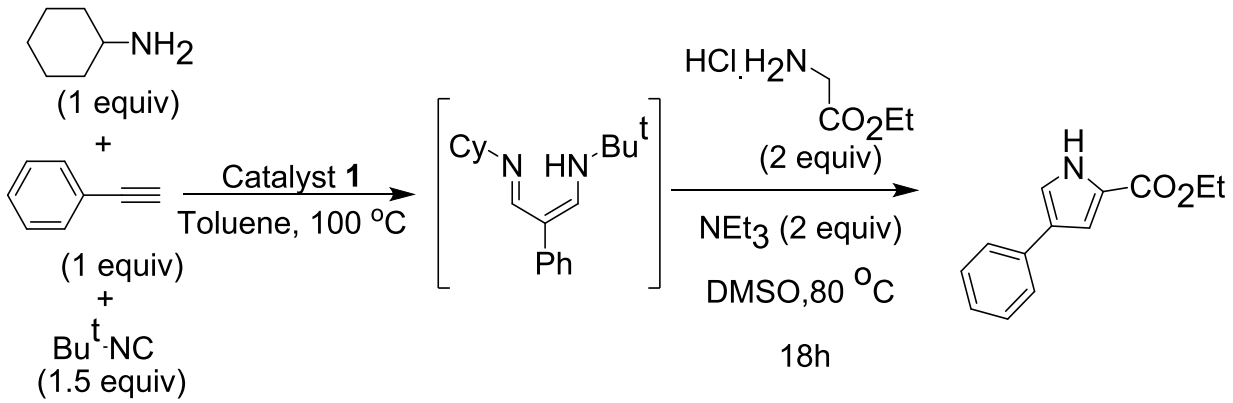
Table 4.2 Examples of pyrrole-2-carboxylates syntheses using glycine ethyl ester hydrochloride with different internal alkynes (**Scheme 4.4**)

Entry	Alkyne	Catalyst	Product	Isolated yield
a		**2**		37% [a]
b		**2**		25% [a]
c		**2**		32% [a]
d		**2**		30% [a]

[a] Reactions carried out with aniline, alkyne, and *tert*-butylisonitrile in a 1:1:1.5 ratio with 10 mol % catalyst (**2)** at 100 °C for 48 h. Once the 3CC is complete, product was heated at 80 °C in DMSO with glycine ethyl ester hydrochloride (2.0 equiv) and triethyl amine (2.0 equiv) for 18 h.

Reaction scaleing up of ethyl 4-phenyl-1H-pyrrole-2-carboxylate

In order to scale up the synthesis of substituted pyrrole-2-carboxylates, one pot synthesis of ethyl 4-phenyl-1H-pyrrole-2-carboxylate was used as a molel study (**Scheme 4.5**). Multicomponent reaction of cyclohexylamine, phenylacetylene, and *tert*-butylisonitrile were carried out in 15 mmol scale with respect to the alkyne and cyclocondensation reaction conditions were varied by the nature of the reaction vesele and the order of addition of the reagents in the second step.



Scheme 4.5 synthesis of ethyl 4-phenyl-1H-pyrrole-2-carboxylate

Observed results are summarized in **Table 4.3,** isolated ethyl 4-phenyl-1H-pyrrole-2-carboxylate yields vary from 21.8%- 26.0%. Even though the Change of reaction vessel Schlenk flask to a roundbottom flask slightly improves the isolated yield, further improvements are currently under investigation.

Table 4.3 Scaleing up of ethyl 4-phenyl-1H-pyrrole-2-carboxylate

Entry	Reaction flask type	Isolated yield
Attempt 1	Schlenk flask (250 mL)	22.3% (720 mg) [a]
Attempt 2	Schlenk flask (250 mL)	24.0% (774 mg) [b]
Attempt 3	Schlenk flask (250 mL)	23.2% (748 mg) [c]
Attempt 4	Schlenk flask (1000 mL)	24.7% (799 mg) [a]
Attempt 5	Schlenk flask flat bottom (250 mL)	21.8% (704 mg) [a]
Attempt 6	Round bottom flask (1000 mL)	26.0% (840 mg) [a]
Attempt 7	Round bottom flask (1000 mL)	23.0% (741 mg) [e]

[a] Reactions carried out with cyclohexylamine (15 mmol), phenylacetylene (15 mmol), and *tert*-butylisonitrile (22.5 mmol) with 10 mol % catalyst (**1)** at 100 °C for 24 h. Once the 3CC is complete, product was heated at 80 °C in DMSO with glycine ethyl ester hydrochloride (2.0 equiv) and triethyl amine (2.0 equiv) for 18 h.

[b] Multicomponent coupling product was isolate and then heated at 80 °C in DMSO with glycine ethyl ester hydrochloride (2.0 equiv) and triethyl amine (2.0 equiv) for 18 h.

[c] Triethyl amine (6.0 equiv) was used for the 2nd step

[d] Multicomponent coupling product was transferred to a round bottom flask for the 2nd step

Table 4.3 (cont'd)

[e] Glycine ethyl ester hydrochloride (2.0 equiv) in DMSO was added to the round bottom flask via a syringe pump over 16h

4.3 Conclusion

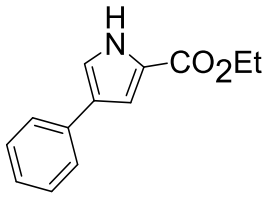
Titanium-catalyzed 3-component coupling of primary a amine, an alkyne, and an isonitrile followed by treatment with glycine ethyl ester hydrochloride provides substituted pyrrole-2-carboxylates in a one-pot procedure. This new procedure has significant flexibility in the types of substituted pyrrole-2-carboxylates that can be accessed. The yields are generally modest, but the products are readily isolated using column chromatography. Reactions with terminal alkynes are more facile and can be accomplished with the milder $Ti(NMe_2)_2$(dpma) (**1**) as catalyst. The more active dipyrrolylmethane catalyst $Ti(NMe_2)_2$(dpm) (**2**) was used for internal alkynes.

The reaction has several points to allow optimization for a specific target of interest. For example, the type of substituent on the isonitrile can potentially be varied in this reaction to improve regioselectivities or yields. This methodology allows access to a large number of 4,5-disubstituted and 4-substituted pyrrole-2-carboxylates in a regioselective manner from internal and terminal alkynes respectively. The catalyst architectures themselves are also quite flexible and could be optimized for specific products.

4.4 Experimental

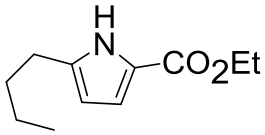
General Considerations*:* All manipulations of air sensitive compounds were carried out in an MBraun dry box under a purified nitrogen atmosphere. Toluene was purified by sparging with dry N_2 and removing water by running through activated alumina systems purchased from Solv-Tek. ^{1}H and ^{13}C spectra were recorded on VXR-500 spectrometers. Melting points were measured on a Mel-Temp II apparatus (Laboratory Devices Inc, USA) with a mercury thermometer and are uncalibrated. $Ti(NMe_2)_2$(dpma) (**1**) and $Ti(NMe_2)_2$(dpm) (**2**) were made following the literature procedures.[26,27] Alkynes were purchased either from Aldrich or from GFS chemicals and were distilled from BaO under dry nitrogen. Amines were purchased from Aldrich, dried over KOH, and distilled under dry N_2. *tert*-Butylisonitrile was made according to the literature procedure and purified by distillation under N_2.[28] Glycine ethyl ester hydrochloride and neutral alumina were purchased Sigma-Aldrich Co and used as received. EtOH (ethanol), CH_2Cl_2, hexanes, tetrahydrofuran (THF) and EtOAc (ethyl acetate) were purchased from Mallinckrodt chemicals and used as received.

Preparation and Characterization of Compounds in Table 4.1



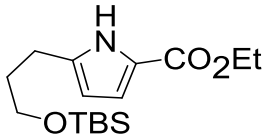
Ethyl 4-phenyl-1H-pyrrole-2-carboxylate (Table 4.1, entry a)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **1** (32.4 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (95 mg, 1 mmol), phenylacetylene (102 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature, and volatiles were removed in vacuo. Then, the tube was charged with glycine ethyl ester hydrochloride (280 mg, 2 mmol) and triethylamine (280 μL, 2 mmol) in DMSO (2 mL). The tube was heated to 80 °C for 18 h in a silicon oil bath. After completion of the reaction, the DMSO solution was diluted with CH_2Cl_2 (40 mL) and washed with 10% $NaHCO_3$ (20 mL) followed by saturated NaCl (20 mL) solution. The organic layer was dried over anhydrous Na_2SO_4, and volatiles were removed in vacuo. The crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (139 mg, 65%) as a light brown solid. M.p.: 97-99 °C (lit. Mp: 98-99 °C).[29] ^{1}H NMR ($CDCl_3$, 500 MHz): 1.29-1.32 (3 H, 7 Hz, t, CH_3), 4.26-4.30 (2 H, 7 Hz, q, CH_2), 7.14-7.18 (3H, m, CH-Ar), 7.27-7.30 (2H, m, 3,5-CH-pyrrole), 7.44-7.46 (2H,

m, CH-Ar), 9.25 (1H, br, NH-pyrrole). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 14.4, 60.5, 112.4, 119.4, 123.7, 125.3, 126.5, 126.8, 128.7, 134.5, 161.2. MS(EI): *m/z* 215. Elemental Analysis: found: %C, 72.42; % H, 6.16; %N, 6.59; expected: %C, 72.54; %H, 6.09; %N, 6.51.



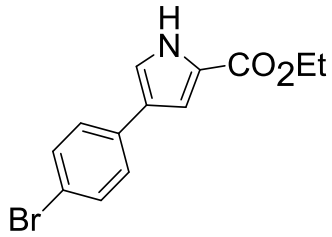
Ethyl 5-butyl-1H-pyrrole-2-carboxylate (Table 4.1, entry b)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), 1-hexyne (82 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature, and volatiles were removed in vacuo. Then, the tube was charged with glycine ethyl ester hydrochloride (280 mg, 2 mmol) and triethylamine (280 μL, 2 mmol) in DMSO (2 mL). The tube was heated to 80 °C for 18 h in a silicon oil bath. After completion of the reaction, the DMSO solution was diluted with CH_2Cl_2 (40 mL) and washed with 10% $NaHCO_3$ (20 mL) followed by saturated NaCl (20 mL) solution. The organic layer was dried over anhydrous Na_2SO_4, and volatiles were removed in vacuo. The crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (82 mg, 42%) as a light brown liquid. ^{1}H NMR ($CDCl_3$, 500

MHz): 0.86-0.91 (3 H, 7 Hz, t, CH_3), 1.31-1.35 (5 H, m, CH_2 and CH_3), 1.57-1.63 (2 H, 7.5 Hz, 7 Hz, quin, CH_2), 2.59-2.62 (2 H, 7.5 Hz, t, CH_2), 4.26-4.31 (2 H, 7 Hz, q, CH_2), 5.93-5.95 (1H, d, 6 Hz 4-CH-pyrrole), 6.80-6.81 (1H, d, 6 Hz 3-CH-pyrrole), 9.40 (1H, br, NH-pyrrole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 13.7, 14.5, 22.2, 27.5, 31.4, 60.0, 107.8, 115.8, 121.0, 139.0, 161.5. MS(EI): *m/z* 195. Elemental Analysis: found: %C, 67.74; % H, 8.70; %N, 7.24; expected: %C, 67.66; %H, 8.78; %N, 7.17.



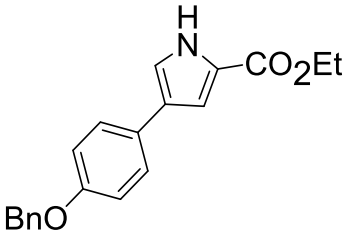
Ethyl 5-(3-((tert-butyldimethylsilyl)oxy)propyl)-1H-pyrrole-2-carboxylate (Table 4.1, entry c)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), *tert*-butyldimethyl(pent-4-yn-1-yloxy)silane (198 mg, 1 mmol), and *tert*-butylisonitrile (171 µL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature, and volatiles were removed in vacuo. Then, the tube was charged with glycine ethyl ester hydrochloride (280 mg, 2 mmol) and triethylamine (280 µL, 2 mmol) in DMSO (2 mL). The tube was heated to 80 °C for 18 h in a silicon oil bath. After completion of the reaction, the DMSO solution was diluted with CH_2Cl_2 (40 mL) and washed with 10% $NaHCO_3$ (20 mL) followed by saturated NaCl (20 mL) solution. The organic layer was dried over anhydrous

Na_2SO_4, and volatiles were removed in vacuo. The crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (118 mg, 38%) as a light brown liquid. ^{1}H NMR ($CDCl_3$, 500 MHz): 0.029 (6H, s, Si-CH_3), 0.89 (9H, s, Si-C(CH_3)$_3$, 1.31-1.40 (3 H, 7 Hz, t, CH_3), 1.79-1.85 (2 H, 7.5 Hz, 7 Hz, quin, CH_2), 2.68-2.71 (2 H, 7.5 Hz, t, CH_2), 3.61-3.63 (2 H, 6 Hz, t, CH_2), 4.25-4.29 (2 H, 7 Hz, q, CH_2), 5.93-5.94 (1H, d, 6 Hz 4-CH-pyrrole), 6.80-6.81 (1H, d, 6 Hz 3-CH-pyrrole), 9.31 (1H, br, NH-pyrrole). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): -5.3, 14.5, 18.3, 24.1, 25.9, 31.9, 59.9, 61.9, 108.0, 115.8, 121.3, 138.1, 161.2. MS(EI): *m/z* 311. Elemental Analysis: found: %C, 61.82; % H, 9.13; %N, 4.78; expected: %C, 61.69; %H, 9.38; %N, 4.50.



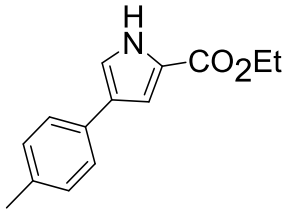
Ethyl 4-(4-bromophenyl)-1H-pyrrole-2-carboxylate (Table 4.1, entry d**):** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **1** (32.4 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (95 mg, 1 mmol), 1-bromo-4-ethynylbenzene (181 mg, 1 mmol), and *tert*-butylisonitrile (171 µL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature, and volatiles were

removed in vacuo. Then, the tube was charged with glycine ethyl ester hydrochloride (280 mg, 2 mmol) and triethylamine (280 μL, 2 mmol) in DMSO (2 mL). The tube was heated to 80 °C for 18 h in a silicon oil bath. After completion of the reaction, the DMSO solution was diluted with CH_2Cl_2 (40 mL) and washed with 10% $NaHCO_3$ (20 mL) followed by saturated NaCl (20 mL) solution. The organic layer was dried over anhydrous Na_2SO_4, and volatiles were removed in vacuo. The crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (103 mg, 35%) as a light brown solid. M.p.: 157-159 °C (lit. Mp: 159-160 °C).[29] ^{1}H NMR ($CDCl_3$, 500 MHz):1.40-1.22 (3 H, 7 Hz, t, CH_3), 4.35-4.40 (2 H, 7 Hz, q, CH_2), 7.18-7.19 (1H, d, 5-CH-pyrrole), 7.23-7.24 (1H, d, 5-CH-pyrrole), 7.40-7.43 (2H, m, CH-Ar), 7.48-7.51 (2H, m, CH-Ar), 9.24 (1H, br, NH-pyrrole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 14.4, 60.6, 112.2, 119.2, 125.7, 126.8, 128.3, 129.6, 131.8, 133.5, 160.9. MS(EI): *m/z* 294. Elemental Analysis: found: %C, 53.17; % H, 4.03; %N, 4.83; expected: %C, 53.08; %H, 4.11; %N, 4.76.



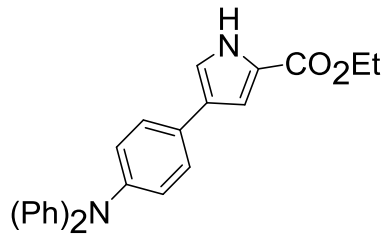
Ethyl 4-(4-(benzyloxy)phenyl)-1H-pyrrole-2-carboxylate (Table 4.1, entry e)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **1** (32.4 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (95 mg, 1 mmol), 1-

(benzyloxy)-4-ethynylbenzene (208 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature, and volatiles were removed in vacuo. Then, the tube was charged with glycine ethyl ester hydrochloride (280 mg, 2 mmol) and triethylamine (280 μL, 2 mmol) in DMSO (2 mL). The tube was heated to 80 °C for 18 h in a silicon oil bath. After completion of the reaction, the DMSO solution was diluted with CH_2Cl_2 (40 mL) and washed with 10% $NaHCO_3$ (20 mL) followed by saturated NaCl (20 mL) solution. The organic layer was dried over anhydrous Na_2SO_4, and volatiles were removed in vacuo. The crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (141 mg, 44%) as a brown solid. M.p.: 146-147 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.35-1.38 (3 H, 7 Hz, CH_3), 4.31-4.35 (2 H, 7 Hz, q, CH_2), 5.06 (2 H, s, CH_2), 6.92-6.98 (2H, m, CH-Ar), 7.12-7.13 (2H, m, CH-Ar), 7.29-7.44 (7H, m, CH-Ar, 3,5-CH-pyrrole), 9.22 (1H, br, NH-pyrrole). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 14.4, 60.3, 70.1, 112.1, 115.2, 118.7, 123.5, 126.4, 126.5, 127.4, 127.6, 127.9, 128.5, 137.1, 157.5, 161.2. MS(EI): *m/z* 321. Elemental Analysis: found: %C, 74.64; % H, 5.89; %N, 4.42; expected: %C, 74.75; %H, 5.96; %N, 4.36.



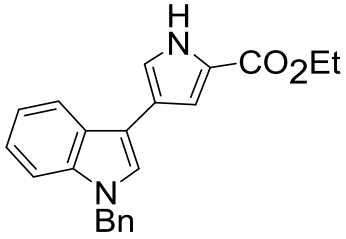
Ethyl 4-(p-tolyl)-1H-pyrrole-2-carboxylate (Table 4.1, entry f)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **1** (32.4 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (95 mg, 1 mmol), 1-ethynyl-4-methylbenzene (116 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature, and volatiles were removed in vacuo. Then, the tube was charged with glycine ethyl ester hydrochloride (280 mg, 2 mmol) and triethylamine (280 μL, 2 mmol) in DMSO (2 mL). The tube was heated to 80 °C for 18 h in a silicon oil bath. After completion of the reaction, the DMSO solution was diluted with CH_2Cl_2 (40 mL) and washed with 10% $NaHCO_3$ (20 mL) followed by saturated NaCl (20 mL) solution. The organic layer was dried over anhydrous Na_2SO_4, and volatiles were removed in vacuo. The crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (103 mg, 40%) as a light brown solid. M.p.: 166-167 °C (lit. Mp: 165-166 °C).[29] ^{1}H NMR ($CDCl_3$, 500 MHz):1.45-1.47 (3 H, 7 Hz, t, CH_3), 4.40-4.45 (2 H, 7 Hz, q, CH_2), 7.25-7.27 (4H, m, CH-Ar 3,5-CH-pyrrole), 7.49-7.50 (2H, d, CH-Ar), 9.45 (1H, br, NH-pyrrole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 14.4, 21.0, 60.4, 112.3,

119.2, 123.6, 125.2, 126.8, 129.4, 131.7, 135.8, 161.2. MS(EI): *m/z* 233. Elemental Analysis: found: %C, 73.42; % H, 6.49; %N, 6.19; expected: %C, 73.34; %H, 6.59; %N, 6.11.



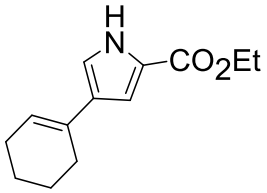
Ethyl 4-(4-(diphenylamino)phenyl)-1H-pyrrole-2-carboxylate (Table 4.1, entry g)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **1** (32.4 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (95 mg, 1 mmol), 4-ethynyl-N,N-diphenylaniline (269 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature, and volatiles were removed in vacuo. Then, the tube was charged with glycine ethyl ester hydrochloride (280 mg, 2 mmol) and triethylamine (280 μL, 2 mmol) in DMSO (2 mL). The tube was heated to 80 °C for 18 h in a silicon oil bath. After completion of the reaction, the DMSO solution was diluted with CH_2Cl_2 (40 mL) and washed with 10% $NaHCO_3$ (20 mL) followed by saturated NaCl (20 mL) solution. The organic layer was dried over anhydrous Na_2SO_4, and volatiles were removed in vacuo. The crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (153 mg, 40%) as a brown solid. M.p.: 128-130 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.39-1.43 (3

H, 7 Hz, CH_3), 4.36-4.41 (2 H, 7 Hz, q, CH_2), 7.01-7.04 (2H, m, CH-Ar), 7.10-7.14 (6H, m, CH-Ar, 3,5-CH-pyrrole), 7.19-7.20 (2H, m, CH-Ar), 7.25-7.27 (4H, m, CH-Ar), 7.42-7.44 (2H, d, 8.5 Hz, CH-Ar), 9.48 (1H, br, NH-pyrrole). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 14.4, 60.5, 112.1, 119.1, 122.5, 123.5, 123.9, 124.5, 126.0, 126.4, 129.2, 146.1, 147.7, 161.2. MS(EI): *m/z* 382. Elemental Analysis: found: %C, 78.64; % H, 5.67; %N, 7.24; expected: %C, 78.51; %H, 5.80; %N, 7.32.



Ethyl 4-(1-benzyl-1H-indol-3-yl)-1H-pyrrole-2-carboxylate (Table 4.1, entry h)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with), aniline (93 mg, 1 mmol), 1-benzyl-3-ethynyl-1H-indole (231 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature, and volatiles were removed in vacuo. Then, the tube was charged with glycine ethyl ester hydrochloride (280 mg, 2 mmol) and triethylamine (280 μL, 2 mmol) in DMSO (2 mL). The tube was heated to 80 °C for 18 h in a silicon oil bath. After completion of the reaction, the DMSO solution was diluted with CH_2Cl_2 (40 mL) and washed with 10% $NaHCO_3$ (20 mL) followed by saturated NaCl (20 mL)

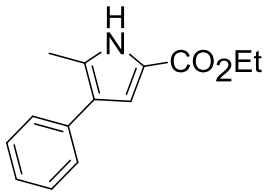
solution. The organic layer was dried over anhydrous Na_2SO_4, and volatiles were removed in vacuo. The crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (127 mg, 37%) as a light brown solid. M.p.: 131-134 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 141-1.44 (3 H, 7 Hz, CH_3), 4.33-4.43 (2 H, 7 Hz, q, CH_2), 5.35 (2 H, s, CH_2), 7.19-7.35 (11H, m, CH-Ar, 3,5-CH-pyrrole), 7.90-7.92 (1H, d, 4 Hz, 2-CH-indole), 9.34 (1H, br, NH-pyrrole). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 14.4, 49.9, 60.3, 109.8, 113.3, 119.4, 119.7, 120.2, 121.9, 123.1, 124.7, 126.5, 126.8, 127.6, 128.3, 128.7, 129.6, 137.3, 161.2. MS(EI): *m/z* 344. Elemental Analysis: found: %C, 76.79; % H, 5.74; %N, 8.19; expected: %C, 76.72; %H, 5.85; %N, 8.13.



Ethyl 4-(cyclohex-1-en-1-yl)-1H-pyrrole-2-carboxylate (Table 4.1, entry i)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **1** (32.4 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (95 mg, 1 mmol), 1-ethynylcyclohex-1-ene (106 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature, and volatiles were removed in vacuo. Then, the tube was charged with glycine ethyl ester hydrochloride (280

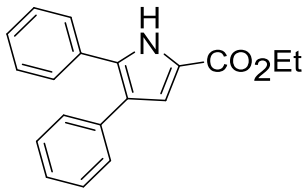
mg, 2 mmol) and triethylamine (280 μL, 2 mmol) in DMSO (2 mL). The tube was heated to 80 °C for 18 h in a silicon oil bath. After completion of the reaction, the DMSO solution was diluted with CH_2Cl_2 (40 mL) and washed with 10% $NaHCO_3$ (20 mL) followed by saturated NaCl (20 mL) solution. The organic layer was dried over anhydrous Na_2SO_4, and volatiles were removed in vacuo. The crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (105 mg, 48%) as a light brown solid. M.p.: 56-59 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.31-1.39 (3 H, 7 Hz, CH_3), 1.58-1.63 (2H, m, CH_2), 1.68-1.73 (2H, m, CH_2), 2.10-2.14 (2H, m, CH_2), 2.24-2.27 (2H, m, CH_2), 4.26-4.30 (2 H, 7 Hz, q, CH_2), 5.98-6.00 (1H, m, CH), 6.95-6.96 (1H, 2 Hz, 5-CH-pyrrole), 6.88-6.89 (1H, 2 Hz, 3-CH-pyrrole), 9.28 (1H, br, NH-pyrrole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 14.4, 22.3, 22.7, 25.3, 27.0, 60.3, 110.9, 118.4, 120.6, 122.8, 129.9, 161.4. MS(EI): *m/z* 219. Elemental Analysis: found: %C, 71.29; % H, 7.64; %N, 6.30; expected: %C, 71.21; %H, 7.81; %N, 6.39.

Preparation and Characterization of Compounds in Table 4.2



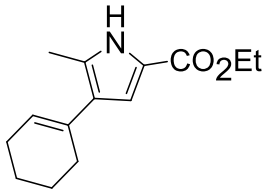
Ethyl 5-methyl-4-phenyl-1H-pyrrole-2-carboxylate (Table 4.2, entry a)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with), aniline (93 mg, 1 mmol), prop-1-yn-1-ylbenzene (116 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature, and volatiles were removed in vacuo. Then, the tube was charged with glycine ethyl ester hydrochloride (280 mg, 2 mmol) and triethylamine (280 μL, 2 mmol) in DMSO (2 mL). The tube was heated to 80 °C for 18 h in a silicon oil bath. After completion of the reaction, the DMSO solution was diluted with CH_2Cl_2 (40 mL) and washed with 10% $NaHCO_3$ (20 mL) followed by saturated NaCl (20 mL) solution. The organic layer was dried over anhydrous Na_2SO_4, and volatiles were removed in vacuo. The crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (84 mg, 37%) as a pale yellow solid. M.p.: 124-126 °C (lit. Mp: 125.5 °C).[30] ^{1}H NMR ($CDCl_3$, 500 MHz): 1.40-1.43 (3 H, 7 Hz, t, CH_3), 2.49 (1 H, s, CH_3), 4.36-4.41 (2 H, 7 Hz, q, CH_2), 7.07-7.08 (1H, d, 3-CH-pyrrole), 7.26-7.30 (1H, m, CH-Ar),7.41-7.46 (4H, m, CH-Ar), 9.63 (1H, br, NH-pyrrole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz):

12.8, 14.4, 60.2, 115.3, 120.6, 123.7, 125.8, 127.6, 128.4, 130.4, 135.8, 161.5. MS(EI): *m/z* 229. Elemental Analysis: found: %C, 73.38; % H, 6.52; %N, 6.04; expected: %C, 73.34; %H, 6.59; %N, 6.11. Further characterized by X-ray diffraction studies.



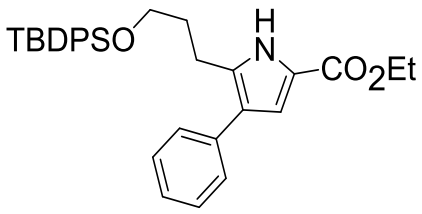
Ethyl 4,5-diphenyl-1H-pyrrole-2-carboxylate (Table 4.2, entry b)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with), aniline (93 mg, 1 mmol), 1,2-diphenylethyne (178 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature, and volatiles were removed in vacuo. Then, the tube was charged with glycine ethyl ester hydrochloride (280 mg, 2 mmol) and triethylamine (280 μL, 2 mmol) in DMSO (2 mL). The tube was heated to 80 °C for 18 h in a silicon oil bath. After completion of the reaction, the DMSO solution was diluted with CH_2Cl_2 (40 mL) and washed with 10% $NaHCO_3$ (20 mL) followed by saturated NaCl (20 mL) solution. The organic layer was dried over anhydrous Na_2SO_4, and volatiles were removed in vacuo. The crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (73 mg, 25%) as a pale yellow solid. M.p.: 139-141

°C (lit. Mp: 141-142 °C).[31] ^{1}H NMR ($CDCl_3$, 500 MHz): 1.11-1.14 (3 H, 7 Hz, t, CH_3), 4.14-4.19 (2 H, 7 Hz, q, CH_2), 7.07-7.13 (3H, m, CH-Ar), 7.14-7.18 (3H, m, CH-Ar), 7.24-7.27 (5H, m, CH-Ar, 3-CH-pyrrole), 9.32 (1H, br, NH-pyrrole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 14.0, 60.2, 120.2, 126.0, 126.7, 126.8, 127.4, 128.1, 128.2, 128.3, 129.3, 129.6, 130.8, 132.9, 134.5, 161.2. MS(EI): *m/z* 291. Elemental Analysis: found: %C, 78.39; % H, 5.81; %N, 4.88; expected: %C, 78.33; %H, 5.88; %N, 4.81.



Ethyl 4-(cyclohex-1-en-1-yl)-5-methyl-1H-pyrrole-2-carboxylate (Table 4.2, entry c)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with), aniline (93 mg, 1 mmol), 1-(prop-1-yn-1-yl)cyclohex-1-ene (120 mg, 1 mmol), and *tert*-butylisonitrile (171 µL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature, and volatiles were removed in vacuo. Then, the tube was charged with glycine ethyl ester hydrochloride (280 mg, 2 mmol) and triethylamine (280 µL, 2 mmol) in DMSO (2 mL). The tube was heated to 80 °C for 18 h in a silicon oil bath. After completion of the reaction, the DMSO solution was diluted with CH_2Cl_2 (40 mL) and washed with 10% $NaHCO_3$ (20 mL)

followed by saturated NaCl (20 mL) solution. The organic layer was dried over anhydrous Na_2SO_4, and volatiles were removed in vacuo. The crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (74 mg, 32%) as a viscous yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.30-1.34 (3 H, 7 Hz, t, CH_3), 2.49 (1 H, s, CH_3), 1.59-1.63 (2 H, m, C*H*$_2$), 1.69-1.73 (2 H, m, CH_2), 2.12-2.16 (2 H, m, CH_2), 2.24-2.27 (2 H, m, CH_2), 2.32 (3 H, s, CH_3), 4.25-4.29 (2 H, 7 Hz, q, CH_2), 5.67-5.69 (1 H, m, CH), 6.78-6.79 (1H, d, 2.5 Hz, 3-CH-pyrrole), 8.94 (1H, br, NH-pyrrole). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 13.5, 14.5, 22.2, 23.1, 25.5, 29.6, 60.0, 114.0, 119.6, 123.4, 125.4, 129.5, 131.5, 161.3. MS(EI): *m/z* 233. Elemental Analysis: found: %C, 72.13; % H, 8.13; %N, 6.08; expected: %C, 72.07; %H, 8.21; %N, 6.00.



Ethyl 5-(3-((tert-butyldiphenylsilyl)oxy)propyl)-4-phenyl-1H-pyrrole-2-carboxylate (Table 4.2, entry d)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with), aniline (93 mg, 1 mmol), *tert*-butyldiphenyl((5-phenylpent-4-yn-1-yl)oxy)silane (398 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap,

taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature, and volatiles were removed in vacuo. Then, the tube was charged with glycine ethyl ester hydrochloride (280 mg, 2 mmol) and triethylamine (280 μL, 2 mmol) in DMSO (2 mL). The tube was heated to 80 °C for 18 h in a silicon oil bath. After completion of the reaction, the DMSO solution was diluted with CH_2Cl_2 (40 mL) and washed with 10% $NaHCO_3$ (20 mL) followed by saturated NaCl (20 mL) solution. The organic layer was dried over anhydrous Na_2SO_4, and volatiles were removed in vacuo. The crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (154 mg, 30%) as a brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.1 (9 H, s, $C(CH_3)_3$, 1.36-1.38 (3 H, 7 Hz, t, CH_3), 1.87-1.91 (2 H, 7.5 Hz, 7 Hz, quin, CH_2), 2.96-2.99 (2 H, 7.5 Hz, t, CH_2), 3.73-3.76 (2 H, 6 Hz, t, CH_2), 4.33-4.37 (2 H, 7 Hz, q, CH_2), 7.06 (1H, s, 3-CH-pyrrole), 7.26-7.30 (2H, m, CH-Ar), 7.37-7.48 (9H, m, CH-Ar), 7.68-7.70 (4H, m, CH-Ar), 9.26 (1H, br, NH-pyrrole).$^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 14.5, 19.2, 22.9, 26.8, 29.7, 60.2, 62.8, 120.9, 123.8, 125.9, 127.7, 127.8, 128.1, 128.5, 129.5, 129.6, 131.5, 133.6, 161.1. Elemental Analysis: found: %C, 75.19; % H, 7.22; %N, 2.82; expected: %C, 75.11; %H, 7.29; %N, 2.74.

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CHAPTER 5. TITANIUM-CATALYZED MULTICOMPONENT COUPLING REACTIONS FOR THE SYNTHESIS OF 5-SUBSTITITED AND 5,6-DISUBSTITITED 2-AMINO-3-CYANO-PYRIDINES

5.1 Introduction

The pyridine core structure is one of the most important heterocyclic ring structures as it is found in many natural products.[1] Among these, 2-amino-3-cyanopyridine derivatives are an important class of heterocyclic compounds in the synthetic community.[2,3] Substituted 2-amino-3-cyano-pyridine derivatives exhibits biological activities (**Figure 5.1**) such as anti-hypertensive,[4] IKK-β-inhibitory,[5] anti-microbial,[6] anti-viral,[7] anti-bacterial,[8] anti-tumour,[9] anti-fungal,[10] and anti-inflammatory activity.[11] They are also used as pigments,[12] and as ligands for transition metal catalysis.[13]

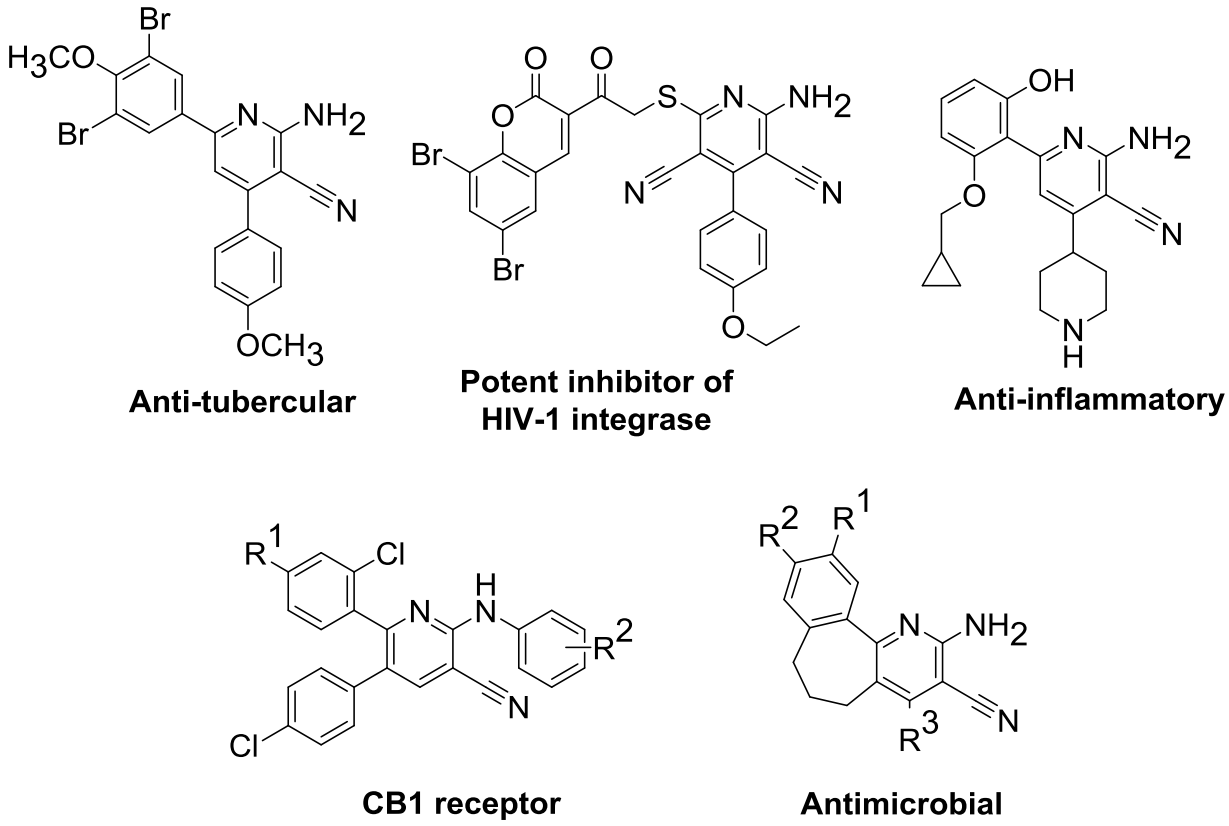
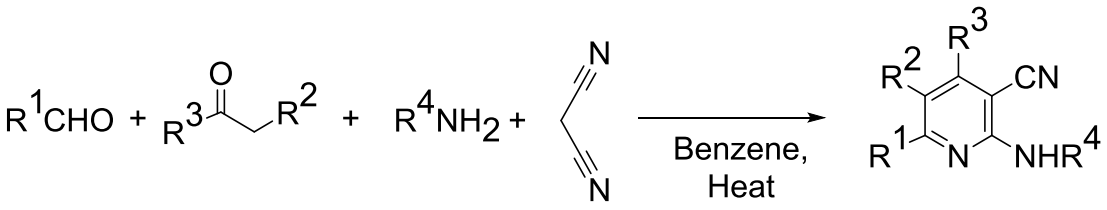


Figure 5.1 Bioactive substitited 2-amino-3-cyano-pyridines

Microwave-assisted multicomponent coupling reactions in organic synthesis have received much interest in recent years due to high atom economy and bond-forming efficiency.[14] In 2010 the Tu group and 2007 the Shi group reported the synthesis of N-substituted aminopyridines by employing a one-pot three-component reaction of α,β-unsaturated ketones, malononitrile and primary amines under micro-wave irridation in good yields *(***Scheme 5.1***)*.[15]

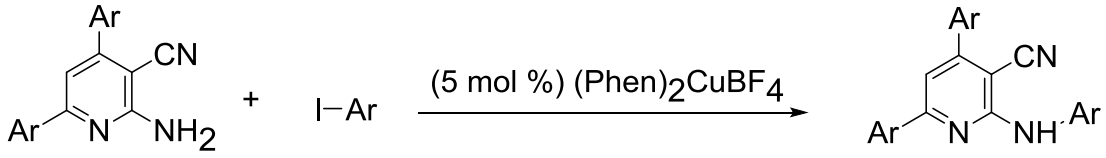
Scheme 5.1 Microwave-assisted 3-component synthesis of substitited 2-amino-3-cyano-pyridines

These three component multicomponent[16] were further extended to four component multicomponent coupling reactions by substituting α,β-unsaturated ketones with an aldehyde and a carbonyl compound to obtain N-arylated-2-amino-3-cyano-pyridine derivatives. These four component reactions can be carried out under thermal or micro-wave irridation conditions (**Scheme 5.2**). Substituted-2-amino-3-cyano-pyridine derivatives can be easily obtained simply by changing the primary amine to ammonium acetate under same reaction conditions.[17]



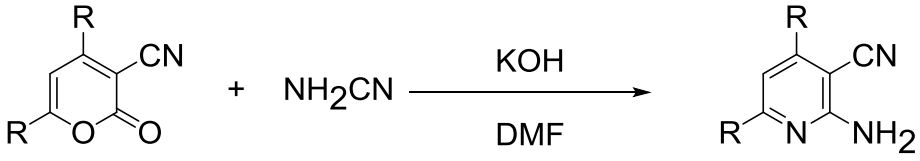
Scheme 5.2 Microwave-assisted 4-component synthesis of substituted 2-amino-3-cyano-pyridines

Recently, Ding and co-workers have reported copper-catalyzed N-arylation of 2-amino-3-cyano-pyridines with aryl halides (Ulmann-type coupling).[18] This new economical and less toxic synthetic protocol has been applied to synthesis of wide range 2-aryamino-3-cyano-pyridine products in good to excellent yields (**Scheme 5.3**).



Scheme 5.3 N-Arylation of 2-amino-3-cyano-pyridines using copper(I) catalyst

Substituted-2-amino-3-cyano-pyridines can also be synthesized by ring transformations of heterocyclic compounds. Ram and co-workers reported the ring transformation of 2*H*-pyran-2-ones to substituted 2-amino-3-cyano-pyridines in moderate yields (**Scheme 5.4**).[19] Similarly Shi and co-workers also demonstrated the ring transformation of chromene-3-carbonitrile to substituted 2-aminoquinoline-3-carbonitriles under microwave irradiation in good yields.[20]



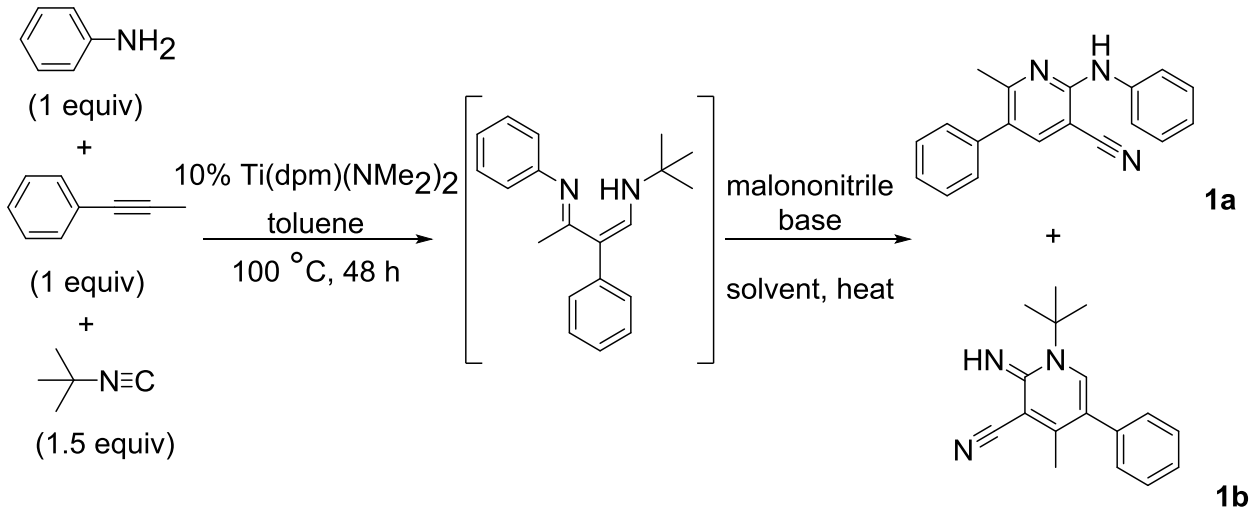
Scheme 5.4 Substituted 2-amino-3-cyano-pyridines from 2*H*-pyran-2-ones

In this study, we demonstrate that a variety of substituted 2-amino-3-cyano-pyridines can be prepared in a one-pot 4-component fashion (**Scheme 5.6**). The methodology uses a titanium-catalyzed 3-component coupling of an alkyne, isonitrile, and primary amine to generate unsymmetrical 1,3-diimine tautomers.[21] Substituted-2-amino-3-cyano-pyridines result from simply removing the volatiles from the multicomponent coupling reaction and treating the crude product with commercially available malononitrile under basic reaction conditions in refluxing ethanol.

5.2 Results and Discussion

Our group has been investigating a titanium-catalyzed 3-component coupling (3CC) reaction that generates tautomers of 1,3-diimines.[21] In this work we report that these 3CC products, can be used as direct precursors for the synthesis of substituted 2-amino-3-cyano-pyridines and related heterocycles in a one-pot procedure simply by adding malononitrile to the multicomponent coupling product (**Scheme 5.5**).

Two titanium catalysts Ti(dpma)$(NMe_2)_2$ (**1**) and Ti(dpm)$(NMe_2)_2$ (**2**) were employed for this study. They can be prepared (refer to chapter 3) in a single step by reacting the ancillary ligands with commertially available $Ti(NMe_2)_4$. The proposed catalytic cycle involved in the synthesis of the 3CC product (discussed in chapter 3) is based on the mechanism for catalytic hydroamination.



Scheme 5.5 Reaction of 3CC product with malononitrile

Our initial studies were focused on the product catalyzed multicomponent reaction of aniline, prop-1-yn-1-ylbenzene and *tert*-butylisonitrile with malononitrile under basic reaction conditions. Preliminary studies resulted in a mixture of substituted 2-amino-3-cyano-pyridine derivative (6-Methyl-5-phenyl-2-(phenylamino)nicotinonitrile) (**1a**) (**Figure 5.2**) and 1,2-dihydropyridine derivative 1-(*tert*-butyl)-2-imino-4-methyl-5-phenyl-1,2-dihydropyridine-3-carbonitrile (**1b**) (**Figure 5.3**). Interestingly substituted 2-amino-3-cyano-pyridine core structure attracted our attention due to its widely use in biological applications.[4-11]

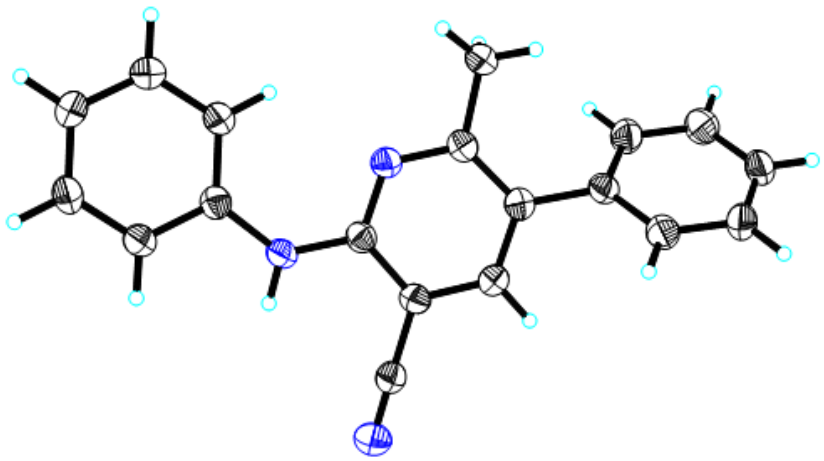


Figure 5.2 Structure of 6-Methyl-5-phenyl-2-(phenylamino)nicotinonitrile by X-ray diffraction (**1a**)

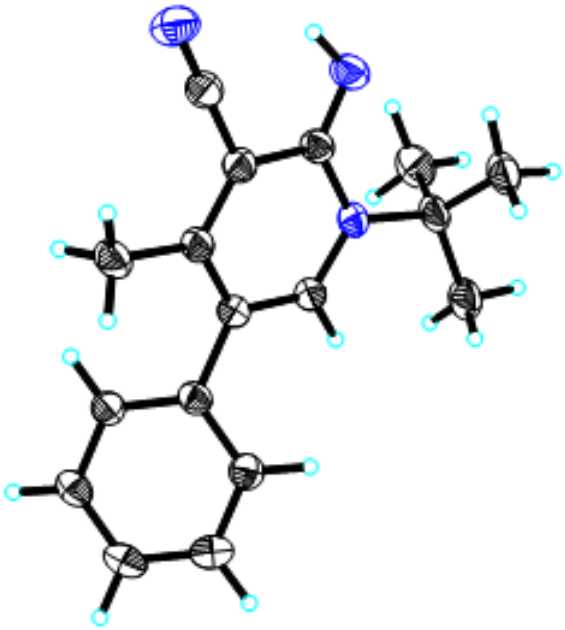
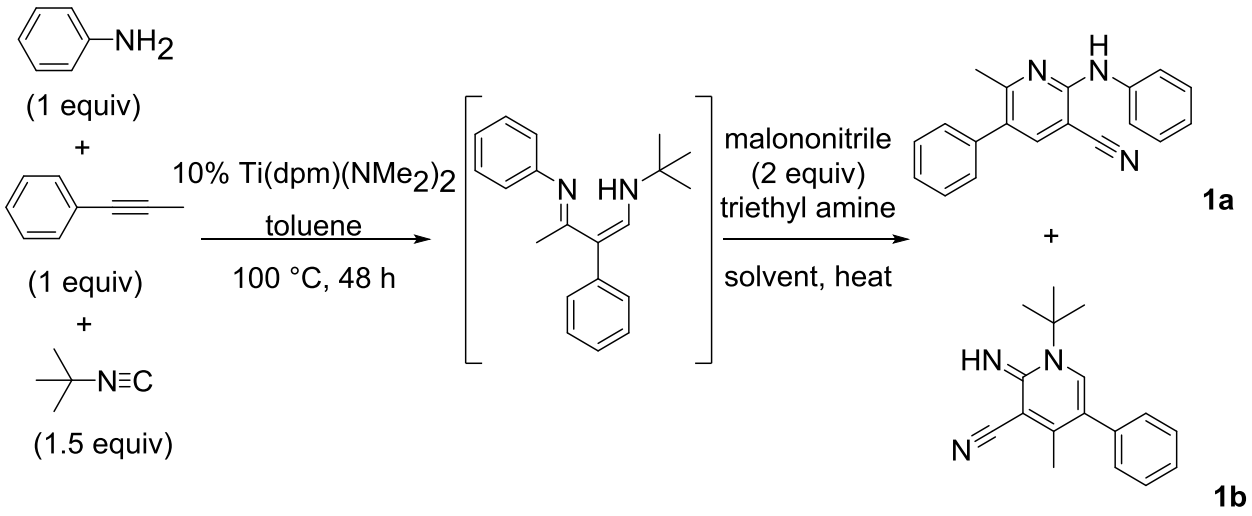
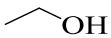
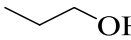
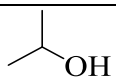
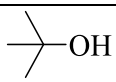
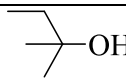
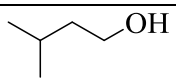


Figure 5.3 Structure of 1-(*tert*-butyl)-2-imino-4-methyl-5-phenyl-1,2-dihydropyridine-3-carbonitrile by X-ray diffraction (**1b**)

Optimization studies were focused on the titanium catalyzed multicomponent reaction of aniline, prop-1-yn-1-ylbenzene and *tert*-butylisonitrile followed by treating with malononitrile (2 equiv) triethyl amine (2 equiv) inprotic solvents at 25 °C. Observed results are summarized in **Table 5.1** and product distribution was determined by GC-FID studies. Preliminary studies resulted a mixture of substituted 2-amino-3-cyano-pyridine derivative (6-Methyl-5-phenyl-2-(phenylamino)nicotinonitrile) (**1a**) and 1,2-dihydropyridine derivative 1-(*tert*-butyl)-2-imino-4-methyl-5-phenyl-1,2-dihydropyridine-3-carbonitrile (**1b**). Solvent ethanol in the prescence of base triethyl amine (2 equiv) found to yield mainly the desire product (**1a**).

Table 5.1. Optimization study for the synthesis of **1a** in protic solvents



Entry	Solvent	T (°C)	Time (h)	Product distribution	
				1a	1b
1		25 (°C)	5 (h) ±	6 £	1 £
2		25 (°C)	5 (h) ±	3.2 £	1 £
3		25 (°C)	5 (h) ±	3 £	1 £
4		25 (°C)	5 (h) ±	2.5 £	1 £
5		25 (°C)	5 (h) ±	2 £	1 £
6		25 (°C)	5 (h) ±	1.4 £	1 £

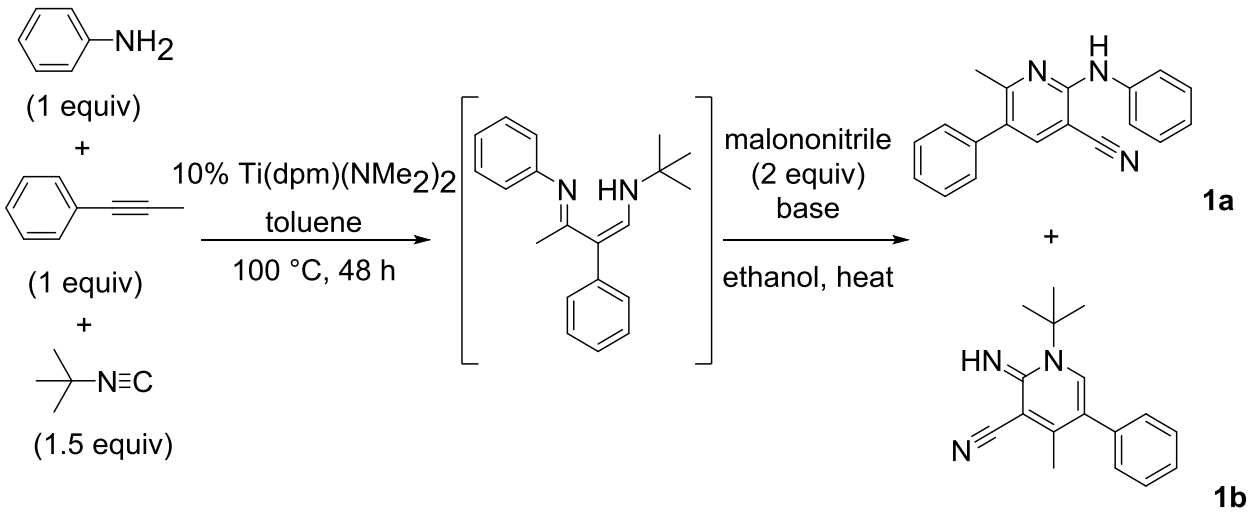
± Multicomponent reactions carried out with aniline, prop-1-yn-1-ylbenzene, and *tert*-butylisonitrile in a 1:1:1.5 ratio with 10 mol % catalyst (**2**) at 100 °C for 48 h. Once the 3CC is complete, product was subjected to appropriate reaction conditions.

Table 5.1 (cont'd)

£ Determined from GC-FID

Further optimization studies were carried out in ethanol varying the organic based used in the cyclization step. Observed results are summarized in **Table 5.2** and product distribution was determined by GC-FID studies. Less bulky base DBU found to be improve the product distribution (**Table 5.2**. entry 1 to 4). Also additive molecular sieves further improves product distribution of the (**Table 5.2**. entry 7).

Table 5.2. Optimization study for the synthesis of **1a** using various organic bases



Entry	Base	T (°C)	Time (h)	Product distribution	
				1a	1b
1	triethyl amine	25 (°C)	5 (h) ±	6 £	1 £
2	triethyl amine	50 (°C)	5 (h) ±	3.2 £	1 £
3	DBU	25 (°C)	5 (h) ±	9 £	1 £

Table 5.2 (cont'd)

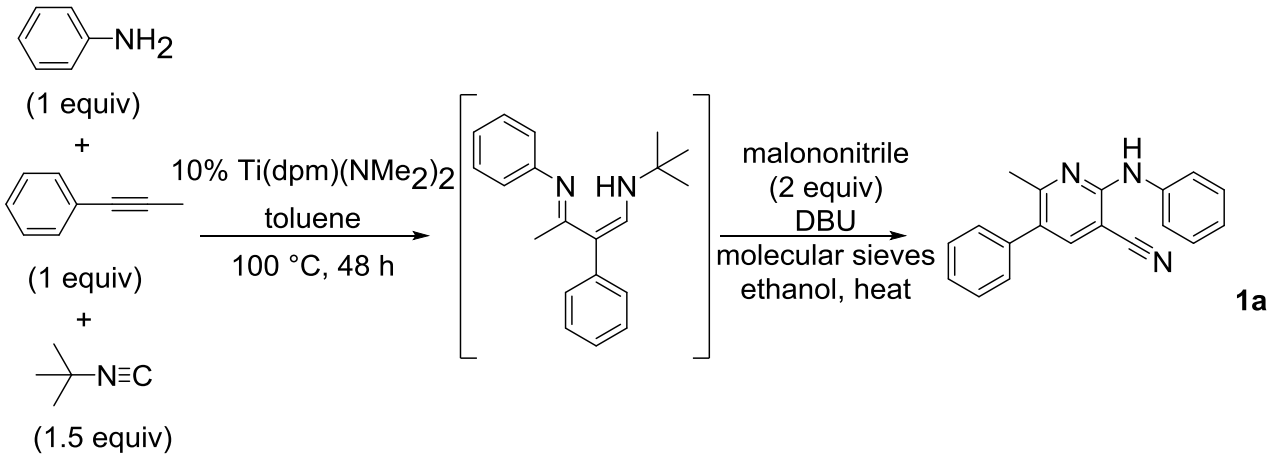
4	DBU	50 (°C)	5 (h) [±]	15 [£]	1 [£]
5	Hunings base	25 (°C)	5 (h) [±]	1.2 [£]	1 [£]
6	diethyl amine	25 (°C)	5 (h) [±]	2 [£]	1 [£]
7 [¥]	DBU	25 (°C)	5 (h) [±]	> 50 [£]	1 [£]

[±] Multicomponent reactions carried out with aniline, prop-1-yn-1-ylbenzene, and *tert*-butylisonitrile in a 1:1:1.5 ratio with 10 mol % catalyst (**2)** at 100 °C for 48 h. Once the 3CC is complete, product was subjected to appropriate reaction conditions.

[£] Determined from GC-FID

[¥] Carried out in the precence of molecular sieves

Table 5.3. Optimization study for the synthesis of **1a**



Entry	DBU	T (°C)	Time (h)	GC Yield (1a)
1	0.1 equiv	60 (°C)	2 (h) [±]	42 % [£,§]
2	0.25 equiv	60 (°C)	2 (h) [±]	54 % [£,§]
3	0.5 equiv	60 (°C)	2 (h) [±]	62 % [£,§]
4	1 equiv	60 (°C)	2 (h) [±]	57 % [£,§]
5	0.25 equiv	80 (°C)	2 (h) [±]	49 % [£,§]
6	0.5 equiv	80 (°C)	2 (h) [±]	71 % [£,§]

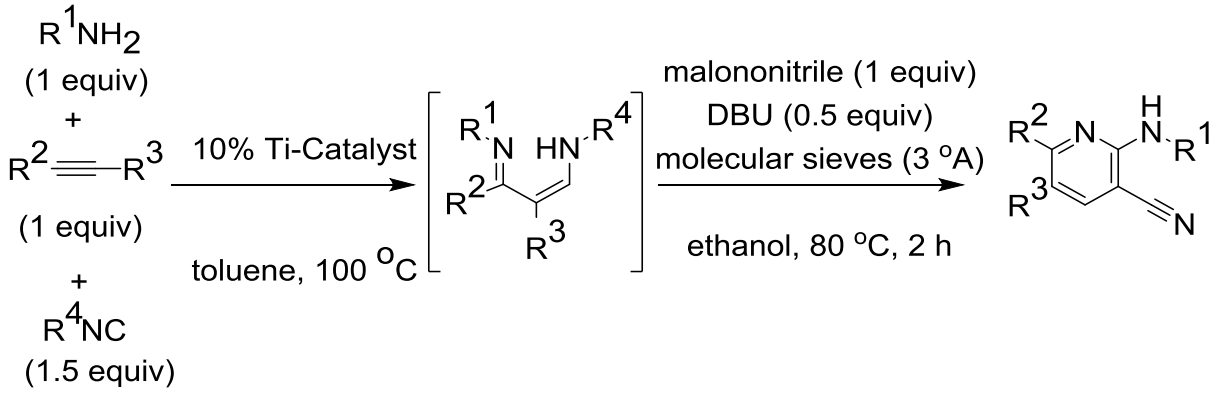
[±] Multicomponent reactions carried out with aniline, prop-1-yn-1-ylbenzene, and *tert*-butylisonitrile in a 1:1:1.5 ratio with 10 mol % catalyst (**2)** at 100 °C for 48 h. Once the 3CC is complete, product was subjected to appropriate reaction conditions.

Table 5.3 (cont'd)

£ Yields are determined by calibrated GC-FID

§ Trace amount of 1-(*tert*-butyl)-2-imino-4-methyl-5-phenyl-1,2-dihydropyridine-3-carbonitrile (**1b**) observed by GC-MS

The one pot stnthesis of 2-amino-3-cyano-pyridine derivative (**1a**) was further optimized by varying the base (DBU) used in the reactionin various reaction temparatures. Observed results are summarized in **Table 5.3** and yields of 6-Methyl-5-phenyl-2-(phenylamino)nicotinonitrile (**1a**) was determined by calibrated GC-FID. Two equivalents of malononitrile, 0.5 equivalents of DBU as the base under reflux reaction conditions in ethanol in two hours results in substituted 2-amino-3-cyano-pyridine derivatives. This reaction is an overall one-pot four component reaction in which all four starting materials are incorporated into the final product. Therefore the study was focused on the optimization of the reaction conditions to obtain substituted 2-amino-3-cyano-pyridine derivatives.



Scheme 5.6 Optimized reaction conditions for the synthesis of substituted 2-amino-3-cyano-pyridine derivatives

The results for the 3CC of some aryl and alkyl amines with prop-1-yn-1-ylbenzene are shown in **Table 5.4**. The yields of the substituted 2-amino-3-cyano-pyridine compounds are moderate to good, A variety of different aniline derivatives have been used in the multicomponent coupling reaction, and in general, the one-pot syntheses of substituted 2-amino-3-cyanopyridine work better for electron rich anilines.

The regiochemistry was determined by an X-ray structure of the product with prop-1-yn-1-ylbenzene (**Figure 5.2**). The regio-chemistry with the other unsymmetrical alkynes were assumed to occure with the incorporation of the largest group in the 5-position. Using this methodology, the 4-position of the 2-amino-3-cyano-pyridine product will be unsubstituted. In addition, the route takes advantage of the abundance of aryl amines that are available commercially to make substituted 2-amino-3-cyano-pyridines. Primary amines such as hexan-1-amine, benzylamine and diphenylmethanamine results in production of the 3CC product in good yields using either catalyst; however, for reasons currently unknown the addition of malononitrile under any reaction conditions we investigated did not result in formation of the substituted 2-amino-3-cyano-pyridines.

Table 5.4 Examples of substituted 2-amino-3-cyanopyridine syntheses using prop-1-yn-1-ylbenzene and a variety of primary aryl and alkyl amines (**Scheme 5.6**)

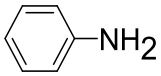
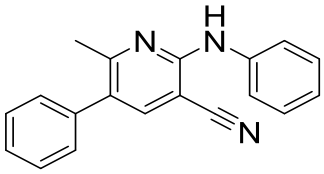
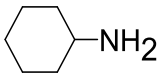
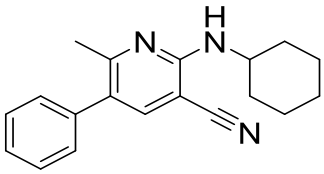
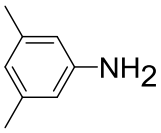
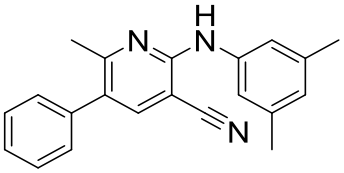
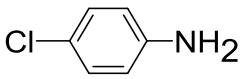
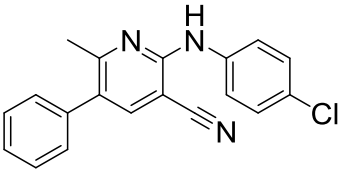
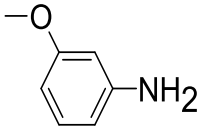
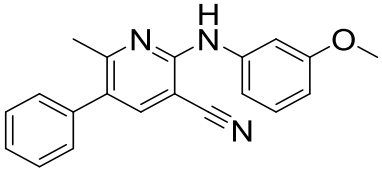
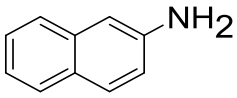
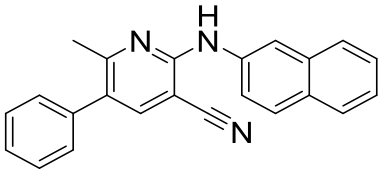
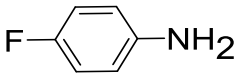
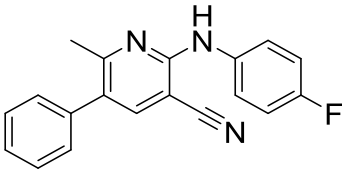
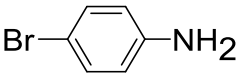
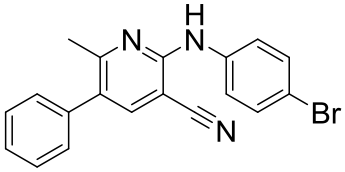
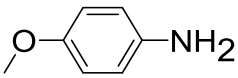
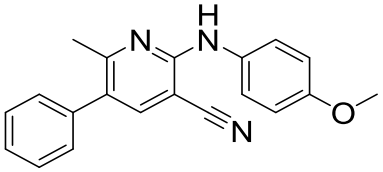
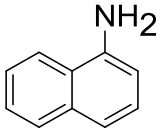
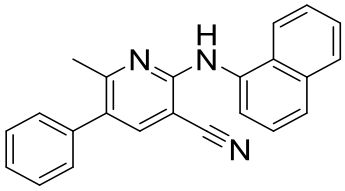
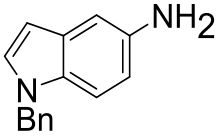
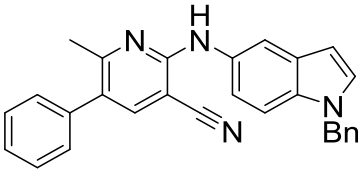
Entry	Amine	Catalyst	Product	Isolated yield
a		**2**		72% [±]
b		**1**		67%
c		**2**		76%
d		**2**		70%
e		**2**		69%

Table 5.4 (cont'd)

f		**2**		63%
g		**2**		42%
h		**2**		68%
i		**2**		73%
j		**2**		52%
k		**2**		54%

± characterized by X-ray diffraction studies

During the second part of the study, The multicomponent coupling product from aniline and various internal and terminal alkynes was treated with malononitrile to obtain 5-substitited and 5,6-disubstituted 2-amino-3-cyano-pyridines respectively (**Table 5.5**). The yields of the substituted 2-amino-3-cyano-pyridine compounds are moderate to good.

Table 5.5 Examples of substituted 2-amino-3-cyanopyridine syntheses using aniline with other alkynes (**Scheme 5.6**)

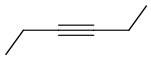
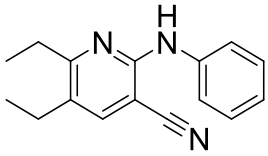
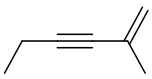
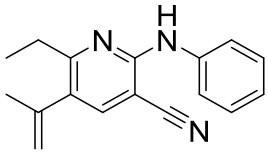
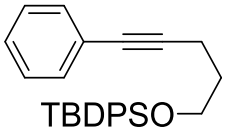
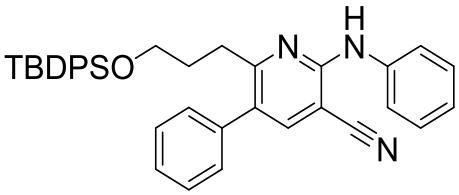
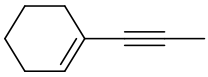
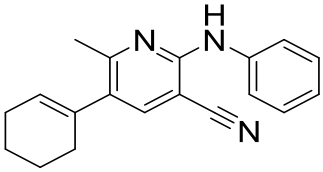
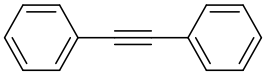
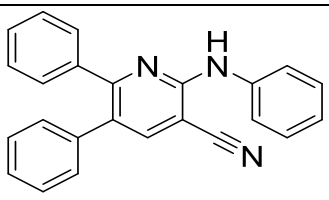
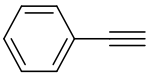
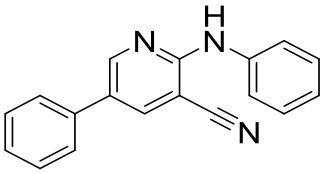
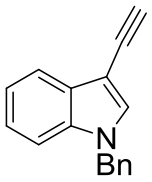
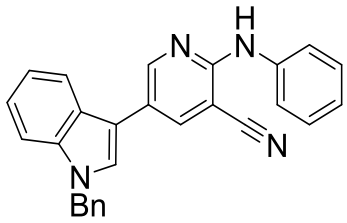
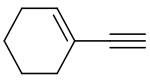
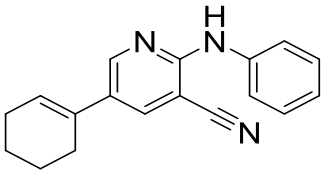
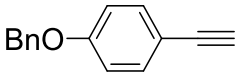
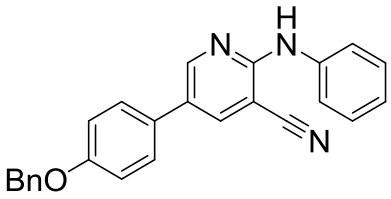
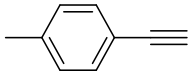
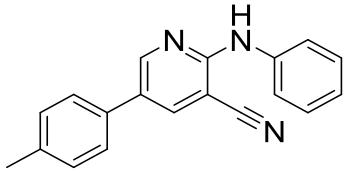
Entry	Alkyne	Catalyst	Product	Isolated yield
l		**2**		64%
m		**2**		60%
n		**2**		68%
o		**2**		55%
p		**2**		43% [±]
q		**2**		62% [±]

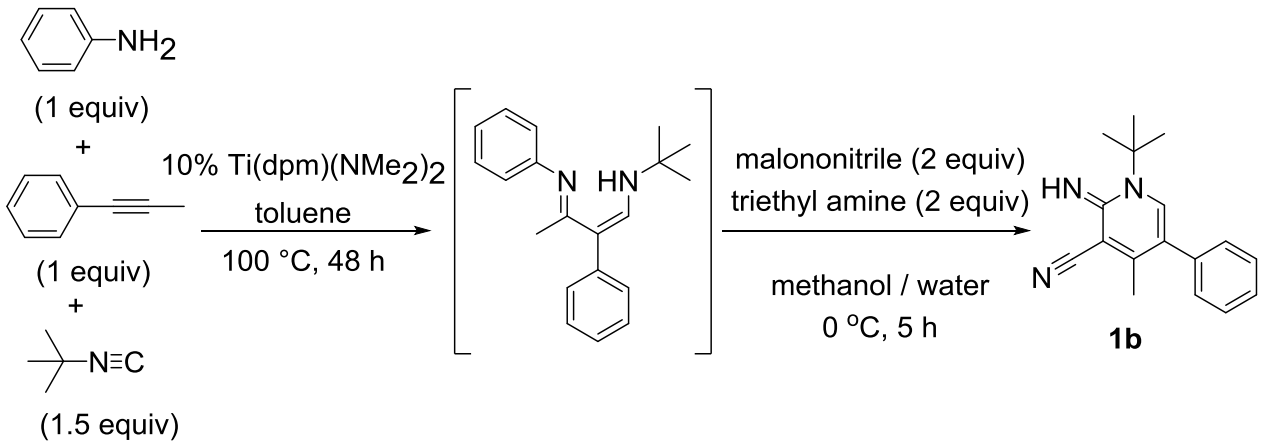
Table 5.5 (cont'd)

r		**2**		49% [±]
s		**2**		56%
t		**2**		66%
u		**2**		58%

[±] characterized by X-ray diffraction studies

We have also optimized the reaction conditions to solely obtain 1,2-dihydropyridine derivative 1-(*tert*-butyl)-2-imino-4-methyl-5-phenyl-1,2-dihydropyridine-3-carbonitrile (**1b**) in good yield. The reaction proceeds in methanol : water (3 : 1) at 0 °C in 5 hours in the presence of non-nucleophilic base triethyl amine (2 equiv). (**Scheme 5.7**). The structure of **1b** was confirmed by X-ray diffraction studies (**Figure 5.3**)

Table 5.6. Optimization study for the synthesis of **1b**



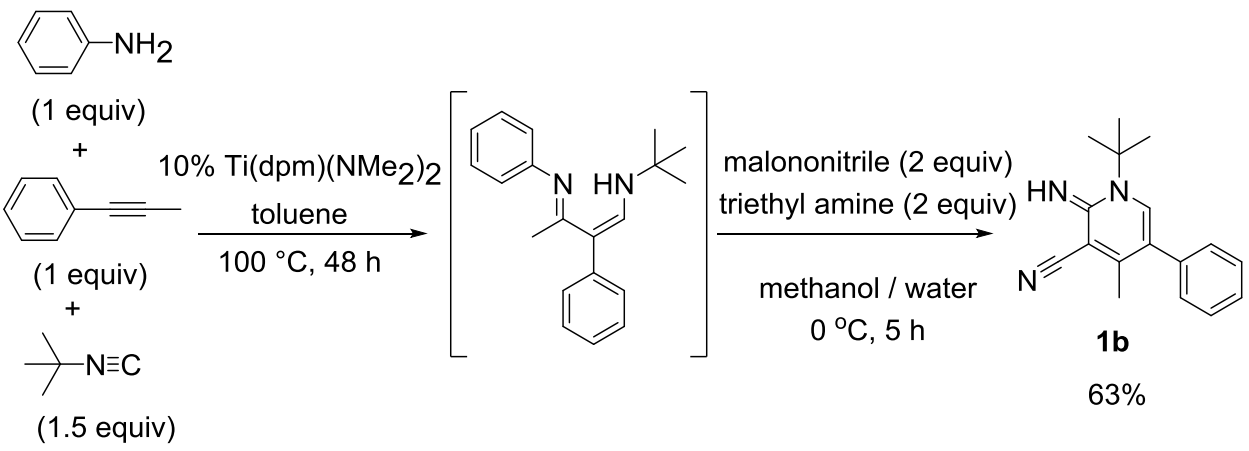
Entry	T (°C)	Time (h)	Solvent mixture		Product distribution	
			Methanol (2 mL)	Water (2 mL)	1a	1b
1	0 °C	5 (h) ±	1.9	0.1	1 £	5.3 £
2	0 °C	5 (h) ±	1.8	0.2	1 £	16 £
3	0 °C	5 (h) ±	1.6	0.4	1 £	23 £
4	0 °C	5 (h) ±	1.5	0.5	1 £	>25 £

± Multicomponent reactions carried out with aniline, prop-1-yn-1-ylbenzene, and *tert*-butylisonitrile in a 1:1:1.5 ratio with 10 mol % catalyst (**2**) at 100 °C for 48 h. Once the 3CC is complete, product was subjected to appropriate reaction conditions.

Table 5.2 (cont'd)

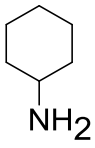
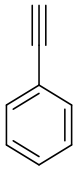
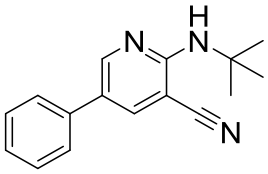
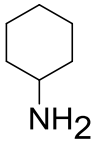
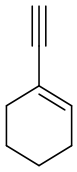
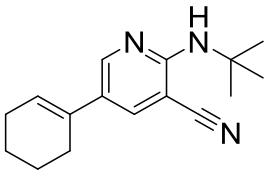
Table 5.6 (cont'd)

£ Determined from GC-FID

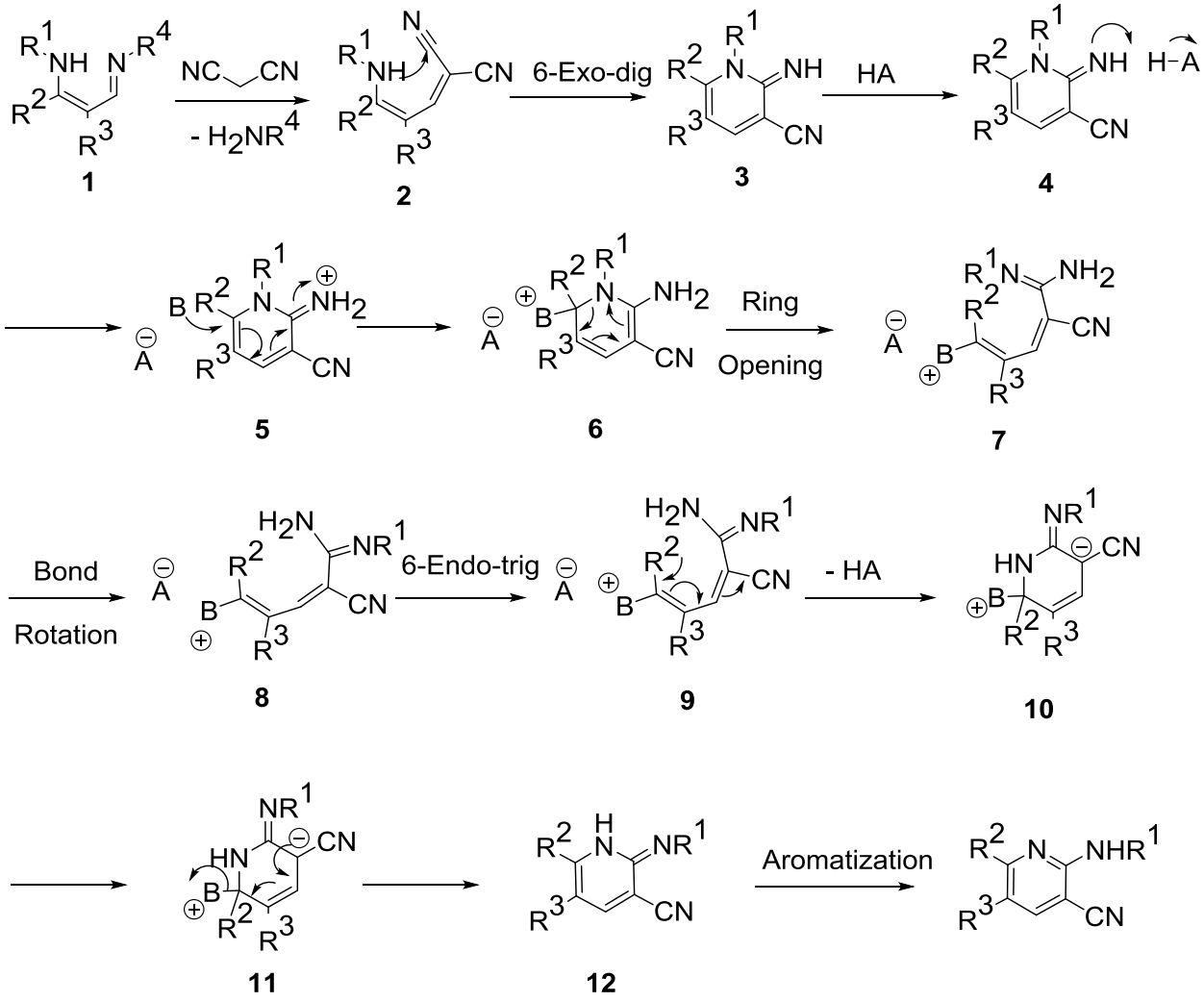


Scheme 5.7 Optimized reaction conditions for synthesis of substituted 1,2-dihydropyridine derivatives

Table 5.7 Examples of substituted 2-amino-3-cyanopyridine syntheses using various amines and with various alkynes (**Scheme 5.6**)

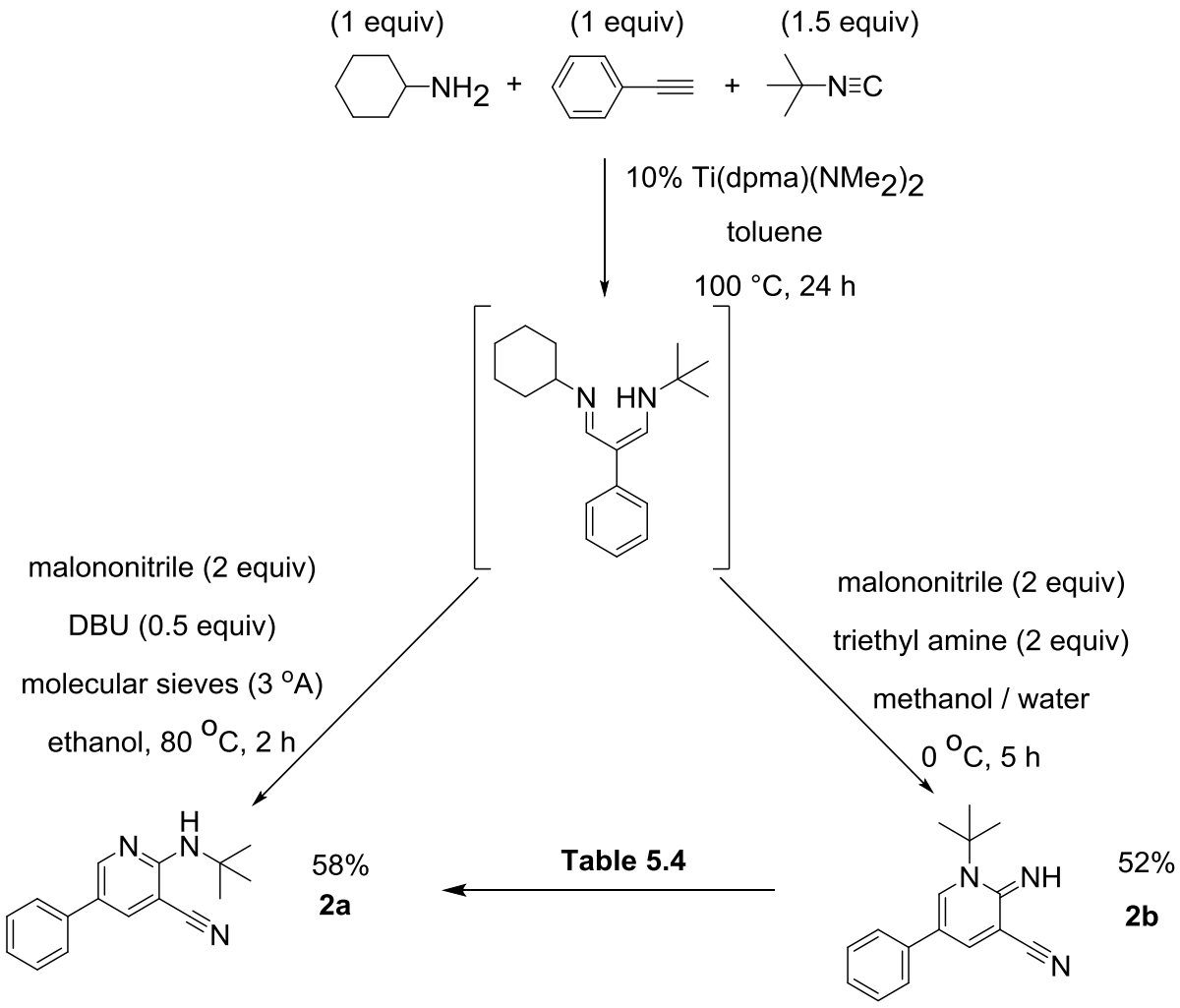
Entry	Amine	Alkyne	Isonitrile	Catalyst	Product	Isolated yield
v				**1**		58%
w				**1**		53%

The proposed mechanism for the one pot synthesis of substituted 2-amino-3-cyanopyridines is similar to the well-known Dimroth rearrangement (**Scheme 5.8**).[21,24] Initially, malononitrile adds to the 1,3-diimine with elimination of H_2NR[4] and results in intermediate **2**. Subsequently, intermediate **2** can undergo intramolecular 6-endo-dig cyclization to give imino-pyridine intermediate **3**. The imino-pyridine intermediate **3** ring opens under reaction conditions to yield intermediate **7**, which can easily undergo C-C bond rotation and 6-endo-trig cyclization to give **10**. Upon loss of nucleophilic base, the resulting imino-pyridine aromatizes to a more stable amino-pyridine derivative.



Scheme 5.8 Proposed mechanism for substituted 2-amino-3-cyano-pyridine synthesis. DBU = B and HA = $CH_2(CN)_2$

To gain evidence for the Dimroth-type transformation of the imino-pyridine intermediate to amino-pyridine derivative, further studies were done. The multicomponent coupling product of cyclohexylamine, ethynylbenzene and *tert*-butylisonitrile was converted to the corresponding imino-pyridine intermediate (**2b**) 1-(*tert*-butyl)-2-imino-5-phenyl-1,2-dihydropyridine-3-carbonitrile under optimized reaction conditions in 52% isolated yield (**Scheme 5.9**).

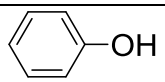


Scheme 5.9 amino-pyridine and imino-pyridines from multicomponent coupling reaction

The imino-pyridine intermediate (**2b**) 1-(*tert*-butyl)-2-imino-5-phenyl-1,2-dihydropyridine-3-carbonitrile was then subjected to various reaction conditions similar to those used to generate the substituted amino-pyridine derivative 2-(*tert*-butylamino)-5-phenylnicotinonitrile (**2a**).

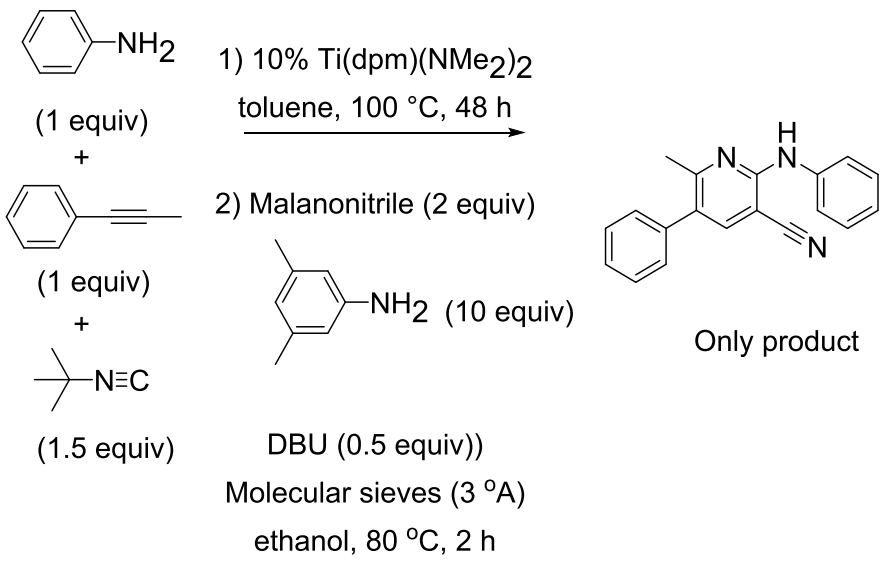
The rearrangement study results are summarized in Table 5.8. In the presence of both malononitrile (2 equiv) and base (DBU) under refluxing conditions in ethanol (**Table 5.4**, entry 1 and 2), imino-pyridine intermediate (**2b**) (1-(*tert*-butyl)-2-imino-5-phenyl-1,2-dihydropyridine-3-carbonitrile) was rearranged to the corresponding substituted amino-pyridine derivative (**2a**) 2-(*tert*-butylamino)-5-phenylnicotinonitrile in 86% isolated yield. Also refluxing imino-pyridine intermediate (**2b**) with malononitrile or DBU separately did not facilitate the molecular rearrangement to the corresponding amino-pyridine derivative (**2a**) (**Table 5.7**, entry 3 and 4). Interestingly, attempted rearrangement of the imino-pyridine (**2b**) in the presence of phenol and DBU (**Table 5.8**, entry 5) results in the amino pyridine derivative (**2a**). These experimental observations provide evidence that the transformation proceeds via a Dimroth-type molecular rearrangement in the presence of a both nucleophilic base and a proton source.

Table 5.8 Reaction conditions to convert 1-(*tert*-butyl)-2-imino-5-phenyl-1,2-dihydropyridine-3-carbonitrile (**2b**) to 2-(*tert*-butylamino)-5-phenylnicotinonitrile (**2a**)

Entry	$CH_2(CN)_2$ (equiv)	Additive (equiv)	DBU (equiv)	T (°C)	Time (h)	Product
1	2.0	--	1.0	80 °C	2	**2a** *
2	2.0	--	0.5	80 °C	2	**2a** £ (86%)
3	--	--	0.5	80 °C	2	**2b***
4	2.0	--	--	80 °C	2	**2b***
5	--	 2.0	0.5	80 °C	2	**2a***

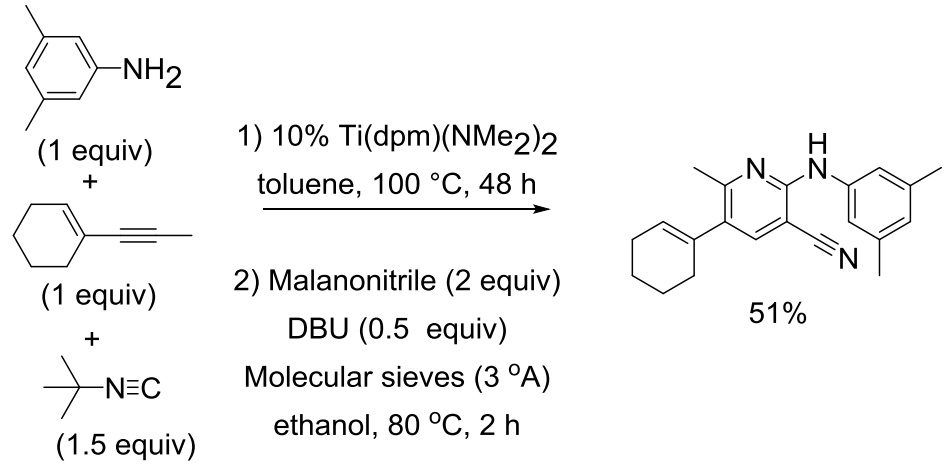
(* Observed by NMR, £ Isolated yield)

Furthermore the multicomponent coupling of prop-1-yn-1-ylbenzene, *tert*-butylisonitrile, and aniline followed by condensation with malononitrile in the presence of 10 equivalents of 3,5-dimethylaniline results exclusively 6-methyl-5-phenyl-2-(phenylamino)nicotinonitrile. No incorporation of the excess 3,5-dimethylaniline in the final 2-amino-3-cyano-pyridine product indicates the transformation undergoes an overall unimolecular rearrangement to result in substituted 2-amino-3-cyano-pyridine (**Scheme 5.10**), a finding that is also consistent with the Dimroth mechanism.



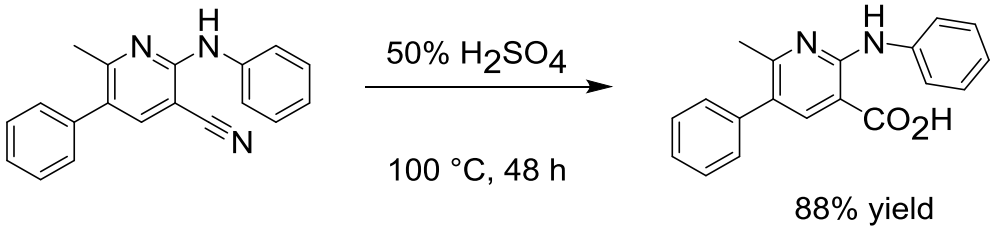
Scheme 5.10 One pot synthesis of 6-methyl-5-phenyl-2-(phenylamino)nicotinonitrile

We have also synthesized 5-(cyclohex-1-en-1-yl)-2-((3,5-dimethylphenyl)amino)-6-methylnicotinonitrile from the multicomponent coupling product of 1-(prop-1-yn-1-yl)cyclohex-1-ene, *tert*-butylisonitrile, 3,5-dimethylaniline followed by condensation with malononitrile in 51% isolated yield (**Scheme 5.11**). This 2-amino-3-cyano-pyridine has the same functional groups as the biologically active quinoline (**AD043**) (For more detail see chapter 6) and currently its biological activity is under investigation.



Scheme 5.11 One-pot synthesis of 5-(cyclohex-1-en-1-yl)-2-((3,5-dimethylphenyl)amino)-6-methylnicotinonitrile

Substituted 2-amino-3-cyano-pyridines can be derivatized for further applications. Under aqueous acidic reaction conditions the nitrile can be hydrolyzed to the corresponding acid derivatives in good yield (**Scheme 5.12)**.[25]



Scheme 5.12 Derivatives from substituted 2-amino-3-cyano-pyridines

Reaction scaleing up of 6-methyl-5-phenyl-2-(phenylamino)nicotinonitrile

In order to scale up the synthesis of substituted 2-amino-3-cyano-pyridine derivatives, one pot synthesis of 6-methyl-5-phenyl-2-(phenylamino)nicotinonitrile was used as a molel study (**Scheme 5.6**). Multicomponent reaction of aniline (20 mmol), 1-phenylpropyne (20 mmol), and *tert*-butylisonitrile (30 mmol) were carried out in a schilnk flask in the prescence of catalyst **2** (10% mol) followed by reacting with malononitrile (40 mmol), DBU (10 mmol), molecular sieves, in absolute ethanol (40 mL) resulted isolated yield of 3.7 g (66%) of the desired product 6-methyl-5-phenyl-2-(phenylamino)nicotinonitrile.

5.3 Conclusion

Titanium-catalyzed 3-component coupling of a primary amine, an alkyne, and an isonitrile followed by treatment with malononitrile under basic conditions provides substituted 2-amino-3-cyanopyridine in a one-pot four component procedure. Reactions with terminal alkynes are more facile and can be accomplished with the milder $Ti(NMe_2)_2$(dpma) (**1**) as catalyst. The more active dipyrrolylmethane catalyst $Ti(NMe_2)_2$(dpm) (**2**) was used for internal alkynes.

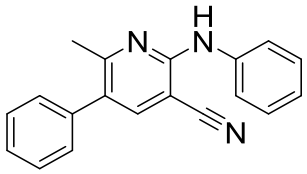
This new procedure has significant flexibility in the type of substituted 2-amino-3-cyano-pyridines that can be accessed. Substituents on the internal and terminal alkynes can easily modify the 5^{th} and 6^{th} position of the pyridine ring, and by varying the substituted anilines in the three component coupling reaction, a vast number of substituted 2-amino-3-cyano-pyridines can be easily prepared from commercially available substituted anilines. The yields are generally good to moderate, and the products are readily isolated using column chromatography. Experimental observations provide evidence that the transformation proceeds via a Dimroth-type molecular rearrangement in the presence of both a nucleophilic base and a proton source.

These one pot substituted 2-amino-3-cyano-pyridines can also be easily converted to other derivatives for further modification and currently the biological activity of substituted 2-amino-3-cyano-pyridines is under investigation

5.4 Experimental

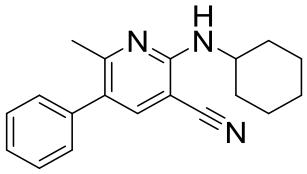
General Considerations: All manipulations of air sensitive compounds were carried out in an MBraun drybox under a purified nitrogen atmosphere. Toluene was purified by sparging with dry N_2 and water was removed by running through activated alumina systems purchased from Solv-Tek. ^{1}H and ^{13}C spectra were recorded on VXR-500 spectrometers. Melting points are uncorrected and measured on a Mel-Temp II apparatus (Laboratory Devices Inc, USA) with a mercury thermometer in an open capillary tube. $Ti(NMe_2)_2$(dpma) (**1**) and $Ti(NMe_2)_2$(dpm) (**2**) were made following the literature procedures.[26] Alkynes were purchased either from Sigma-Aldrich or Oakwood chemicals and were distilled from CaO under dry nitrogen. Amines were purchased from Sigma-Aldrich, dried over KOH, and distilled under dry nitrogen. *tert*-Butylisonitrile was made according to the literature procedure and purified by distillation under dry nitrogen.[27] Malononitrile, 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), and silica gel were purchased from Sigma-Aldrich and used as received. Molecular sieves 3 Å, 1/16" pellets were purchased from Spectrum chemicals. Absolute ethanol was purchased from KOPTEC and used as received. Hexanes and ethyl acetate were purchased from Mallinckrodt Chemicals and used as received. Extinction coefficients for all compounds were acquired in CH_2Cl_2 solutions using a Varian Cary 50 UV-Visible spectrophotometer.

Preparation and Characterization of Compounds in Table 5.4



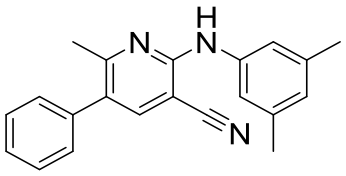
6-Methyl-5-phenyl-2-(phenylamino)nicotinonitrile (Table 5.4, entry a)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with aniline (95 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (205 mg, 72%) as a yellow solid. M.p.: 119-121 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 2.53 (3 H, s, CH_3), 7.14-7.17 (2H, br, CH-Ar, NH-aniline), 7.32-7.34 (2H, d, 8 Hz, CH-Ar), 7.40-7.45 (3H, m, CH-Ar), 7.47-7.51 (2H, m, CH-Ar), 7.66 (1H, s, 4-CH-pyridine), 7.76-7.78 (2H, d, 8.5 Hz, CH-Ar). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 23.9, 90.3, 116.5, 119.9, 123.2, 127.5, 127.9, 128.4, 128.7, 128.9, 138.0, 138.9, 141.9, 153.9, 159.9. MS(EI): *m/z* 285. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 294 (24,800), 342 (1,100). Elemental Analysis: found:

%C, 80.10; % H, 5.25; %N, 14.65; expected: %C, 79.98; %H, 5.30; %N, 14.73. Further characterized by X-ray diffraction studies.



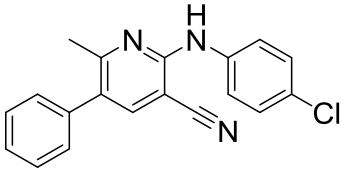
2-(cyclohexylamino)-6-methyl-5-phenylnicotinonitrile (Table 5.4, entry b)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (99 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (195 mg, 67%) as a brown solid. M.p.: 144-147 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.25-1.32 (4 H, m, CH_2), 1.43-1.48 (2 H, m, CH_2) 1.79-1.83 (2 H, m, CH_2), 2.07-2.12 (2 H, m, CH_2), 2.42 (3 H, s, CH_3), 4.12-4.13 (1 H, m, CH), 4.96-4.98 (1H, d, 8 Hz, NH-cyclohexyl), 7.26-7.27 (2H, d, 7 Hz, CH-Ar), 7.36-7.39 (1H, m, 7 Hz, CH-Ar), 7.44-7.41 (2H, t, 7 Hz, CH-Ar), 7.50 (1H, s, 4-CH-pyridine), $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 24.1, 24.9, 25.7, 33.2, 49.7, 88.3, 117.2, 125.6, 127.2, 128.4, 129.1, 138.8, 141.8, 156.4, 160.3.

MS(EI): *m/z* 291. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 272 (14,400), 347 (4,400). Elemental Analysis: found: %C, 78.29; % H, 7.20; %N, 14.51; expected: %C, 78.32; %H, 7.26; %N, 14.42.



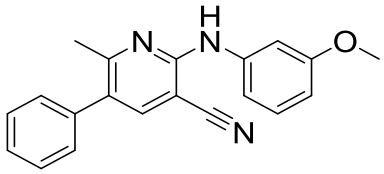
2-((3,5-dimethylphenyl)amino)-6-methyl-5-phenylnicotinonitrile (Table 5.4, entry c)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 3,5-dimethylaniline (121 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (237 mg, 76%) as a brwn solid. M.p.: 98-100 °C. ^1H NMR ($CDCl_3$, 500 MHz): 2.40 (6 H, s, CH_3), 2.54 (3 H, s, CH_3), 6.82 (1H, br, NH-3,5-dimethylaniline), 7.01 (1H, s, CH-Ar), 7.32-7.34 (2H, d, 8.5 Hz, CH-Ar), 7.39 (2H, s, CH-Ar), 7.43-7.44 (1H, m, CH-Ar), 7.47-7.51 (2H, m, CH-Ar), 7.65 (1H, s, 4-CH-pyridine), $^{13}C\{^1H\}$

NMR ($CDCl_3$, 125 MHz): 21.3, 23.9, 90.2, 116.5, 117.8, 125.1, 127.4, 127.7, 128.4, 128.9, 138.1, 138.4, 138.7, 141.9, 154.1, 160.0. MS(EI): *m/z* 313. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 297 (20,600), 342 (4,900). Elemental Analysis: found: %C, 80.53; % H, 6.19; %N, 13.28; expected: %C, 80.48; %H, 6.11; %N, 13.41.



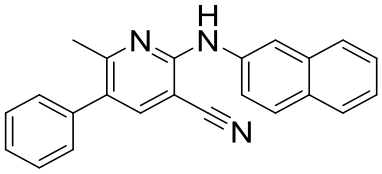
2-((4-chlorophenyl)amino)-6-methyl-5-phenylnicotinonitrile (Table 5.4, entry d)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 4-chloroaniline (127 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (223 mg, 70%) as a brown solid. M.p.: 167-169 °C. ^1H NMR ($CDCl_3$, 500 MHz): 2.51 (3 H, s, CH_3), 7.08 (1H, br, NH- 4-chloroaniline), 7.30-7.32 (2H, d, 8.5 Hz, CH-Ar), 7.34-7.36 (2H, d, 9 Hz, CH-Ar), 7.42-7.44 (1H, m, CH-Ar), 7.46-7.49 (2H, m, CH-

Ar), 7.67 (1H, s, 4-CH-pyridine), 7.69-7.70 (2H, d, 9 Hz, CH-Ar). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 24.0, 90.5, 103.6, 107.7, 121.2, 127.6, 128.1, 128.2, 128.4, 128.5, 128.8, 128.9, 142.1, 153.7, 160.1. MS(EI): *m/z* 319. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 298 (24,400), 347 (4,900). Elemental Analysis: found: %C, 71.25; % H, 4.37; %N, 13.21; expected: %C, 71.36; %H, 4.41; %N, 13.14.



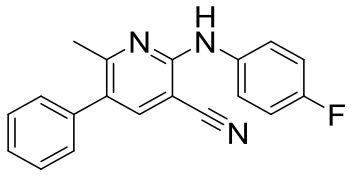
2-((3-methoxyphenyl)amino)-6-methyl-5-phenylnicotinonitrile (Table 5.4, entry e)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 3-methoxyaniline (123 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (217 mg, 69%) as a brown solid. M.p.: 129-130 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 2.53 (3 H, s, CH_3), 3.88 (3 H, s, OCH_3), 6.69-6.71 (2H, dd, 1 Hz, 6 Hz, CH-Ar), 7.09 (1H, br, NH- 3-methoxyaniline), 7.20-7.28 (1H, m, CH-Ar), 7.29-7.33 (3H, m,

CH-Ar), 7.42-7.44 (2H, d, 7.5 Hz, CH-Ar), 7.46-7.50 (2H, m, CH-Ar). 7.59-7.60 (1H, m, CH-Ar). 7.66 (1H, s, 4-CH-pyridine), $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 21.3, 23.9, 90.2, 116.5, 117.8, 125.1, 127.4, 127.7, 128.4, 128.9, 138.1, 138.4, 138.7, 141.9, 154.1, 160.0. MS(EI): *m/z* 315. Elemental Analysis: found: %C, 76.02; % H, 5.37; %N, 13.39; expected: %C, 76.17; %H, 5.43; %N, 13.32. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 299 (22,900), 340 (4,700). Elemental Analysis: found: %C, 76.02; % H, 5.37; %N, 13.39; expected: %C, 76.17; %H, 5.43; %N, 13.32.



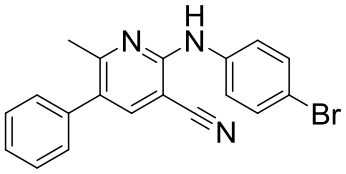
6-methyl-2-(naphthalen-2-ylamino)-5-phenylnicotinonitrile (Table 5.4, entry f)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with naphthalen-2-amine (143 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (211 mg, 63%) as a yellow solid. M.p.: 144-146 °C. ^{1}H NMR

($CDCl_3$, 500 MHz): 2.56 (3 H, s, CH_3), 7.21 (1H, br, NH- naphthalen-1-amine), 7.32-7.34 (2H, m, CH-Ar), 7.42-7.43 (2H, m, CH-Ar), 7.44-7.51 (3H, m, CH-Ar), 7.69 (1H, s, 4-CH-pyridine), 7.70-7.73 (1H, d, 8.5 Hz, CH-Ar), 7.83-7.87 (3H, m, CH-Ar). 8.37-8.38 (1H, d, 2 Hz, CH-Ar). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 24.1, 90.6, 120.8, 124.5, 126.4, 127.4, 127.5, 127.6, 128.1, 128.3, 128.5, 128.6, 129.0, 130.2, 131.4, 134.0, 136.5, 138.0, 142.0, 154.0, 160.2. MS(EI): *m/z* 335. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 278 (32,900), 311 (31,900). Elemental Analysis: found: %C, 82.41; % H, 5.16; %N, 12.43; expected: %C, 82.36; %H, 5.11; %N, 12.53.



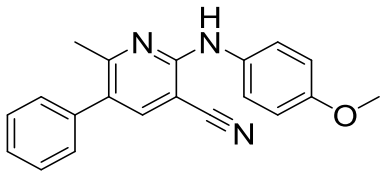
2-((4-fluorophenyl)amino)-6-methyl-5-phenylnicotinonitrile (Table 5.4, entry g)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 4-fluoroaniline (111 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product

was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (127 mg, 42%) as a light brown solid. M.p.: 126-128 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 2.50 (3 H, s, CH_3), 7.08-7.11 (1H, t, 9 Hz, CH-Ar), 7.16 (1H, br, NH-4-fluoroaniline), 7.31-7.33 (2H, d, 5.5 Hz, CH-Ar), 7.43-7.44 (1H, m, CH-Ar), 7.47-7.50 (2H, m, CH-Ar), 7.65 (1H, s, 4-CH-pyridine), 7.68-7.71 (2H, m, CH-Ar). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 23.9, 90.0, 103.5, 107.6, 115.2, 116.5, 121.9, 127.5, 128.4, 134.9, 137.9, 142.0, 154.0, 157.8, 159.7. ^{19}F NMR ($CDCl_3$, 500 MHz): - 119.1 (m). MS(EI): *m/z* 303. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 291 (23,200), 342 (4,700). Elemental Analysis: found: %C, 75.31; % H, 4.69; %N, 13.79; expected: %C, 75.23; %H, 4.65; %N, 13.85.



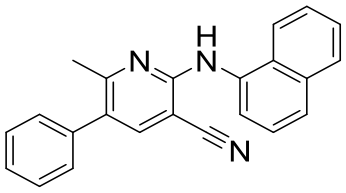
2-((4-bromophenyl)amino)-6-methyl-5-phenylnicotinonitrile (Table 5.4, entry h)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 4-bromoaniline (170 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butylisonitrile (171 µL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was

heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (247 mg, 68%) as a brown solid. M.p.: 164-166 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 2.51 (3 H, s, CH_3), 7.08 (1H, br, NH- 4-bromoaniline), 7.30-7.32 (2H, d, 8 Hz, CH-Ar), 7.42-7.43 (1H, m, CH-Ar), 7.46-7.50 (4H, m, CH-Ar), 7.64-7.67 (3H, m, CH-Ar, 4-CH-pyridine). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 21.3, 90.2, 116.5, 117.8, 125.1, 127.4, 127.7, 128.4, 128.9, 138.1, 138.4, 138.7, 141.9, 154.1, 160.0. MS(EI): *m/z* 363. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 299 (41,600), 342 (7,400). Elemental Analysis: found: %C, 62.57; % H, 3.82; %N, 11.59; expected: %C, 62.65; %H, 3.87; %N, 11.54.



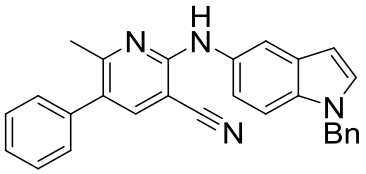
2-((4-methoxyphenyl)amino)-6-methyl-5-phenylnicotinonitrile (Table 5.4, entry i)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 4-methoxyaniline (123 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol),

DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (230 mg, 73%) as a yellow solid. M.p.: 108-110 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 2.48 (3 H, s, CH_3), 3.86 (3 H, s, OCH_3), 6.95-6.97 (2H, d, 8.5 Hz, CH-Ar), 6.99 (1H, br, NH- 4-methoxyaniline), 7.30-3.32 (2H, d, 8.5 Hz, CH-Ar), 7.41-7.42 (1H, m, CH-Ar), 7.46-7.49 (2H, m, CH-Ar), 7.60-7.63 (3H, m, CH-Ar, 4-CH-pyridine). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 23.9, 55.3, 89.6, 103.5, 114.0, 116.7, 122.4, 127.4, 128.4, 128.9, 131.9, 138.1, 142.0, 154.4, 155.9, 160.1. MS(EI): *m/z* 315. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 296 (19,100), 345 (3,900). Elemental Analysis: found: %C, 76.26; % H, 5.51; %N, 13.22; expected: %C, 76.17; %H, 5.43; %N, 13.32.



6-methyl-2-(naphthalen-1-ylamino)-5-phenylnicotinonitrile (Table 5.4, entry j)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with naphthalen-1-amine (143 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure

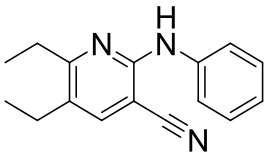
tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (174 mg, 52%) as a brown solid. M.p.: 152-156 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 2.45 (3 H, s, CH_3), 7.32 (1H, br, NH- naphthalen-2-amine), 7.33-7.34 (1H, m, CH-Ar), 7.41-7.50 (4H, m, CH-Ar), 7.56-7.62 (3H, m, CH-Ar), 7.71 (1H, s, 4-CH-pyridine), 7.77-7.79 (1H, d, 8.5 Hz, CH-Ar), 7.94-7.96 (1H, d, 8 Hz, CH-Ar), 8.09-8.11 (1H, d, 8 Hz, CH-Ar), 8.18-8.19 (1H, d, 7.5 Hz, CH-Ar), ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 24.0, 90.2, 116.6, 120.0, 120.9, 125.1, 125.5, 125.9, 126.2, 127.5, 127.7, 128.1, 128.5, 128.6, 128.9, 133.7, 134,2, 138.1, 142.1, 155.1, 160.3. MS(EI): *m/z* 335. Elemental Analysis: found: %C, 82.14; % H, 5.21; %N, 12.65; expected: %C, 82.36; %H, 5.11; %N, 12.53. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 272 (11,100), 328 (12,500).



2-((1-benzyl-1H-indol-5-yl)amino)-6-methyl-5-phenylnicotinonitrile (Table 5.4, entry k)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 1-benzyl-1H-indol-5-amine (222

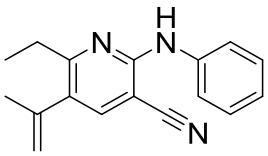
mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (223 mg, 54%) as a yellow solid. M.p.: 143-146 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 2.47 (3 H, s, CH_3), 5.36 (2 H, s, CH_2), 6.57-6.58 (1 H, d, J = 4 Hz, 2-pyrrole-C*H*), 7.03 (1H, br, NH- 1-benzyl-1H-indol-5-amine), 7.11-7.18 (3H, m, CH-Ar), 7.27-7.41 (9H, m, CH-Ar), 7.44-7.46 (2H, t, 1.5 Hz, CH-Ar), 7.63 (1H, s, 4-CH-pyridine), 8.00 (1H, s, CH-Ar), ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 24.1, 50.2, 89.5, 101.7, 109.8, 113.6, 116.9, 117.3, 126.7, 127.3, 127.4, 127.6, 128.5, 128.7, 128.9, 129.0, 129.0, 131.2, 133.7, 137.4, 138.4, 142.1, 155.6, 160.2. MS(EI): *m/z* 414. Elemental Analysis: found: %C, 81.33; % H, 5.27; %N, 13.40; expected: %C, 81.13; %H, 5.35; %N, 13.52. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 283 (21,000), 353 (3,800).

Preparation and Characterization of Compounds in Table 5.5



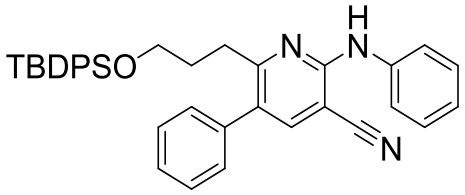
5,6-diethyl-2-(phenylamino)nicotinonitrile (Table 5.5, entry l)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), hex-3-yne (82 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (160 mg, 64%) as a brown solid. M.p.: 100-102 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.21-1.25 (3 H, t, J = 8 Hz, CH_3), 1.34-1.37 (3 H, t, J = 8 Hz, CH_3), 2.57-2.62 (2 H, t, J = 8 Hz, CH_2), 2.79-2.84 (2 H, t, J = 8 Hz, CH_2), 6.96 (1H, br, NH-aniline), 7.09-7.11 (1H, t, 2.5 Hz, CH-Ar), 7.36-7.39 (2H, m, CH-Ar), 7.54 (1H, s, 4-CH-pyridine), 7.72-7.74 (2H, d, 8.5 Hz, CH-Ar). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 12.4, 14.2, 23.9, 28.0, 90.0, 117.0, 119.5, 122.6, 127.2, 128.6, 139.4, 140.4, 153.6, 164.8. MS(EI): *m/z* 251. Elemental Analysis: found: %C, 76.32; % H,

6.92; %N, 16.76; expected: %C, 76.46; %H, 6.82; %N, 16.72. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 286 (14,500), 342 (3,600).



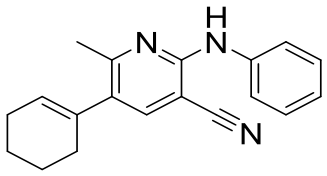
6-ethyl-2-(phenylamino)-5-(prop-1-en-2-yl)nicotinonitrile (Table 5.5, entry m)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), 2-methylhex-1-en-3-yne (94 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (157 mg, 60%) as a brown solid. M.p.: 72-74 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.26-1.30 (3 H, t, 7.5 Hz CH_3), 2.00 (3 H, m, CH_3), 2.75-1.79 (2 H, q, 7.5 Hz, CH_2), 4.88-4.89 (1 H, m, CH), 5.22-5.23 (1 H, m, CH), 6.94 (1H, br, NH-aniline), 7.05-7.07 (1H, t, 7.5 Hz, CH-Ar), 7.32-7.35 (2H, m, CH-Ar), 7.48 (1H, s, 4-CH-pyridine), 7.66-7.68 (2H,

d, 10 Hz, CH-Ar), $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 13.1, 24.4, 28.9, 89.8, 116.7, 116.9, 119.8, 123.1, 128.8, 129.3, 139.1, 140.7, 142.1, 154.1, 164.0. MS(EI): *m/z* 263. Elemental Analysis: found: %C, 77.47; % H, 6.58; %N, 15.95; expected: %C, 77.54; %H, 6.51; %N, 15.96. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 290 (20,700), 344 (4,400).



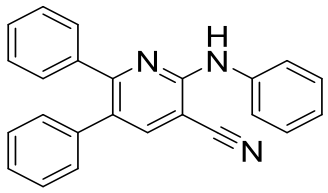
6-(3-((tert-butyldiphenylsilyl)oxy)propyl)-5-phenyl-2-(phenylamino)nicotinonitrile (Table 5.5, entry n)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), *tert*-butyldiphenyl((5-phenylpent-4-yn-1-yl)oxy)silane (398 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (345 mg, 61%) as a yellow solid. M.p.: 90-92 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.15 (9H, s, Si-

CCH_3), 2.16-2.19 (2H, m, $CH_2CH_2CH_2OTBDMS$), 3.01-3.04 (2H, t, J=7.5 Hz, $CH_2CH_2CH_2OTBDMS$), 3.81-3.84 (2H, t, J=6 Hz, $CH_2CH_2CH_2OTBDMS$), 7.19-7.22 (1H, t, 7.5 Hz, CH-Ar), 7.29 (1H, br, NH-aniline), 7.38-7.39 (2H, m, CH-Ar), 7.45-7.55 (12H, m, CH-Ar), 7.72 (1H, s, 4-CH-pyridine), 7.75-7.76 (4H, m, CH-Ar), 7.84-7.86 (2H, d, 8.5 Hz, CH-Ar), $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 19.0, 26.7, 31.2, 32.3, 63.3, 90.0, 116.5, 120.0, 123.0, 127.4, 127.5, 127.9, 128.4, 128.6, 129.0, 129.3, 133.7, 135.3, 135.4, 137.9, 138.9, 142.1, 154.1, 163.1. ^{29}Si NMR ($CDCl_3$, 500 MHz): -4.39 $OSi(Ph)_2C(CH_3)_3$. Elemental Analysis: found: %C, 78.22; % H, 6.64; %N, 7.32; expected: %C, 78.27; %H, 6.57; %N, 7.40. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 294 (15,000), 344 (3,300).



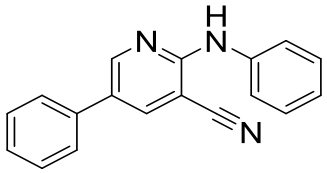
5-(cyclohex-1-en-1-yl)-6-methyl-2-(phenylamino)nicotinonitrile (Table 5.5, entry o)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), 1-(prop-1-yn-1-yl)cyclohex-1-ene (120 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol),

DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (159 mg, 55%) as a brown solid. M.p.: 127-129 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.70-1.73 (2 H, m, CH_2), 1.78-1.81 (2 H, m, CH_2), 2.19-2.21 (4 H, m, CH_2), 2.51 (3 H, s, CH_3), 5.65-5.66 (1 H, d, 1.5 Hz, CH), 7.02 (1H, br, NH-aniline), 7.10-7.11 (1H, t, 8 Hz, CH-Ar), 7.36-7.39 (2H, m, CH-Ar), 7.49 (1H, s, 4-CH-pyridine), 7.71-7.72 (2H, d, 8.5 Hz, CH-Ar), $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 21.7, 22.7, 23.3, 25.2, 29.7, 89.8, 116.6, 119.7, 122.8, 128.1, 128.6, 130.4, 135.2, 139.1, 140.8, 153.5, 159.8. MS(EI): *m/z* 289. Elemental Analysis: found: %C, 78.94; % H, 6.56; %N, 14.50; expected: %C, 78.86; %H, 6.62; %N, 14.52. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 290 (19,000), 344 (3,900).



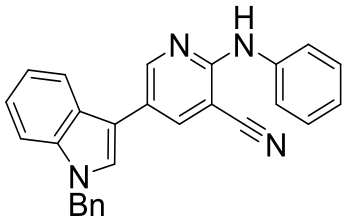
5,6-diphenyl-2-(phenylamino)nicotinonitrile (Table 5.5, entry p)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (62.6 mg, 0.2 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), 1,2-diphenylethyne (178 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After

completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (149 mg, 43%) as a yellow solid. M.p.: 140-142 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.11-7.15 (4H, m, CH-Ar, NH-aniline), 7.25-7.31 (6H, m, CH-Ar), 7.36-7.39 (2H, t, 8 Hz, CH-Ar), 7.42-7.43 (2H, d, 7.5 Hz, CH-Ar), 7.75-7.76 (2H, d, 8 Hz, CH-Ar), 7.83 (H, s, 4-CH-pyridine). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 91.5, 116.5, 120.1, 123.4, 127.1, 127.3, 127.8, 128.5, 128.8, 128.9, 129.3, 130.0, 138.4, 138.8, 138.9, 143.9, 153.9, 159.3. Elemental Analysis: found: %C, 82.82; % H, 5.00; %N, 12.18; expected: %C, 82.97; %H, 4.93; %N, 12.10. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 299 (37,900), 366 (8,800). Further characterized by X-ray diffraction studies.



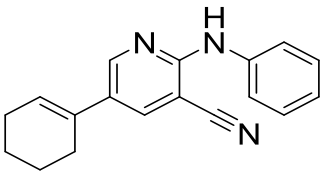
5-phenyl-2-(phenylamino)nicotinonitrile (Table 5.5, entry q)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.1 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), ethynylbenzene (102 mg, 1 mmol), and *tert*-butylisonitrile (137 μL, 1.2 mmol). The pressure tube was sealed with a Teflon

screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (168 mg, 62%) as a yellow solid. M.p.: 142-144 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 7.04 (1H, br, NH-aniline), 7.13-7.14 (1H, t , 1 Hz, CH-Ar), 7.36-7.39 (3H, m, CH-Ar), 7.43-7.49 (5H, m, CH-Ar), 7.60-7.62 (2H, d, 8.5Hz, CH-Ar), 7.97-7.98 (1H, d, 7 Hz, 4-CH-pyridine), 8.61-8.62 (1H, d, 7 Hz, 1-CH-pyridine). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 93.2, 116.3, 120.9, 124.0, 126.2, 127.7, 127.9, 129.0, 129.2, 136.0, 138.4, 139.6, 150.7, 155.0. MS(EI): *m/z* 271. Elemental Analysis: found: %C, 79.77; % H, 4.77; %N, 15.55; expected: %C, 79.68; %H, 4.83; %N, 15.49. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 302 (25,500), 350 (4,300). Further characterized by X-ray diffraction studies.



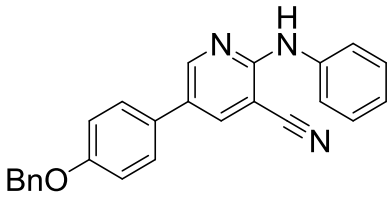
5-(1-benzyl-1H-indol-3-yl)-2-(phenylamino)nicotinonitrile (Table 5.5, entry r)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.1 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), 1-benzyl-3-ethynyl-1H-indole (231 mg, 1 mmol), and *tert*-butylisonitrile (137 μL, 1.2 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (196 mg, 49%) as a brown solid. M.p.: 148-151 °C**.** ^{1}H NMR ($CDCl_3$, 500 MHz): 5.32 (2 H, s, CH_2), 7.04 (1H, br, NH-aniline), 7.09-7.112 (1H, t , 7 Hz, CH-Ar), 7.15-7.17 (2H, d, 7 Hz, CH-Ar), 7.20-7.38 (9H, m, CH-Ar), 7.60-7.62 (2H, d, 8 Hz, CH-Ar), 7.79-7.80 (1H, d, 7.5 Hz, CH-Ar), 8.01-8.02 (1H, d, 2.5 Hz, 4-CH-pyridine), 8.68-8.69 (1H, d, 2.5 Hz, 6-CH-pyridine). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 50.2, 93.3, 110.3, 112.0, 116.5, 119.2, 120.6, 122.7, 122.7, 123.7, 125.5, 125.9, 126.9, 127.9, 128.9, 129.1, 136.7, 136.9, 138.6, 139.7, 150.6, 153.9. Elemental Analysis: found: %C, 80.86; % H, 5.10; %N, 14.04; expected:

%C, 80.98; %H, 5.03; %N, 13.99. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 315 (13,300), 367 (1,900). Further characterized by X-ray diffraction studies.



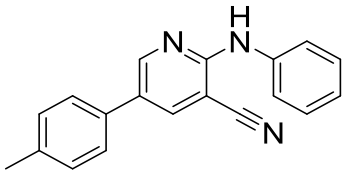
5-(cyclohex-1-en-1-yl)-2-(phenylamino)nicotinonitrile (Table 5.5, entry s)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.1 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), 1-ethynylcyclohex-1-ene (106 mg, 1 mmol), and *tert*-butylisonitrile (137 μL, 1.2 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (154 mg, 56%) as a yellow solid. M.p.: 110-112 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.61-1.66 (2 H, m, CH_2), 1.74-1.79 (2 H, m, CH_2), 2.17-2.20 (2 H, m, CH_2), 2.28-2.31 (2 H, m, CH_2), 6.04-6.06 (1 H, d, 1.5 Hz, CH), 6.97 (1H, br, NH-aniline), 7.08-7.11 (1H, t, 8 Hz, CH-Ar),

7.33-7.36 (2H, m, CH-Ar), 7.55-7.57 (2H, m, CH-Ar), 7.75-7.76 (1H, d, 2 Hz, 4-CH-pyridine), 8.39-8.40 (1H, d, 2 Hz, 6-CH-pyridine). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 21.7, 22.6, 25.7, 26.8, 92.7, 116.5, 120.6, 123.8, 125.4, 129.0, 129.1, 131.9, 137.8, 138.6, 148.8, 154.4. MS(EI): *m/z* 275. Elemental Analysis: found: %C, 78.37; % H, 6.29; %N, 15.34; expected: %C, 78.52; %H, 6.22; %N, 15.26. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 302 (13,700), 359 (2,100). Further characterized by X-ray diffraction studies.



5-(4-(benzyloxy)phenyl)-2-(phenylamino)nicotinonitrile (Table 5.5, entry t)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.1 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), 1-(benzyloxy)-4-ethynylbenzene (208 mg, 1 mmol), and *tert*-butylisonitrile (137 μL, 1.2 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to

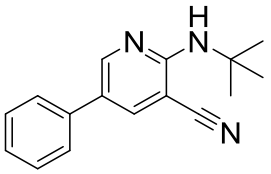
afford the desired compound (248 mg, 66%) as a yellow solid. M.p.: 132-135 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 5.01 (2 H, s, CH_2), 6.99 (1H, br, NH-aniline), 7.04-7.06 (2H, dd , 2.5 Hz and 5.5 Hz CH-Ar), 7.10-7.13 (1H, t, 8 Hz, CH-Ar), 7.32-7.45 (8H, m, CH-Ar), 7.58-7.60 (2H, dd , 2.5 Hz and 5.5 Hz CH-Ar), 7.91-7.92 (1H, d, 2.5 Hz, 4-CH-pyridine), 8.56-8.57 (1H, d, 2.5 Hz, 6-CH-pyridine). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 70.1, 93.2, 115.6, 116.4, 120.7, 123.9, 127.42, 127.44, 127.5, 128.1, 128.6, 128.7, 129.1, 136.6, 138.5, 139.2, 150.3, 154.6, 158.7. MS(EI): *m/z* 377. Elemental Analysis: found: %C, 79.47; % H, 5.13; %N, 11.08; expected: %C, 79.55; %H, 5.07; %N, 11.13. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 306 (11,600), 353 (1,600).



2-(phenylamino)-5-(p-tolyl)nicotinonitrile (Table 5.5, entry u)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.1 mmol) in dry toluene (2 mL) was loaded with aniline (93 mg, 1 mmol), 1-ethynyl-4-methylbenzene (116 mg, 1 mmol), and *tert*-butylisonitrile (137 μL, 1.2 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C

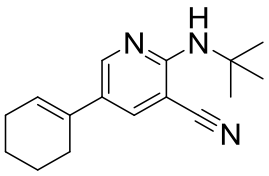
in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (165 mg, 58%) as a yellow solid. M.p.: 137-139 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 2.38 (3 H, s, CH_3), 7.01 (1H, br, NH-aniline), 7.10-7.13 (1H, t , 7.5 Hz, CH-Ar), 7.25-7.26 (2H, d, 7.5 Hz, CH-Ar), 7.35-7.38 (3H, m, CH-Ar), 7.59-7.61 (2H, dd, 1 Hz and 3 Hz CH-Ar), 7.95-7.96 (1H, d, 3 Hz, 4-CH-pyridine), 8.59-8.60 (1H, d, 3 Hz, 6-CH-pyridine). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 21.1, 93.2, 116.4, 120.8, 123.9, 126.0, 127.7, 129.0, 129.9, 133.1, 138.5, 139.4, 150.5, 154.8. MS(EI): *m/z* 285. Elemental Analysis: found: %C, 79.91; % H, 5.34; %N, 14.75; expected: %C, 79.98; %H, 5.30; %N, 14.73. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 305 (25,200), 354 (2,400).

Preparation and Characterization of Compounds in Table 5.7



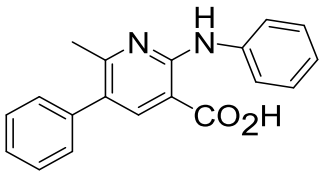
2-(tert-butylamino)-5-phenylnicotinonitrile (Table 5.7, entry v)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **1** (32.4 mg, 0.1 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (95 mg, 1 mmol), ethynylbenzene (102 mg, 1 mmol), and *tert*-butylisonitrile (137 μL, 1.2 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (145 mg, 58%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.43 (9 H, s, $C(CH_3)_3$), 5.43 (1H, br, NH-2-methylpropan-2-amine), 7.25-7.27 (1H, m, CH-Ar), 7.31-7.36 (4H, m, CH-Ar), 7.00-7.01 (1H, d, 2 Hz, 4-CH-pyridine), 8.40-8.41 (1H, d, 2 Hz, 6-CH-pyridine). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 28.9, 52.5, 91.7, 117.1, 124.6, 125.9, 127.3, 129.0, 136.6, 139.1, 150.4, 157.2. MS(EI): *m/z* 251. Elemental Analysis: found: %C, 76.48; % H, 6.76; %N, 16.76;

expected: %C, 76.46; %H, 6.82; %N, 16.72. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 284 (21,800), 352 (4,200).

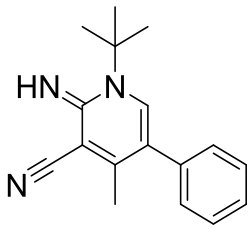


2-(tert-butylamino)-5-(cyclohex-1-en-1-yl)nicotinonitrile (Table 5.7, entry w)**:** In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **1** (32.4 mg, 0.1 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (95 mg, 1 mmol), 1-ethynylcyclohex-1-ene (106 mg, 1 mmol), and *tert*-butylisonitrile (137 μL, 1.2 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (135 mg, 53%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.46 (9 H, s, $C(CH_3)_3$), 1.60-1.63 (2 H, m, CH_2), 1.71-1.74 (2 H, m, CH_2), 2.13-2.16 (2 H, m, CH_2), 2.24-2.26 (2 H, m, CH_2), 4.95 (1H, br, NH-2-methylpropan-2-amine), 5.95 (1 H, m, CH), 7.57-7.58 (1H, d, 2.5 Hz, 4-CH-pyridine), 8.28-8.29 (1H, d, 2.5 Hz, 6-CH-pyridine), $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 21.8, 22.7, 25.6, 26.8, 29.1, 52.4, 91.2, 117.5, 123.9, 126.1,

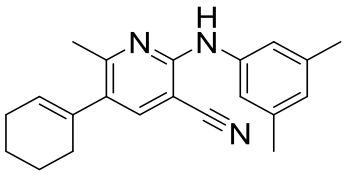
132.3, 137.2, 148.8, 157.0. MS(EI): *m/z* 255. Elemental Analysis: found: %C, 75.24; % H, 8.21; %N, 16.55; expected: %C, 75.26; %H, 8.29; %N, 16.46. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 280 (20,300), 344 (3,900).



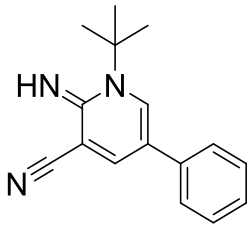
6-Methyl-5-phenyl-2-(phenylamino)nicotinic acid: 6-Methyl-5-phenyl-2-(phenylamino) nicotinonitrile (0.17 mmol) was added to a 50% aqueous sulfuric acid solution (2 mL). The resulting solution was refluxed in a silicone oil bath for 48 h. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2, and neutralized with saturated $NaHCO_3$ solution. The organic layer was washed with water, dried over Na_2SO_4, and concentrated on a rotary evaporator. The crude product was purified by recrystallized from CH_2Cl_2 and hexane (1 : 1) solvent mixture. (47.4 mg, 88.5%) as a brown solid. M.p.: 154-157 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 2.47 (3 H, s, CH_3), 6.99-7.02 (H, t, 7.5 Hz, CH-Ar), 7.28-7.41 (8H, m, CH-Ar, NH-aniline), 7.75-7.76 (2H, d, 8 Hz, CH-Ar), 8.15 (1H, s, 4-CH-pyridine), 10.12 (H, br, COOH). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 23.8, 120.3, 122.5, 127.1, 127.3, 128.4, 128.7, 129.1, 129.2, 139.2, 139.9, 142.1, 154.5, 161.0, 172.2. Elemental Analysis: found: %C, 74.92; % H, 5.35; %N, 9.24; expected: %C, 74.98; %H, 5.30; %N, 9.20.



1-(tert-butyl)-2-imino-4-methyl-5-phenyl-1,2-dihydropyridine-3-carbonitrile: In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with aniline (95 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature. Then, the tube was charged with malononitrile (132 mg, 2 mmol), triethylamine (280 μL, 2 mmol) in methanol (1.5 mL) and water (0.5 mL) solvent mixture. The mixture was stirred for 5 h at 0 °C. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (167 mg, 63%) as a brown solid. M.p.: 120-122 °C. MS(EI): m/z 265. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.72 (3 H, s, $C(CH_3)_3$), 2.15 (3 H, s, CH_3), 7.14 (H, br, NH), 7.15-7.16 (H, d, 1.5 Hz, CH-Ar), 7.32-7.33 (2H, m, CH-Ar), 7.35-7.37 (3H, m, CH-Ar), $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 19.4, 27.8, 63.0, 104.0, 116.7, 117.5, 127.5, 128.6, 129.4, 136.4, 137.8, 152.8, 155.8. Elemental Analysis: found: %C, 77.04; % H, 7.17; %N, 15.79; expected: %C, 76.95; %H, 7.22; %N, 15.84. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 278 (14,400), 402 (5,100). MS(EI): *m/z* 265.



5-(cyclohex-1-en-1-yl)-2-((3,5-dimethylphenyl)amino)-6-methylnicotinonitrile: In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 3,5-dimethylaniline (121 mg, 1 mmol), 1-(prop-1-yn-1-yl)cyclohex-1-ene (120 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (132 mg, 2 mmol), DBU (76 mg, 0.5 mmol), molecular sieves (200 mg), in absolute ethanol (2 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (161 mg, 51%) as a yellow brown solid. M.p.: 98-100 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.64-1.68 (2 H, m, CH_2), 1.71-1.76 (2 H, m, CH_2), 2.11-2.16 (4 H, m, CH_2), 2.31 (6 H, s, CH_3), 2.44 (3 H, s, CH_3), 5.59-6.0 (1 H, d, 1.5 Hz, CH), 6.71 (1H, br, NH-3,5-dimethylaniline), 6.79 (1H, s, CH-Ar), 7.27 (2H, m, CH-Ar), 7.43 (1H, s, 4-CH-pyridine), ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 21.4, 21.8, 22.8, 23.4, 25.3, 29.8, 89.8, 116.8, 117.6, 124.9, 128.1, 130.3, 135.3, 138.4, 138.9, 140.8, 153.7, 160.0. MS(EI): *m/z* 317. Elemental Analysis: found: %C, 79.50; % H, 7.32; %N, 13.18; expected: %C, 79.46; %H, 7.30; %N, 13.24



1-(tert-butyl)-2-imino-5-phenyl-1,2-dihydropyridine-3-carbonitrile: In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **1** (32.4 mg, 0.1 mmol) in dry toluene (2 mL) was loaded with cyclohexylamine (95 mg, 1 mmol), ethynylbenzene (102 mg, 1 mmol), and *tert*-butylisonitrile (137 μL, 1.2 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. The pressure tube was cooled to room temperature, Then, the tube was charged with malononitrile (132 mg, 2 mmol), triethylamine (280 μL, 2 mmol) in methanol (1.5 mL) and water (0.5 mL) solvent mixture. The mixture was stirred for 5 h at 0 °C. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (130 mg, 52%) as a yellow brown solid. M.p.: 94-96 °C. MS(EI): m/z 251. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.81 (9 H, s, $C(CH_3)_3$), 7.29-7.34 (3H, m, CH-Ar, NH), 7.40-7.44 (2H, m, CH-Ar), 7.47-7.48 (1H, m, CH-Ar), 7.56 (1H, s 4-CH-pyridine), 7.76 (1H, s, 6-CH-pyridine). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 27.7, 63.9, 105.1, 114.8, 116.8, 124.9, 127.1, 129.1, 136.0, 137.6, 141.7, 155.3. Elemental Analysis: found: %C, 76.47; % H, 6.86; %N, 16.67; expected: %C, 76.46; %H, 6.82; %N, 16.72. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 272 (12,800), 398 (4,600). MS(EI): *m/z* 251.

Convertion of 1-(*tert*-butyl)-2-imino-5-phenyl-1,2-dihydropyridine-3-carbonitrile to 2-(*tert*-butylamino)-5-phenylnicotinonitrile (Table 5.8, entry 2)

1-(*tert*-butyl)-2-imino-5-phenyl-1,2-dihydropyridine-3-carbonitrile (**2b**) (60 mg, 0.24 mmol) was dissolved in 1 mL of absolute ethanol in a pressure tube equipped with a magnetic stirbar. Then, the pressure tube was charged with malononitrile (32 mg, 0.48 mmol), DBU (18 mg, 0.24 mmol), molecular sieves (50 mg), in absolute ethanol (1 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound 2-(*tert*-butylamino)-5-phenylnicotinonitrile (**2a**) (51 mg, 86%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.43 (9 H, s, $C(CH_3)_3$), 5.43 (1H, br, NH-2-methylpropan-2-amine), 7.25-7.27 (1H, m, CH-Ar), 7.31-7.36 (4H, m, CH-Ar), 7.00-7.01 (1H, d, 2 Hz, 4-CH-pyridine), 8.40-8.41 (1H, d, 2 Hz, 6-CH-pyridine). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 28.9, 52.5, 91.7, 117.1, 124.6, 125.9, 127.3, 129.0, 136.6, 139.1, 150.4, 157.2. MS(EI): *m/z* 251.

Reaction scaleing up of 6-methyl-5-phenyl-2-(phenylamino)nicotinonitrile

In a N_2 filled glove box, a 250 mL Schlenk flask, equipped with a magnetic stirbar, containing catalyst **2** (616 mg, 0.10 mmol) in dry toluene (40 mL) was loaded with aniline (1.9 g, 20 mmol), 1-phenylpropyne (2.32 g, 20 mmol), and *tert*-butylisonitrile (5.13 mL, 30 mmol). The Schlenk flask was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. After completion of the reaction, the pressure tube was cooled to room temperature. Then, the pressure tube was charged with malononitrile (5.28 mg, 40 mmol), DBU (1.52 g, 10 mmol), molecular sieves (4 g), in absolute ethanol (40 mL). The mixture was heated for 2 h at 80 °C in a silicone oil bath. After completion of the reaction, the crude product was purified by flash column chromatography over silica gel with 9:1 hexanes to ethyl acetate to afford the desired compound (3.7 g, 66%) as a yellow solid. M.p.: 119-121 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 2.53 (3 H, s, CH_3), 7.14-7.17 (2H, br, CH-Ar, NH-aniline), 7.32-7.34 (2H, d, 8 Hz, CH-Ar), 7.40-7.45 (3H, m, CH-Ar), 7.47-7.51 (2H, m, CH-Ar), 7.66 (1H, s, 4-CH-pyridine), 7.76-7.78 (2H, d, 8.5 Hz, CH-Ar). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 23.9, 90.3, 116.5, 119.9, 123.2, 127.5, 127.9, 128.4, 128.7, 128.9, 138.0, 138.9, 141.9, 153.9, 159.9. MS(EI): *m/z* 285. Electronic absorption (CH_2Cl_2) λ, nm (ε, M^{-1} cm^{-1}): 294 (24,800), 342 (1,100).

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CHAPTER 6. SUBSTITUTED QUINOLINES AS NON-COMPETETIVE INHIBITION OF THE HUMAN PROTEASOME

6.1 Introduction

Quinolines are benzo-fused pyridine heterocyclic compounds, and they are also known as 1-azanaphthalenes or 1-benzazines.[1] A large number of substituted quinoline derivatives are known to possess antimalarial (Chloroquine and Primaquine), antimicrobial, antitumor, antifungal, hypotensive, anti HIV (γ-Fagarine), analgesics and anti-inflamatory activities (**Figure 6.1)**.[2] They are also found in photonic materials[3] and redox switches.[4]

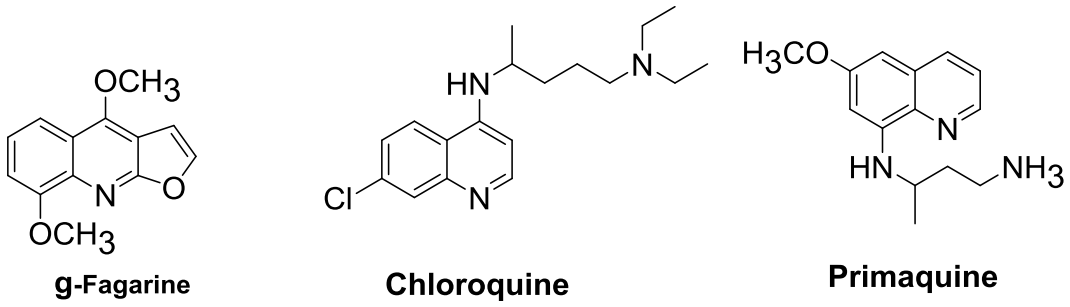
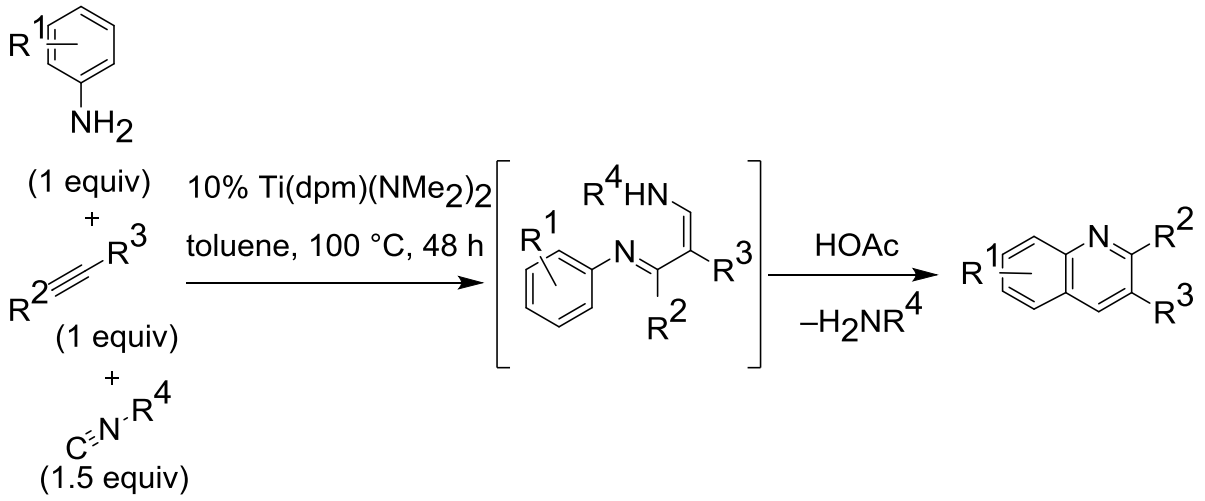


Figure 6.1 Structures of bioactive quinolines

Skraup reported the first substituted quinoline synthesis[5] in 1882 by reaction of aniline and acrolein in the presence of catalytic sulfuric acid. There after, several conventional named reactions were introduced for the synthesis of the quinoline core structure. These condensations of substituted anilines with various carbonyl compounds include the Doebner-Von Miller,[6] Conrad–Limpach,[7] Friedlander,[8] Pfitzinger,[9] Combes,[10] Camps,[11] Povarov,[12] and Knorr reactions.[13]

However in recent years, research have mainly focused on transition metal-catalyzed reactions due to their mild conditions and high degrees of chemo-, regio-, and even stereoselectvity.[14] Many transition metal catalyzed reactions have been developed for the synthesis of substituted quinolines. For example, several ruthenium,[15] rhodium,[16] palladium,[17] and iron[18] complexes have been shown to catalyze the formation of 2,3-substituted quinolines from nitrobenzene and aldehydes or alcohols in the presence of CO gas.



Scheme 6.1 Quinoline synthesis using titanium-catalyzed multicomponent coupling

In 2009, our group demonstrated that a variety of substituted quinolines can be prepared in a one-pot fashion.[19] This methodology uses a titanium-catalyzed 3-component coupling of an alkyne, isonitrile, and aromatic amine to generate unsymmetrical 1,3-diimine tautomers, followed by treatment with acetic acid, provides substituted quinolines in a one-pot procedure (**Scheme 6.1**). This methodology can also be applied to the synthesis of benzoquinolines and unique heterocyclic structures, which could be difficult to access using traditional organic synthetic methods.

In order to maintain regulation of intercellular processes and biological homeostasis, the 26S proteasome is responsible for ubiquitylated protein degradation. Proteasomes are present in all mammalian cells[20] and they are the main non-lysosomal body within the cells. The functionally active 26S proteasome is a very large 2.4 MDa ATP-dependent proteolytic complex.[21] The core structure of the proteasome is the cylindrical 20S particle consisting of four stacked rings (α- and β-rings), each consisting of seven different subunits, which host the catalytic centers. Both ends of the 20S segment are capped with 19S regulatory units containing polyubiquitin-binding sites for recognition.[22] The 20S catalytic core is a threonine protease that exhibits three distinct proteolytic activities: chymotrypsin like (CT-L), trypsin-like (T-L) and caspase like (Casp-L) activity.[23] The proteasome is involved in numerous cell processes, including cell cycle progression, transcriptional regulation,[24] stress response[25] and in regulation of apoptosis.[27]

Therefore, inhibition of the proteasome has been identified as key target for various cancers such as multiple myeloma (MM).[28] Over the last decade several proteasome inhibitors have been developed, and they are currently at various stages of clinical development, these inhibitors fall in structurally diverse classes of organic compounds, including epoxyketones (epoxymicin),[29] cyclic peptides,[30] β-lactones,[31] vinyl sulfones,[32] peptide aldehydes[33] and boronic acids (e.g. bortezomib formerly known as PS-341).[34] The FDA approved, peptide-based proteasome inhibitors such as bortezomib and carfizomib significantly improve the clinical

outcome of patients with MM and Mantle Cell Lymphoma (MCL),[28] even though these peptide based inhibitors exhibit inherent toxicity and cross-resistance.[35]

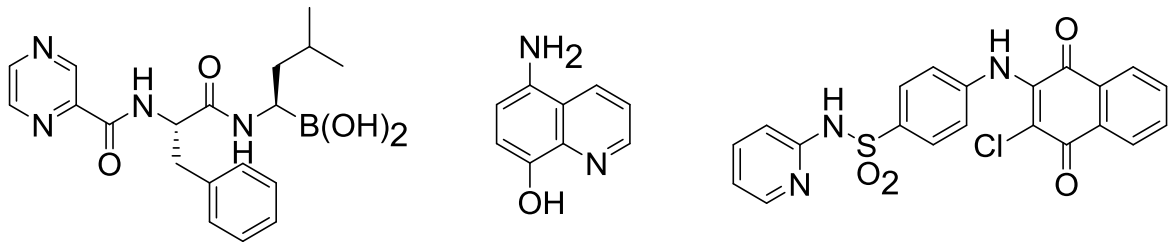


Figure 6.2 Structures of non-competitive proteasome inhibitors

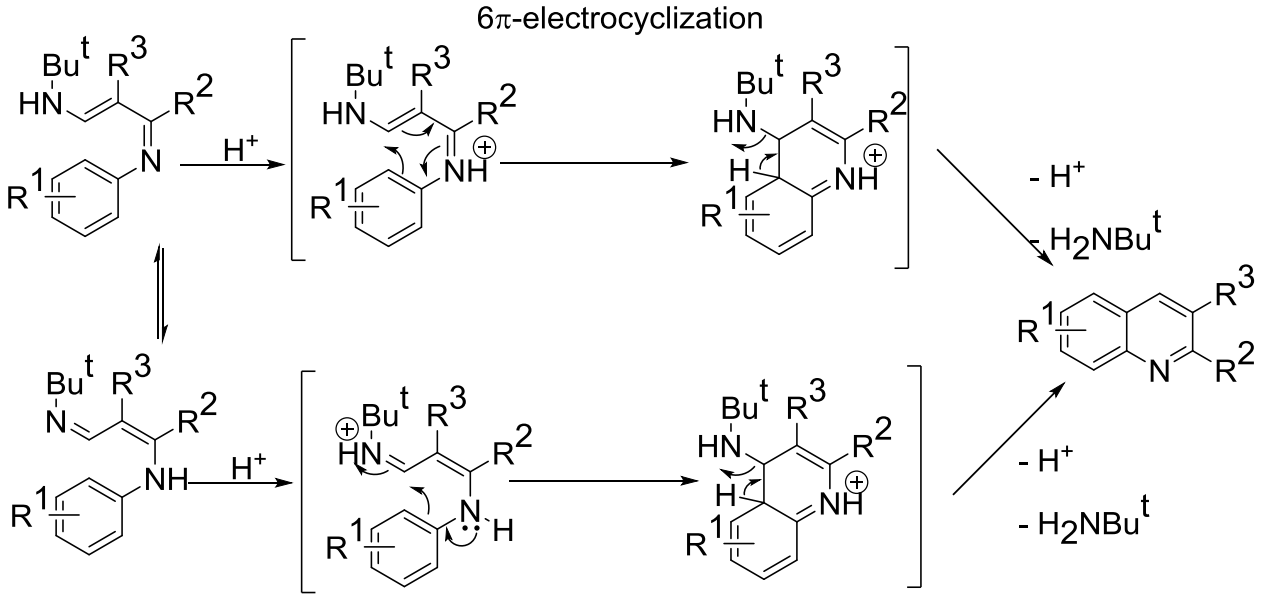
In 2010 Lawrence and co-workers discovered and developed hydrophthoquinone derivates (**PI-083**) as novel class of proteasome inhibitors, which demonstrated selectivity for cancer cells over non-transformed cells (**Figure 6.2**).[36] Schimmer co-workers (2010) reported **5-AHQ** (5-amino-8-hydroxyquinoline), a quinoline-based compound which inhibited proteasome noncompetitively.[37] These substituted quinoline based inhibitors present new strategies for inhibition of the human proteasome and a potential lead for a new class of small molecule therapeutic agents for cancer treatment

In this study, a small library of substituted quinolines was prepared by one pot titanium catalyzed multicomponent coupling reactions (**Table 6.1)** and was tested for its ability to inhibit the chymotryptic activity of the purified 20S human proteasome. I acknowledge Mrs. Lauren Azevedo in Professor Tepe's laboratory for conducting proteasome inhibition studies.

6.2 Results and Discussion

The titanium-catalyzed 3-component coupling (3CC) reactions that generate tautomers of 1,3-diimines, prepared from aromatic amines, can be used as direct precursors for substituted quinolines and related heterocycles in a one-pot procedure simply by adding acetic acid to the multicomponent coupling product (**Scheme 6.2**).

Two titanium catalysts Ti(dpma)$(NMe_2)_2$ (**1**), and Ti(dpm)$(NMe_2)_2$ (**2**) were employed for these studies. They can be prepared (refer to chapter 3) in a single step by reacting the ancillary ligands with commertially available $Ti(NMe_2)_4$. The proposed catalytic cycle involved in the synthesis of the 3CC product (discussed in chapter 3) is based on the mechanism for catalytic hydroamination.



Scheme 6.2 Possible mechanisms for quinoline synthesis

The cyclization of the multicomponent coupling product involves Brönsted acid-catalyzed intramolecular attack on the pendant aromatic ring (**Scheme 6.2**), followed by the loss of *tert*-butylamine in the aromatization of the nitrogen heterocycles.[38] This proposed mechanism is similar to the Povarov reaction.[39] Using this novel methodology, the 4-position of the substituted quinoline product will be unsubstituted.

Table 6.1 Examples of quinoline syntheses (**Scheme 6.1**)

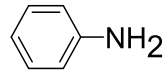
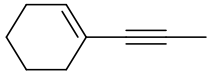
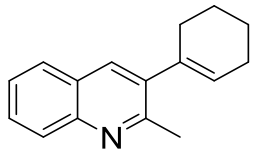
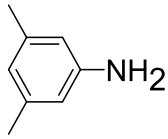
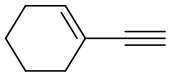
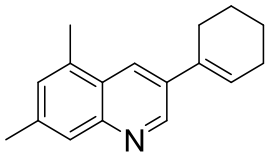
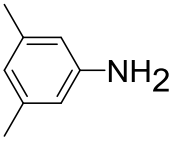
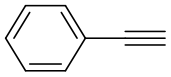
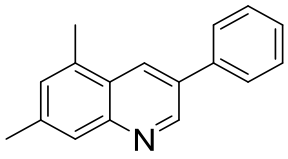
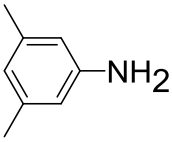
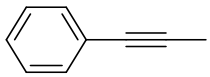
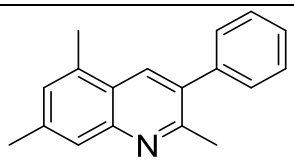
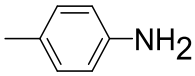
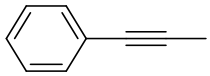
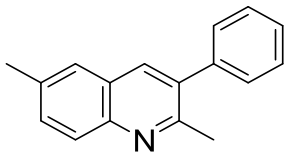
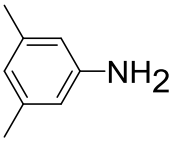
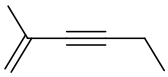
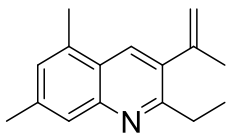
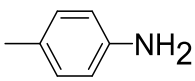
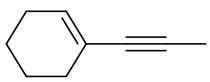
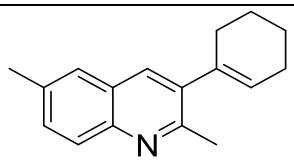
Amine	Alkyne	Product	Isolated yield	Compound ID
			28% [a]	**AD100**
			42% [a]	**AD102**
			55% [a]	**AD104**
			68% [a]	**AD049**
			68% [a]	**AD108**
			62% [a]	**AD112**
			52% [a]	**AD113**

Table 6.1 (cont'd)

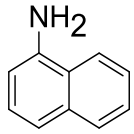
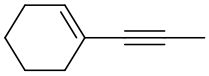
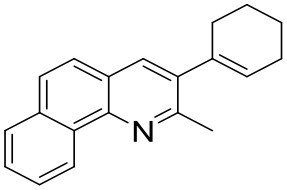
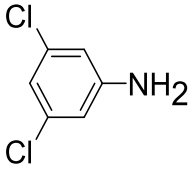
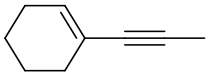
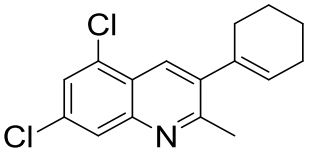
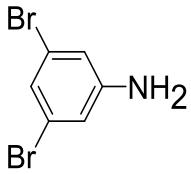
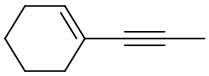
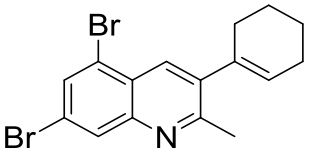
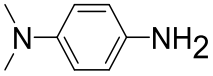
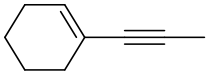
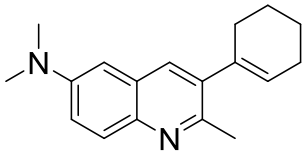
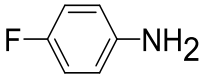
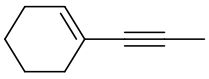
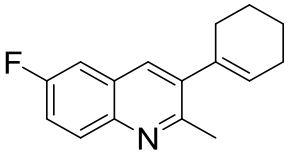
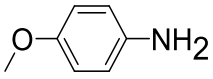
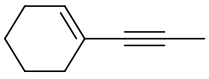
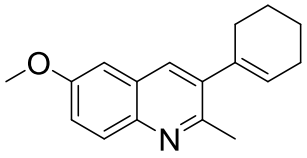
Amine	Alkyne	Product	Isolated yield	Compound ID
			37% [a]	**AD114**
			45% [a]	**AD115**
			32% [a]	**AD116**
			44% [a]	**AD117**
			15% [a]	**AD118**
			43% [a]	**AD119**

Table 6.1 (cont'd)

[a] Reactions carried out with arylamine, alkyne, and *tert*-butylisonitrile in a 1:1:1.5 ratio with 10 mol % catalyst (**2)** at 100 °C for 48 h. Once the 3CC is complete, product was heated at 150 °C in acetic acid (2 mL) for 18 h.

The ability of the substituted quinolines to inhibit CT-L activity of purified human 20S proteasome was determined in vitro using a fluorogenic peptide as substrate, Suc-LLVY-AMC.[40] The rates of hydrolysis were monitored by fluorescence increase at 37 °C over 30 minutes, and the linear portion of the curves were used to calculate the IC_{50} values. The activities of the quinolines are listed in **Table 6.2**.

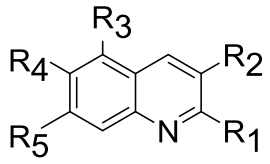
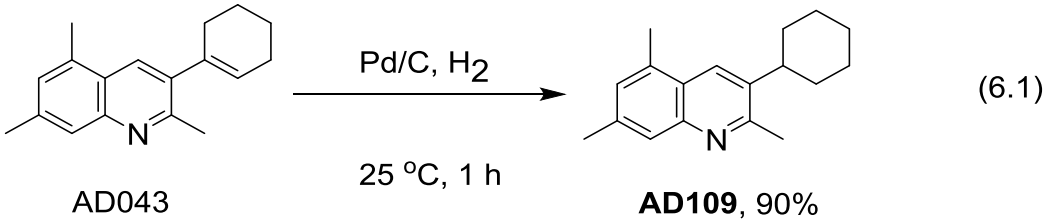


Figure 6.3 Structure of substituted quinolines

Our initial study focused on the commercially available, 2-methylquinoline (**AD110**) and 3-methylquinoline (**AD111**), which did not show any proteasome inhibition activity (**Table 6.1**). Incorporation of methyl groups in the 5- and 7-position (**AD104**) provided a compound with modest inhibition of proteasome activity (IC_{50} = 12.3 μM). The addition of another methyl

group in the 2-position (R_1) improved activity as illustrated by compound **AD039** (IC_{50} = 8.5 μM). Interestingly, partially hydrogenated cyclohexene (**AD043**), yielded a new lead compound for proteasome inhibition (IC_{50} = 5.4 μM) and replacement of the partially hydrogenated cyclohexene to the fully hydrogenated cyclohexane ring (**AD109**), diminishes all proteasome inhibition activity (**Equation 6.1**).



AD043 **AD109**, 90% (6.1)

Equation 6.1 Synthesis of 3-cyclohexyl-2,5,7-trimethylquinoline **(AD109)**

Table 6.2 Structure and IC_{50} values of substituted quinolines

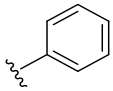
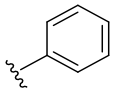
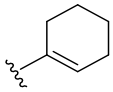
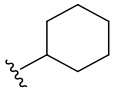
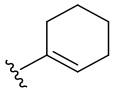
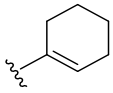
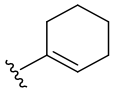
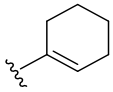
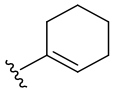
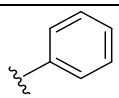
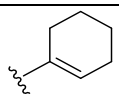
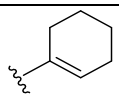
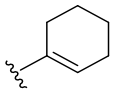
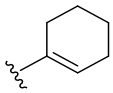
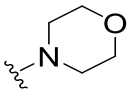
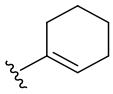
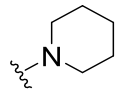
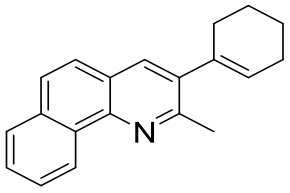
Entry	Compound number	R_1	R_2	R_3	R_4	R_5	IC_{50} (μM)
1	**AD110**	CH_3	H	H	H	H	>25 [a]
2	**AD111**	H	CH_3	H	H	H	>25 [a]
3	**AD104**	H		CH_3	H	CH_3	12.3 [a]
4	**AD039**	CH_3		CH_3	H	CH_3	8.5 [a]
5	**AD043**	CH_3		CH_3	H	CH_3	5.4 [a]
6	**AD109**	CH_3		CH_3	H	CH_3	>25 [a]
7	**AD100**	CH_3		H	H	H	>25 [a]
8	**AD102**	H		CH_3	H	CH_3	>25 [a]
9	**AD112**	CH_2CH_3		CH_3	H	CH_3	>25 [a]
10	**AD115**	CH_3		Cl	H	Cl	>25 [a]
11	**AD116**	CH_3		Br	H	Br	>25 [a]

Table 6.2 (cont'd)

Entry	Compound number	R_1	R_2	R_3	R_4	R_5	IC_{50} (μM)
12	**AD113**	CH_3		H	CH_3	H	8.4 [a]
13	**AD108**	CH_3		H	CH_3	H	19.7 [a]
14	**AD119**	CH_3		H	OCH_3	H	>25 [a]
15	**AD118**	CH_3		H	F	H	>25 [a]
16	**AD117**	CH_3		H	$N(CH_3)_2$	H	5.4 [a]
17	**AD120**	CH_3		H		H	17.3 [a]
18	**AD121**	CH_3		H		H	10.1 [a]
19	**AD114**						>25 [a]

[a] The ability of the substituted quinolines to inhibit CT-L activity of purified human 20S proteasome was determined in vitro using a fluorogenic peptide as substrate, Suc-LLVY-AMC.

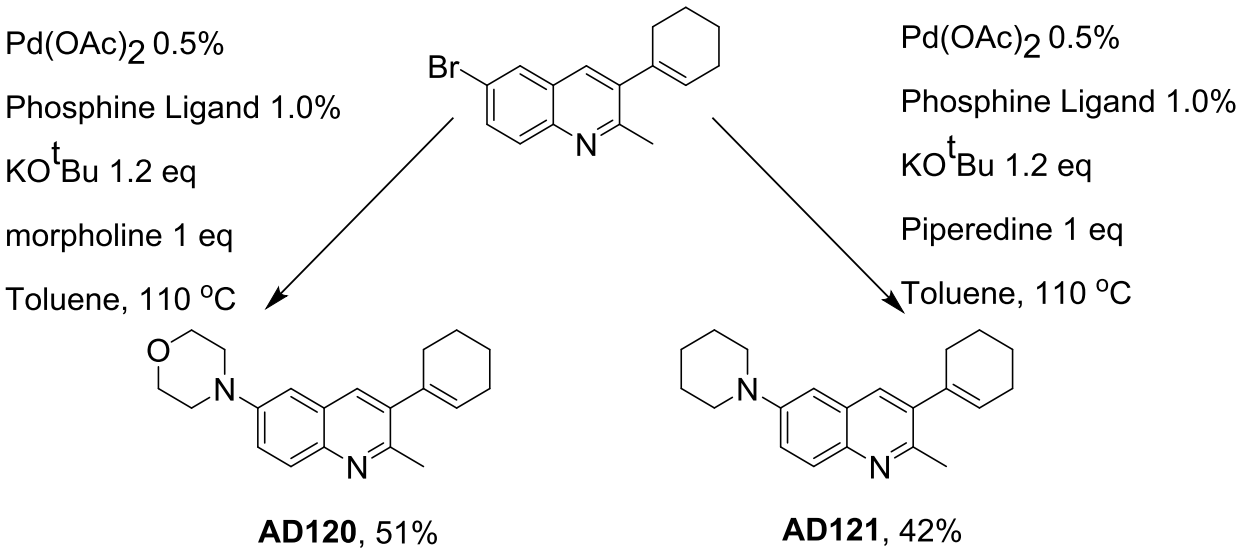
Table 6.2 (cont'd)

The rates of hydrolysis were monitored by fluorescence increase at 37 °C over 30 minutes, and the linear portion of the curves were used to calculate the IC_{50} values

Replacement of the cyclohexene, with an isopropenyl group and R_1 with an ethyl group (**AD112**), results an inactive quinoline compound, indicating the significance of the cyclohexene moiety of the substituted quinoline substrates for the proteasome inhibition activity. Eliminating either the R_1 or R_3 and R_5 methyl groups, also results inactive compounds (**AD100** and **AD102**, respectively), indicating the need of hydrophobic groups in these domains. This was further confirmed by replacing the methyl groups with halogens, which also reduced overall proteasome inhibition activity (**AD115** and **AD116**). Also further functionalization of the R_4-position followed a similar trend, where methylation (**AD113**) resulted in modest activity (IC_{50} = 8.4 μM). Replacement of R_5 position with naphthyl group (**AD114**) derivative results no proteasome inhibition activity.

Consistent with the drop of activity seen between the R_2 = phenyl (**AD039**) and R_2 = cyclohexene derivative (**AD043**), the derivative **AD108** was significantly less active than its cyclohexene counterpart (**AD113**). Incorporation of electron donating (**AD119**) or electron withdrawing (**AD118**) moieties in the R_4 position did not restore activity compared to the R_4 = H (**AD102**); however, dimethyl amino analogue **AD117**, mimicked the activity seen in dimethyl derivative **AD043**. Considering the lack of proteasome inhibition activity of **AD118** and **AD119**,

this restoration of inhibition activity is most likely due to positioning of the two methyl groups of dimethylamine **AD117** in two hydrophobic binding pockets, rather than a possible hydrogen bond accepting role.



Scheme 6.3 Synthesis of 4-(3-(cyclohex-1-en-1-yl)-2-methylquinolin-6-yl)morpholine **(AD120)** and 3-(cyclohex-1-en-1-yl)-2-methyl-6-(piperidin-1-yl)quinoline **(AD121)**

Considering the apparent requirement of the alkyl groups in the R_3 and R_5 position in **AD043**, it is likely that the two methyl groups on dimethylamine **AD117** occupy similar pockets given the close special proximity to the R_3 and R_5 position. Lastly, substituted quinolines **AD120** and **AD121** was prepared by Buchwald–Hartwig amination of 6-bromo-3-(cyclohex-1-en-1-yl)-2-methylquinoline to substitute R_4 position with morpholine and piperidine moieties **(Scheme 6.3**). These novel R_4 substituted quinolines results modest proteasome inhibition activity (IC_{50} = 17.3 μM and IC_{50} = 10.1 μM respectively).

From the screened substituted quinolines, the most active substituted quinoline **AD043** was subsequently evaluated for its inhibition of the proteasome's tryptic and caspase activity *in vitro* using purified human 20S proteasome and the following fluorogenic peptide as substrates: Boc-LRR-AMC (substrate for T-L activity) and Z-LLE-AMC (substrate for casp-L activity). According to the data, the substituted quinoline **AD043** inhibits the casp-L but not the tryptic-L activities of the 20S catalytic core (IC_{50} = 17.7 μM and IC_{50} >25 μM respectively).

6.3 Conclusion

Titanium-catalyzed 3-component coupling of primary amine, alkyne, and isonitrile followed by treatment with acetic acid provides quinolines in a one-pot procedure. This methodology has significant flexibility in the types of substituted quinolines that can be accessed. The yields are generally modest, but the products are readily isolated using either column chromatography or crystallization. Reactions with terminal alkynes can be accomplished with the milder Ti(dpma)$(NMe_2)_2$ **(1)** as catalyst. The more active dipyrrolylmethane catalyst, Ti(dpm)$(NMe_2)_2$ **(2),** was used for internal alkynes.

In conclusion, our SAR quinoline studies suggest that the 2-position (R_1) substituted with cyclohexene is important for the human proteasome inhibition action. Quinoline **AD043** was found to be the most active analogue in this series and inhibited the chymotryptic activity of the 20S proteasome with an IC_{50} = 5.4 μM. Hydrophobic groups are also need in the R_3 and R_5 (methyl groups) positions. However, dimethyl amino analogue **AD117**, mimicked the activity seen in dimethyl derivative **AD043**. Further studies show substituted quinoline **AD043** inhibits the casp-L activities of the 20S catalytic core (IC_{50} = 17.7 μM).

Currently, further optimization of this new substituted quinoline template is currently ongoing in our laboratories.

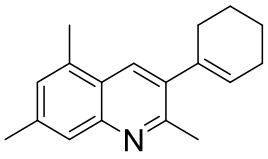
6.4 Experimental

General Considerations: All manipulations of air sensitive compounds were carried out in an MBraun drybox under a purified nitrogen atmosphere. Toluene was purified by sparging with dry N_2 and removing water by running through activated alumina systems purchased from Solv-Tek. ^{1}H and ^{13}C spectra were recorded on Varian VXR-500 spectrometers. Ti(dpma)$(NMe_2)_2$ (**1**), and Ti(dpm)$(NMe_2)_2$ (**2**) was made following the literature procedure.[41] Alkynes were purchased either from Aldrich or from GFS chemicals and dried from CaO under dry nitrogen. Amines were purchased from Aldrich, dried over KOH and distilled under dry nitrogen. Palladium(II) acetate, potassium *tert*-butoxide and 2-(dicyclohexylphosphino)biphenyl (97%) were also purchased from Aldrich and used as received. 2-methylquinoline **(AD110)** and 3-methylquinoline **(AD111)** were purchased from TCI America. *tert*-Butylisonitrile was made according to the literature procedure and purified by distillation under nitrogen.[42]

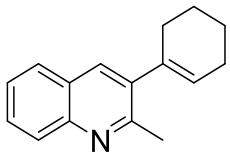
General Procedure for Quinoline Synthesis: In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst (10-20 mol%) in dry toluene (2 mL) was loaded with arylamine (1 mmol), alkyne (1 mmol), and isonitrile (1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated at the temperature listed for the time given with stirring. After completion of the reaction (checked by GC-FID), the pressure tube was cooled to room temperature and volatiles were removed in vacuo. Then the same pressure tube was charged with glacial acetic acid (2 mL) and heated to 150 $^{\circ}C$ for 24 h. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2, and neutralized with

saturated $NaHCO_3$ solution. The organic layer was washed with water, dried over Na_2SO_4, and concentrated on a rotary evaporator. The crude product was purified by column chromatography as described.

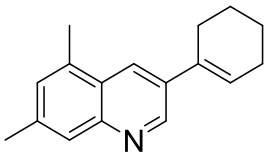
Preparation and Characterization of Compounds in Table 6.1



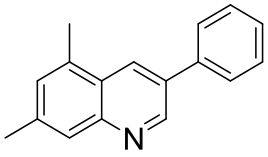
3-cyclohexenyl-2,5,7-trimethylquinoline (AD043): In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 3,5-dimethylaniline (121 mg, 1 mmol), 1-(prop-1-ynyl)cyclohex-1-ene (120 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. Volatiles were removed in vacuo and glacial acetic acid (2 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (100 mg, 40%) as a bright red viscous liquid. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.70-1.72 (2 H, m, C*H*$_2$), 1.70-1.79 (2 H, m, C*H*$_2$), 2.18-2.19 (2 H, m, C*H*$_2$), 2.20-2.24 (2 H, m, C*H*$_2$), 2.46 (3 H, s, C*H*$_3$), 2.59 (3 H, s, C*H*$_3$), 2.64 (3 H, s, C*H*$_3$), 5.67 (1 H, m, C*H*), 7.10 (1 H, s, Ar-*H*), 7.61(1 H, s, Ar-*H*), 7.84 (1 H, s, 4C*H*). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 18.4, 21.7, 22.0, 23.0, 23.5, 25.4, 30.2, 124.1, 125.6, 127.2, 128.4, 130.7, 133.6, 136.9, 137.7, 138.4, 147.2, 156.8. MS (EI): *m/z* 251 (M^+). Elemental Analysis: found: %C, 85.94; % H, 8.45; %N, 5.61; expected: %C, 86.01; %H, 8.42; %N, 5.57.



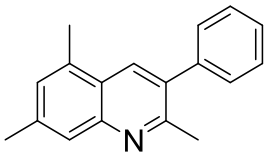
3-cyclohexenyl-2-methylquinoline (AD100)*:* In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with aniline (92 mg, 1 mmol), 1-(prop-1-ynyl)cyclohex-1-ene (120 mg, 1 mmol) and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. Volatiles were removed in vacuo, and glacial acetic acid (2 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (60 mg, 28%) as a yellow liquid. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.68-1.72 (2 H, m, CH_2), 1.76-1.80 (2 H, m, CH_2), 2.17-2.23 (2 H, m, CH_2), 2.23-2.26 (2 H, m, CH_2), 2.67 (3 H, s, CH_3), 5.67-5.68 (1 H, m, C*H*), 7.40-7.43 (1 H, m, Ar-*H*), 7.58-7.61 (1 H, m, Ar-*H*), 7.69-7.71 (1 H, d, J = 8.5 Hz, Ar-*H*), 7.75 (1 H, s, 4C*H*), 7.96-7.98 (1 H, d, J = 8.5 Hz, Ar-*H*). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 21.9, 22.9, 23.7, 25.4, 30.1, 125.6, 126.9, 127.1, 127.4, 128.2, 128.7, 134.3, 137.3, 138.1, 146.6, 157.6. MS (EI): *m/z* 223 (M^+). Elemental Analysis: Found %C, 86.12; %H, 7.60; %N, 6.28; Expected: %C, 86.06; %H, 7.67; %N, 6.27.



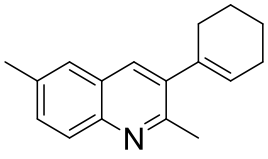
3-cyclohexenyl-5,7-dimethylquinoline (AD102)*:* In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 3,5-dimethylaniline (121 mg, 1 mmol), 1-ethynylcyclohexene (106 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. Volatiles were removed in vacuo, and glacial acetic acid (2 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (99 mg, 42%) as a pale yellow solid M.p.: 58-59 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.69-1.71 (2 H, m, CH_2), 1.82-1.84 (2 H, m, CH_2), 2.26-2.28 (2 H, m, CH_2), 2.47 (3 H, s, CH_3), 2.48-2.52 (2 H, m, CH_2), 2.63 (3 H, s, CH_3), 6.29-6.30 (1 H, m, CH), 7.17 (1 H, s, Ar-*H*), 7.66 (1 H, s, 4C*H*), 8.07-8.08 (1 H, d, *J* = 2 Hz, Ar-*H*), 8.94-8.95 (1 H, d, *J* = 2 Hz, Ar-*H*), ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 18.6, 21.7, 21.9, 22.9, 26.0, 27.3, 125.2, 126.1, 126.8, 126.9, 128.3, 129.5, 129.6, 133.9, 134.1, 134.3, 148.1. MS (EI): m/z *237* (M^+). Elemental Analysis: Found %C, 86.22; %H, 7.96; %N, 5.82; Expected: %C, 86.03; %H, 8.07; %N, 5.90.



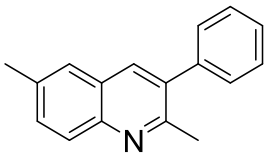
5,7-dimethyl-3-phenylquinoline (AD104)*:* In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 3,5-dimethylaniline (121 mg, 1 mmol), phenylacetylene (102 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 24 h at 100 °C in a silicone oil bath. Volatiles were removed in vacuo, and glacial acetic acid (2 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (128 mg, 55%) as a pale yellow solid. M.p.: 76-78 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 2.51 (3 H, s, CH_3), 2.68 (3 H, s, CH_3), 7.23 (1 H, s, 6C*H*), 7.39-7.42 (1 H, m, Ar-*H*), 7.48-7.52 (2 H, m, Ar-*H*), 7.68-7.70 (2 H, m, Ar-*H*), 7.74 (1 H, s, 8C*H*), 8.36-8.37 (1 H, d, 2 Hz, 4C*H*), 9.10 (1 H, d, 2 Hz, 2C*H*). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 18.5, 21.8, 125.3, 126.4, 127.4, 127.8, 129.1, 129.6, 129.8, 132.6, 134.2, 138.4, 139.3, 147.9, 149.3. MS (EI): *m/z* 233 (M^+). Elemental Analysis: Found %C, 87.42; %H, 6.52; %N, 6.06; Expected: %C, 87.52; %H, 6.48; %N, 6.00.



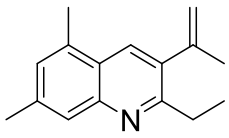
2,5,7-trimethyl-3-phenylquinoline (AD049): In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 3,5-dimethylaniline (121 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. Volatiles were removed in vacuo, and glacial acetic acid (2 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (170 mg, 68%) as a pale yellow solid. M.p.: 79-80 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 2.50 (3 H, s, CH_3), 2.59 (3 H, s, CH_3), 2.63 (3 H, s, $2CH_3$), 7.15 (1 H, s, 6C*H*), 7.38-7.41 (3 H, m, Ar-*H*), 7.44-7.47 (2 H, m, Ar-*H*), 7.69 (1 H, s, 8C*H*), 8.02 (1 H, s, 4C*H*). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 18.4, 21.8., 24.3, 124.1, 125.6, 127.3, 128.3, 128.8, 129.3, 132.5, 133.9, 134.3, 139.1, 140.4, 147.5, 156.5. MS (EI): *m/z* 247 (M^+). Elemental Analysis: Found %C, 87.42; %H, 6.99; %N, 5.59; Expected: %C, 87.41; %H, 6.93; %N, 5.66.



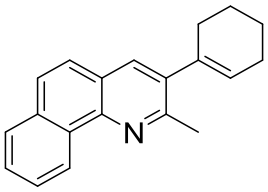
3-(cyclohex-1-en-1-yl)-2,6-dimethylquinoline (AD113): In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 4-methylaniline (107 mg, 1 mmol), 1-(prop-1-ynyl)cyclohex-1-ene (120 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. Volatiles were removed in vacuo, and glacial acetic acid (2 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (123 mg, 52%) as a brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.68-1.72 (2 H, m, CH_2), 1.75-1.78 (2 H, m, CH_2), 2.17-2.20 (2 H, m, CH_2), 2.22-2.24 (2 H, m, CH_2), 2.46 (3 H, s, CH_3), 2.64 (3 H, s, CH_3), 5.65-5.67 (1 H, m, C*H*), 7.42-7.45 (2 H, m, Ar-*H*), 7.66 (1 H, s, Ar-*H*), 7.85-7.86 (1 H, d, J = 8.5 Hz, Ar-*H*), ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 21.4, 22.0, 22.9, 23.6, 25.4, 30.1, 126.0, 126.9, 127.3, 127.9, 130.9, 133.7, 135.3, 137.4, 138.1, 145.3, 156.6. MS (EI): *m/z* 237 (M^+). Elemental Analysis: Found %C, 86.04; %H, 8.09; %N, 5.87; Expected: %C, 86.03; %H, 8.07; %N, 5.90.



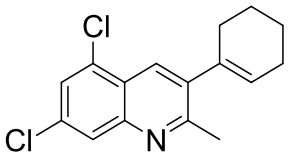
2,6-dimethyl-3-phenylquinoline (AD108)*:* In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 4-methylaniline (107 mg, 1 mmol), 1-phenylpropyne (116 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. Volatiles were removed in vacuo, and glacial acetic acid (2 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (158 mg, 68%) as a pale yellow solid. M.p.: 80-81 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 2.50 (3 H, s, CH_3), 2.63 (3 H, s, CH_3), 7.37-7.39 (3 H, m, Ar-*H*), 7.40-7.43 (2 H, m, Ar-*H*), 7.49-7.51 (2 H, m, Ar-*H*), 7.83 (1 H, s, 4C*H*), 7.94-7.96 (1 H, d, 2 Hz, Ar-*H*). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 21.5, 24.4, 126.2, 126.7, 127.4, 128.0, 128.3, 129.1, 131.5, 135.4, 135.6, 135.7, 140.0, 145.6, 156.2. MS (EI): *m/z* 233 (M^+). Elemental Analysis: Found %C, 87.62; %H, 6.42; %N, 5.96; Expected: %C, 87.52; %H, 6.47; %N, 6.00.



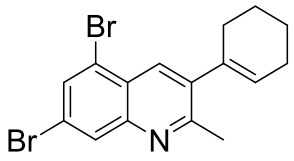
2-ethyl-5,7-dimethyl-3-(prop-1-en-2-yl)quinoline (AD112): In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 3,5-dimethylaniline (121 mg, 1 mmol), 2-methylhex-1-en-3-yne (94 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. Volatiles were removed in vacuo, and glacial acetic acid (2 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (158 mg, 62%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.34-1.37 (3 H, t, J = 7.5 Hz ,CH_3), 2.12 (3 H, s, CH_3), 2.46 (3 H, s, CH_3), 2.57 (3 H, s, CH_3), 2.96-3.00 (2 H, q, J = 7.5 Hz , CH_2), 4.98-4.99 (1 H, d, 1 Hz, C*H*), 5.27-5.28 (1 H, d, 1 Hz, C*H*), 7.08 (1 H, s, 5C*H*), 7.67 (1 H, s, 3C*H*), 7.89 (1 H, s, 7C*H*), ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 14.1, 18.3, 21.6, 24.9, 29.1, 116.1, 123.8, 125.7, 128.4, 130.7, 133.5, 135.7, 138.4, 144.5, 147.5, 160.6. MS (EI): *m/z* 255 (M^+). Elemental Analysis: Found %C, 85.32; %H, 8.53; %N, 6.15; Expected: %C, 85.28; %H, 8.50; %N, 6.22.



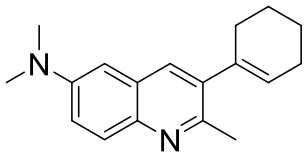
3-(cyclohex-1-en-1-yl)-2-methylbenzo[h]quinoline (AD114): In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with naphthalen-1-amine (143 mg, 1 mmol), 1-(prop-1-ynyl)cyclohex-1-ene (120 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. Volatiles were removed in vacuo, and glacial acetic acid (2 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (101 mg, 37%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.74-1.76 (2 H, m, CH_2), 1.82-1.84 (2 H, m, CH_2), 2.23-2.25 (2 H, m, CH_2), 2.30-2.32 (2 H, m, CH_2), 2.81 (3 H, s, CH_3), 5.74-5.75 (1 H, m, C*H*), 7.61-7.66 (2 H, m, Ar-*H*), 7.69-7.73 (2 H, m, Ar-*H*), 7.81 (1 H, s, Ar-*H*). 7.86-7.88 (1 H, d,8 Hz, Ar-*H*), 9.33-9.35 (1 H, d, 8 Hz, Ar-*H*). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 22.0, 23.0, 23.8, 25.5, 30.0, 124.2, 124.5, 125.1, 126.6, 126.7, 127.3, 127.5, 127.6, 131.2, 133.4, 134.5, 137.4, 138.4, 144.4, 155.9. MS (EI): *m/z* 273 (M^+). Elemental Analysis: Found %C, 87.81; %H, 7.03; %N, 5.16; Expected: %C, 87.87; %H, 7.01; %N, 5.12.



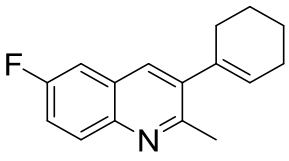
5,7-dichloro-3-cyclohexenyl-2-methylquinoline (AD115)*:* In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 3,5-dichloroaniline (160 mg, 1 mmol), 1-(prop-1-ynyl)cyclohex-1-ene (120 mg, 1 mmol), and *tert*-butylisonitrile (171 µL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. Volatiles were removed in vacuo, and glacial acetic acid (2 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (131 mg, 45%) as a brown solid. M.p.: 56-58 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.70-1.73 (2 H, m, C CH_2), 1.77-1.80 (2 H, m, CH_2), 2.18-2.23 (2 H, m, CH_2), 2.23-2.26 (2 H, m, CH_2), 2.65 (3 H, s, CH_3), 5.69-5.71 (1 H, m, C*H*), 7.46-7.47 (1 H, d, *J* = 2 Hz Ar-*H*), 7.87-7.89 (1 H, m, *J* = 3 Hz Ar-*H*), 8.06 (1 H, s, Ar-*H*), ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 21.9, 22.8, 23.6, 25.4, 29.9, 123.6, 126.4, 126.7, 128.3, 130.9, 131.6, 133.6, 136.7, 139.3, 147.2, 159.9. MS (EI): *m/z* 292 (M^+). Elemental Analysis: Found %C, 65.81; %H, 5.20; %N, 4.72; Expected: %C, 65.77; %H, 5.17; %N, 4.79.



5,7-dibromo-3-(cyclohex-1-en-1-yl)-2-methylquinoline (AD116)*:* In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 3,5-dibromoroaniline (248 mg, 1 mmol), 1-(prop-1-ynyl)cyclohex-1-ene (120 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. Volatiles were removed in vacuo, and glacial acetic acid (2 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (122 mg, 32%) as a yellow solid. M.p.: 89-90 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.71-1.73 (2 H, m, CH_2), 1.78-1.80 (2 H, m, CH_2), 2.20-2.23 (2 H, m, CH_2), 2.24-2.26 (2 H, m, CH_2), 2.66 (3 H, s, CH_3), 5.71-5.72 (1 H, m, C*H*), 7.80-7.81 (1 H, d, J = 2 Hz Ar-*H*), 8.01 (1 H, s, Ar-*H*), 8.11-8.12 (1 H, d, J = 1.5 Hz, Ar-*H*), ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 21.9, 22.8, 23.5, 25.4, 29.9, 121.8, 121.9, 125.2, 128.4, 130.7, 132.1, 133.5, 136.7, 139.8, 147.4, 159.9. MS (EI): *m/z* 381 (M^+). Elemental Analysis: Found %C, 50.51; %H, 3.93; %N, 3.64; Expected: %C, 50.43; %H, 3.97; %N, 3.68.

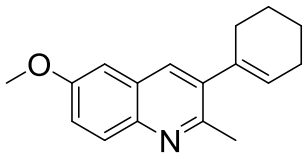


3-(cyclohex-1-en-1-yl)-N,N,2-trimethylquinolin-6-amine (AD117): In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with N^1,N^1-dimethylbenzene-1,4-diamine (136 mg, 1 mmol), 1-(prop-1-ynyl)cyclohex-1-ene (120 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. Volatiles were removed in vacuo, and glacial acetic acid (2 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (117 mg, 44 %) as a brown solid. M.p.: 81-83 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.72-1.74 (2 H, m, CH_2), 1.75-1.73 (2 H, m, CH_2), 2.22-2.24 (2 H, m, CH_2), 2.23-2.29 (2 H, m, CH_2), 2.64 (3 H, s, CH_3), 3.04 (6 H, s, $N(CH_3)_2$), 5.68-5.70 (1 H, m, C*H*), 6.78-6.79 (1 H, d, J = 3 Hz, Ar-*H*), 7.29- 7.32 (1 H, dd, J = 3 Hz, 9 Hz, Ar-*H*), 7.63 (1 H, s, Ar-*H*), 7.86-7.88 (1 H, d, J = 9 Hz, Ar-*H*). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 22.1, 23.0, 23.2, 25.4, 30.1, 40.8, 105.2, 118.8, 126.8, 128.2, 128.8, 132.7, 137.7, 138.3, 140.8, 148.2, 153.1. MS (EI): *m/z* 266 (M^+). Elemental Analysis: Found %C, 81.14; %H, 8.40; %N, 10.46; Expected: %C, 81.16; %H, 8.32; %N, 10.52.

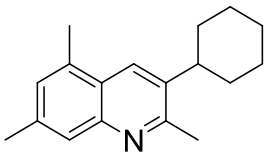


3-(cyclohex-1-en-1-yl)-6-fluoro-2-methylquinoline (AD118): In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 4-fluoroaniline (111 mg, 1 mmol), 1-(prop-1-ynyl)cyclohex-1-ene (120 mg, 1 mmol), and *tert*-butylisonitrile (171 µL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. Volatiles were removed in vacuo, and glacial acetic acid (2 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (38 mg, 15 %) as a brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.69-1.71 (2 H, m, CH_2), 1.72-1.78 (2 H, m, CH_2), 2.17-2.19 (2 H, m, CH_2), 2.20-2.25 (2 H, m, CH_2), 2.65 (3 H, s, CH_3), 5.67-5.68 (1 H, m, CH), 7.29-7.31 (1 H, dd, J = 3 Hz, 9 Hz, Ar-*H*), 7.34- 7.38 (1 H, ddd, J = 3 Hz, 9 Hz, 9 Hz, Ar-*H*), 7.70 (1 H, s, Ar-*H*), 7.94-7.97 (1 H, dd, J = 5.5 Hz, 9.5 Hz, Ar-*H*). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 21.9, 22.9, 23.5, 25.4, 30.0, 110.0 - 110.1 (d, J_{CF} = 21.2 Hz), 118.6 – 118.8 (d, J_{CF} = 25.6 Hz), 127.4 -127.5 (d, J_{CF} = 10 Hz), 127.7, 130.5 – 130.6 (d, J_{CF} = 9.1 Hz), 113.7 – 133.8 (d, J_{CF} = 5 Hz), 137.0, 138.9, 143.7, 157.0 – 157.1 (d, J_{CF} = 2.7 Hz), 159.1. ^{19}F NMR ($CDCl_3$, 500 MHz): - 115.0 (m), MS (EI): *m/z* 241 (M^+). Elemental

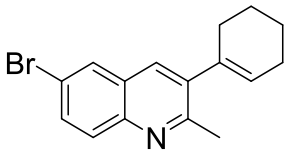
Analysis: Found %C, 79.59; %H, 6.65; %N, 5.75; Expected: %C, 79.64; %H, 6.68; %N, 5.80.



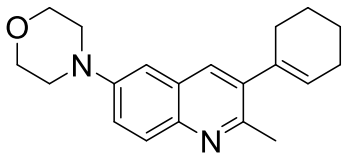
3-(cyclohex-1-en-1-yl)-2,6-dimethylquinoline (AD119): In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 4-methoxyaniline (123 mg, 1 mmol), 1-(prop-1-ynyl)cyclohex-1-ene (120 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. Volatiles were removed in vacuo, and glacial acetic acid (2 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (108 mg, 43%) as a brown solid. M.p.: 50-52 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.72-1.75 (2 H, m, CH_2), 1.80-1.82 (2 H, m, CH_2), 2.22-2.23 (2 H, m, CH_2), 2.25-2.28 (2 H, m, CH_2), 2.66 (3 H, s, CH_3), 3.89 (3 H, s, OCH_3), 5.69-5.70 (1 H, m, CH), 7.00-7.01 (1 H, d, J = 3 Hz, Ar-*H*), 7.27- 7.30 (1 H, dd, J = 3 Hz, 9 Hz, Ar-*H*), 7.69 (1 H, s, Ar-*H*), 7.89-7.91 (1 H, d, J = 9 Hz, Ar-*H*). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): 22.0, 22.9, 23.3, 25.4, 30.1, 55.4, 104.8, 121.1, 127.2, 127.7, 129.7, 133.4, 137.4, 138.4, 142.7, 154.9, 157.1. MS (EI): *m/z* 253 (M^+). Elemental Analysis: Found %C, 80.49; %H, 7.60; %N, 5.57; Expected: %C, 80.60; %H, 7.56; %N, 5.53.



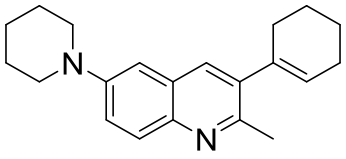
3-cyclohexyl-2,5,7-trimethylquinoline (AD109)*:* 3-cyclohexenyl-2,5,7-trimethylquinoline (60 mg, 0.024 mmol) was dissolved in 6 mL of ethanol and hydrogenated at low pressure over 100 mg of 10% palladium on carbon at room temperature (25 °C) for an hour.[43] Purification was accomplished by after separation of the catalyst by filtration through neutral alumina and removal of the ethanol under reduced pressure then column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (54 mg, 90%) as a pale white liquid. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.42-1.49 (4 H, m, CH_2), 1.79-1.82 (2 H, m, CH_2), 1.89-1.95 (4 H, m, CH_2) 2.46 (3 H, s, CH_3), 2.61 (3 H, s, CH_3), 2.73 (3 H, s, CH_3), 2.79-2.81 (1 H, m, CH), 7.10 (1 H, s, 4C*H*), 7.62 (1 H, s, 6C*H*), 7.96 (1 H, s, 8C*H*). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz):18.5, 22.8, 26.2, 27.1, 29.7, 33.9, 40.1, 124.7, 125.4, 128.1, 128.4, 128.5, 133.5, 138.2, 157.3. MS (EI): *m/z* 253 (M^+). Elemental Analysis: Found %C, 85.29; %H, 9.23; %N, 5.48; Expected: %C, 85.32; %H, 9.15; %N, 5.53.



6-bromo-3-(cyclohex-1-en-1-yl)-2-methylquinoline: In a N_2 filled glove box, a 40 mL pressure tube, equipped with a magnetic stirbar, containing catalyst **2** (30.8 mg, 0.10 mmol) in dry toluene (2 mL) was loaded with 4-bromoaniline (172 mg, 1 mmol), 1-(prop-1-ynyl)cyclohex-1-ene (120 mg, 1 mmol), and *tert*-butylisonitrile (171 μL, 1.5 mmol). The pressure tube was sealed with a Teflon screw cap, taken out of the dry box, and heated for 48 h at 100 °C in a silicone oil bath. Volatiles were removed in vacuo, and glacial acetic acid (2 mL) was added. The mixture was heated to 150 °C for 24 h. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 9:1, which afforded the desired compound (132 mg, 44%) as a brown liquid. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.69-1.71 (2 H, m, CH_2), 1.77-1.80 (2 H, m, CH_2), 2.21-2.24 (4 H, m, CH_2), 2.64 (3 H, s, CH_3), 5.67-5.68 (1 H, m, CH), 7.65- 7.67 (2 H, m, Ar-*H*), 7.82-7.86 (2 H, m, Ar-*H*). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): 21.9, 22.9, 25.4, 28.6, 30.0, 127.9, 128.1, 128.3, 129.2, 129.6, 130.0, 132.2, 133.4, 136.8, 139.1, 158.3. MS (EI): *m/z* 302 (M^+). Elemental Analysis: Found %C, 63.50; %H, 5.29; %N, 4.68; Expected: %C, 63.59; %H, 5.34; %N, 4.63.



4-(3-(cyclohex-1-en-1-yl)-2-methylquinolin-6-yl)morpholine (AD120): A pressure tube was loaded with $Pd(OAc)_2$ (0.4 mg, 2 nmol), 2-(dicyclohexylphosphino)biphenyl (1.4 mg, 4 nmol %), and KO^tBu (53 mg, 48 mmol) under a nitrogen atmosphere. Anhydrous toluene was added, followed by 6-bromo-3-(cyclohex-1-en-1-yl)-2-methylquinoline (120 mg, 40 mmol) and morpholine (41 µl, 48 mmol). The tube was sealed, and then the mixture was stirred for 18 h at 110 °C.[44] After cooling, the mixture was diluted with dichloromethane (20 mL) and washed with water (20 mL) and then brine (20 mL). The organic phase was dried over $MgSO_4$, and then the solvent was removed invacuo. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 19:1, which afforded the desired compound (63 mg, 51%) as a viscous brown oil. ^1H NMR ($CDCl_3$, 500 MHz): 1.68-1.78 (4 H, m, CH_2), 2.18-2.22 (4 H, m, CH_2), 2.62 (3 H, s, CH_3), 3.21-3.23 (4 H, m, NCH_2), 3.85-3.89 (4 H, m, OCH_2), 5.63-5.67 (1 H, m, CH), 6.94-6.95 (1 H, d, 2.5 Hz, Ar-*H*), 7.63 (1 H, s, Ar-*H*), 7.88-7.90 (2 H, d, 4.5 Hz, Ar-*H*), 8.00-8.02 (2 H, d, 4.5 Hz, Ar-*H*). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 22.0, 23.1, 25.4, 29.6, 30.1, 49.6, 66.8, 121.5, 127.2, 127.8, 128.2, 128.8, 129.6, 132.9, 133.5, 138.5, 148.8, 154.7. MS (EI): *m/z* 308 (M^+). Elemental Analysis: Found %C, 77.81; %H, 7.80; %N, 9.01; Expected: %C, 77.89; %H, 7.84; %N, 9.08.



3-(cyclohex-1-en-1-yl)-2-methyl-6-(piperidin-1-yl)quinoline (AD121): A pressure tube was loaded with $Pd(OAc)_2$ (0.3 mg, 1.6 nmol), 2-(dicyclohexylphosphino)biphenyl (1.1 mg, 3.3 nmol %), and KO^tBu (44 mg, 39 mmol) under a nitrogen atmosphere. Anhydrous toluene was added, followed by 6-bromo-3-(cyclohex-1-en-1-yl)-2-methylquinoline (100 mg, 33 mmol) and piperidine (40 µl, 40 mmol). The tube was sealed, and then the mixture was stirred for 18 h at 110 °C.[44] After cooling, the mixture was diluted with dichloromethane (20 mL) and washed with water (20 mL) and then brine (20 mL). The organic phase was dried over $MgSO_4$, and then the solvent was removed in vacuo. Purification was accomplished by column chromatography on neutral alumina. The eluent was hexanes:ethyl acetate 19:1, which afforded the desired compound (42 mg, 42%) as a viscous brown oil. ^1H NMR ($CDCl_3$, 500 MHz): 1.56-1.60 (2 H, m, CH_2), 1.61-1.78 (8 H, m, CH_2), 2.17-2.23 (4 H, m, CH_2), 2.61 (3 H, s, CH_3), 3.21-3.23 (4 H, m, NCH_2), 5.64-5.65 (1 H, m, CH), 6.94-6.95 (1 H, d, 2.5 Hz, Ar-*H*), 7.51-7.54 (1 H, m, Ar-*H*), 7.60 (1 H, s, Ar-*H*), 7.82-7.84 (2 H, d, 9.5 Hz, Ar-*H*). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): 22.0, 23.0, 23.2, 24.3, 25.4, 25.7, 30.1, 50.8, 128.3, 128.6, 129.6, 130.0, 132.9, 133.3, 137.6, 138.2, 149.7, 154.2, 166.5. MS (EI): *m/z* 306 (M^+). Elemental Analysis: Found %C, 82.36; %H, 8.49; %N, 9.15; Expected: %C, 82.31; %H, 8.55; %N, 9.14.

20S Proteasomal Activity Measurement.

The fluorogenic substrates Suc-LLVY-AMC (substrate for CT-L activity), Boc-LRRAMC (substrate for T-L activity), and Z-LLE-AMC (substrate for Casp-L activity) were used to measure proteasome activity. Assays were carried out in black, clear-bottom 96-well plates in a 200 μL reaction volume containing 1 nM purified human 20S proteasome in 50 mM Tris-HCL pH 7.5 and 0.03% SDS containing fluorogenic substrate (at concentrations corresponding to their respective Km value) at 37 °C. The rate of cleavage of fluorogenic peptide substrates was determined by monitoring the fluorescence of released aminomethylcoumarin using a SpectraMax M5e multiwall plate reader at an excitation wavelength of 380 nm and emission wavelength of 460 nm. Fluorescence was measured every minute over a period of 30 min, and the maximum increase in fluorescence per minute was used to calculate specific activities of each sample.

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