DESIGN AND OPTIMIZATION OF PYRROLE SYNTHESES FROM TITANIUM-CATALYZED MULTICOMPONENT COUPLING INTERMEDIATES

By

Cody Michael Pasko

A THESIS

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

Chemistry - Master of Science

2016

ABSTRACT

DESIGN AND OPTIMIZATION OF PYRROLE SYNTHESES FROM TITANIUM-CATALYZED MULTICOMPONENT COUPLING INTERMEDIATES

By

Cody Michael Pasko

Nitrogen containing heterocycles have expressed themselves as being a rich source of biological activity, structural rigidity, and diverse ligand sets for metal-mediated transformations. Classical examples of heterocyclic syntheses provides an excellent platform for methodology development to access new scaffolds. Titanium-catalyzed multicomponent coupling reactions developed by Odom group formulate unique substrates for the preparation of multiple classes of heterocycles (Chapter 1). In this research, procedures for creating pyrrole frameworks and how the methodology can be adapted to synthesizing biologically active natural products is described (Chapter 2 and 3).

The research is divided into four separate, but complimentary chapters organized chronologically from their inception. A one-pot procedure to generate pyrrole-2-carboxylates from the multicomponent coupling reaction of amine, alkyne, and isonitrile catalyzed by titanium (IV) metal complexes is described (Chapter 2). Elucidation of the optimal conditions for this reaction (design of experiment) and some mechanistic insight are included as well.

Applications and unusual deviations of the work above deserves its own chapter along with utilizing new coupling partners to form alternate pyrroles (Chapter 3). Lastly, preliminary results of a novel single step synthesis of pyrrole-2-amidates, using multicomponent coupling chemistry is described with great potential for expanding to other classes of heterocycles (Chapter 4).

I dedicate this thesis to my parents, Mrs. Debbie Pasko and Mr. Larry Pasko, for their enumerable and unconditional support while I define my path through life.

ACKNOWLEDGMENTS

With the greatest appreciation, I would like to extend the first acknowledgment to my major advisor, Professor Aaron L. Odom, for guidance and insight into the extensive and exhaustive process that is the scientific method. I have been equipped with the necessary techniques to extend my scientific career because of his tutelage.

Secondly, I would like to thank my advisory committee members Professor Milton R. Smith III, my second reader, Professor Jetze J. Tepe, and Professor William D. Wulff for not only the contributions to research, but the guidance during coursework that amended my thought process about tackling chemical problems from all different angles.

I would like to acknowledge current and past group members who have specifically impacted my life as well as my research: Tanner McDaniel for his never-ending enthusiasm of chemistry, Brennan Billow for being a good friend when times were difficult, Kelly Aldrich and Ross Bemowski for wonderful discussions about different areas of chemistry, and Nicholas Boersma for his professionalism in the lab. Amila Dissanayake for contributions to the research expounded in this document. A special thanks goes to Evan Beaumier who helped me decided that the Odom group was the right place for me.

Several supporting staff members who informed me throughout my time in the Department of Chemistry also need to be thanked. First, Dr. Daniel Holmes (NMR facility) for the patience and instruction into the various array NMR techniques. Second, Dr. Richard J. Staples (X-ray

facility) for helping collect and refine single crystal data, without which key assignments of structure would have been exceedingly difficult. Bob Rasico, Mellissa Parsons, Marvey Olson, and Bill Flick for their various rolls in keeping the Chemistry Department functioning.

Thank you to my instructors at the University of West Georgia, especially Dr. Spencer J. Slattery for the numerous conversations about Chemistry, History, Religion, and all other facets of life. Without his encouragement I would not be where I am today.

Lastly, I will close with acknowledging my fiancé Erika M. Blair for the journey that we have completed so far and the adventures that are yet to come. With her support anything is achievable.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

KEY OF ABBREVIATIONS

MCR	multicomponent coupling reaction
MCC	multicomponent coupling chemistry
4CC	four component coupling product
3CC	three component coupling product
H_2dpma	*N*,*N*-di(pyrrolyl-α-methyl)-*N*-methylamine
H_2dpm	5,5-dimethyldipyrrolylmethane
BA	biologically active
NP	natural product
Cp	cyclopentadienyl
DBU	1,8-diazabicycloundec-7-ene
DMSO	dimethylsulfoxide
H_2pyxn	2-(4-phenyl-1H-pyrrol-2-yl)-4,5-dihydrooxazole
Cy	cyclohexyl
Ph	phenyl
^{t}Bu	*tert*-butyl
^{n}Bu	butyl
Me	methyl
Et	ethyl

CHAPTER 1. INTRODUCTION TO METAL MEDIATED MULTICOMPONENT COUPLING REACTIONS

1.1 Introduction to multicomponent coupling chemistry

Synthetic organic chemistry can be broken down into two parts: theoretical deconstruction of molecules and practical experimental methodology. Both are equally important when it comes to the assessment of efficiency for a series of chemical reactions that lead to the desired product.[1] In terms of rational retrosynthetic designs, it would be most beneficial to construct as much complexity as needed in the shortest amount of steps. Practical synthetic chemists prefer convergent routes as this offers greater modularity, expedites the discovery of insufficient pathways, and decrease wait times for starting materials (**Figure 1.1**).

One way to incorporate both parts *a priori* and gain complexity rapidly is the use of multicomponent coupling reactions (MCR).[2] The inherent convergent nature of this class of reactions is quite suitable for designing exotic frameworks, the types of which are seen in many natural products.[3] Advancements of multicomponent coupling partners lead to desirable intermediates; opening new routes to challenging targets.

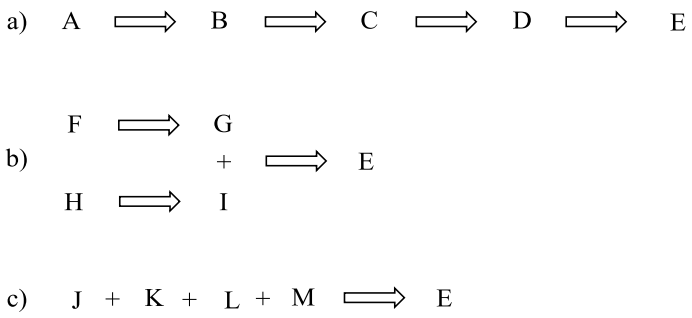
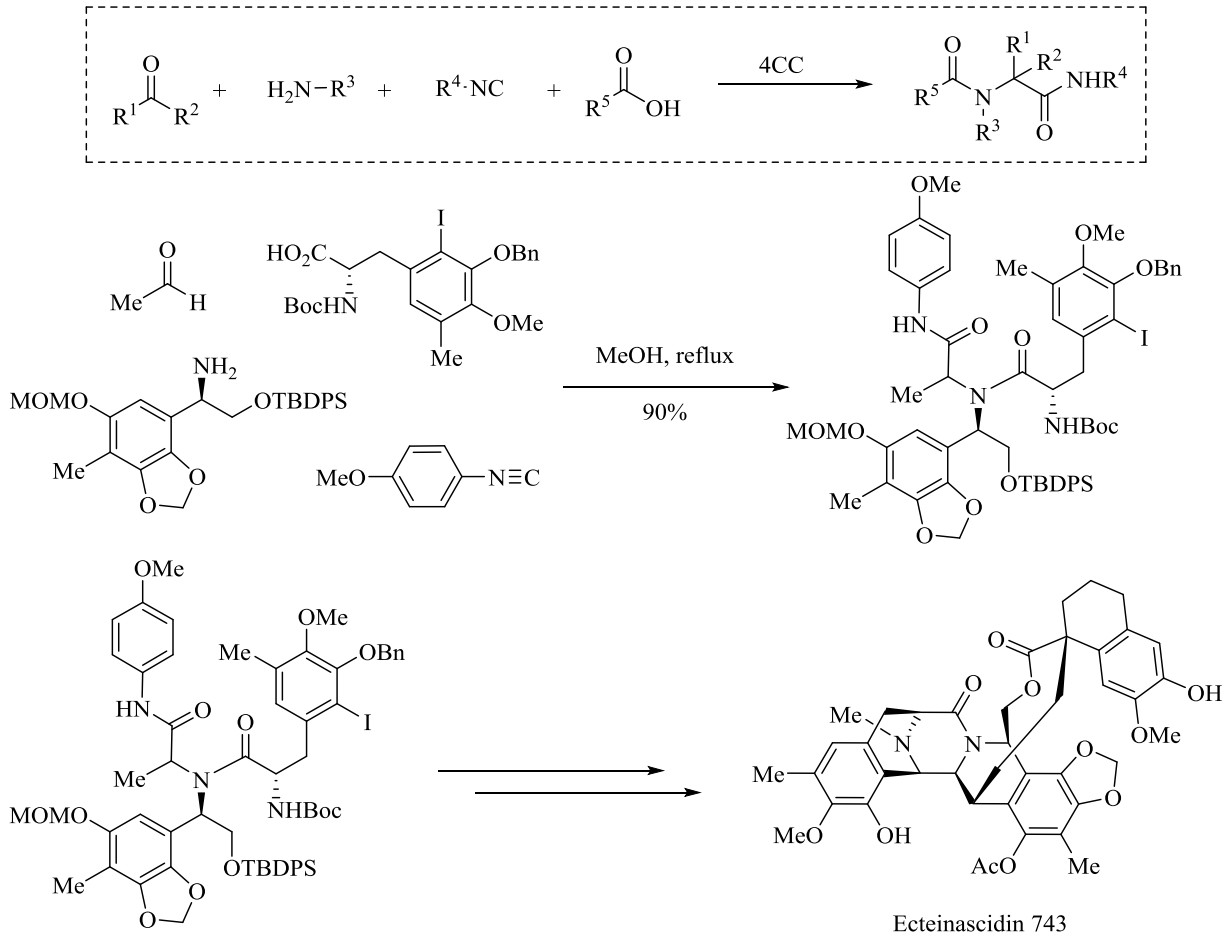


Figure 1.1 a) linear synthesis of general compound E. b) convergent synthesis of compound E. c) multicomponent coupling synthesis of compound E shown as one step.

MCR with high functional group coupling selectivity can produce modular scaffolds achievable by altering the peripheral attachments in the starting material. An example of this is the Ugi MCR, where a mixture of aldehyde or ketone, primary amine, isonitrile, and carboxylic acid

in one-pot leads to dipeptide products (**Scheme 1.1**).[4] Fukuyama and coworkers utilized this powerful reaction to generate the key dipeptide intermediate in the total synthesis of Ecteinascidin 743.[5] The Ugi reaction has been modified several times and a vast array of structurally diverse compounds have resulted from this.[6]



Scheme 1.1 Ugi multicomponent coupling reaction general scheme and application to Ecteinascidin 743.[5]

In some regards an MCR is similar to a cascade reaction, whereby reaction of two components generates a reactive intermediate propagating the synthesis further.[7] It is befitting that isonitriles have a rich history in multicomponent coupling chemistry, providing carbon sources, as they behave as both electrophile and nucleophile.[6a,8] Primary resonance forms can be used to

demonstrate this dual reactivity: 1) a carbanion-like carbon that reacts as a nucleophile first and 2) a carbene with vacant p-orbital that behaves like an electrophile (**Figure 1.2**). This dual reactivity allows for several possibilities: subsequent attack of carbanion nitrogen followed by 1,2-addition of second nucleophile, addition of a nucleophile to carbene-like carbon generating a carbanion, or 1,1-insertion type reactions.

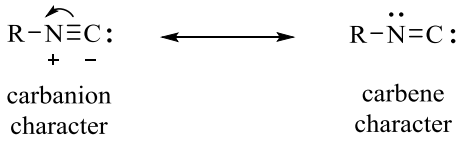


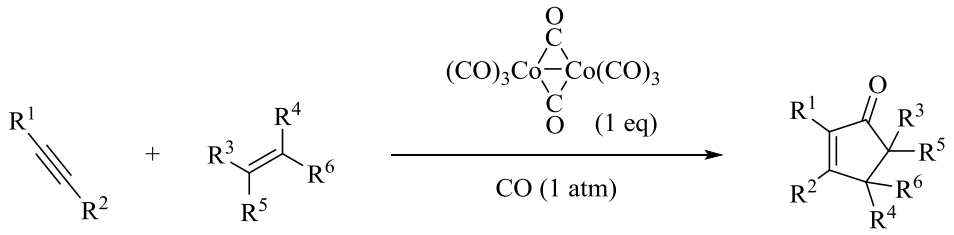
Figure 1.2 Resonance forms of isonitrile.

Expediency in both academia and industry to optimize biologically active natural products or previously reported inhibitors, can make use of the inherent efficiency MCRs.[9] Libraries of compounds can be developed with MCR from simple starting materials. This allows for a timely assembly of structure activity relationships (SAR). Biological activity is an important driving force for synthetic methodology development and SAR's are part of assessing priority of various functional sites in a compound.

The difficulty in designing MCR most often comes from the incompatibility of substrates. Side reactions are likely to occur, however, with proper care they may be minimized or eliminated. Understanding the reactivity and structure of the intermediates is as one way to begin mitigating these side reactions.

1.2 Metal-mediated MCR

Current literature trends in MCR show an increasing use of metal-mediated or metal-catalyzed procedures.[10] This is, in part, due to the necessity of activating certain coupling partners via the addition of a Lewis acid, metal-promoter, or creating a coupling site at the metal center. An early example of this is the Pauson-Khand [2+2+1] cycloaddition reaction between alkyne, alkene, and carbon monoxide (**Scheme 1.2**).[11] Seminal work utilized stoichiometric amounts of $Co_2(CO)_8$ metal complex to create cyclopentenone core structures.



Scheme 1.2 Pauson-Khand MCR.

Commonly employed coupling partners in metal-mediated MCR are alkynes, alkenes, and isonitriles.[2a,6a,12] Two ways alkynes are activated by metal complexes is through π-system coordination to the metal center and 1,1-metal insertion between the s-sp bond (**Figure 1.3**).[13] Part of this is due to the nature of the alkyne or the metal. Isonitriles, as previously stated, are frequently utilized for their ability to perform 1,1-insertion between M-X bonds where X can be heteroatoms (N, O, S), carbon and hydrogen. Metal mediated MCRs open the door for new couplings to occur which broadens the pool of both substrate possibilities and the product variability of these reactions.

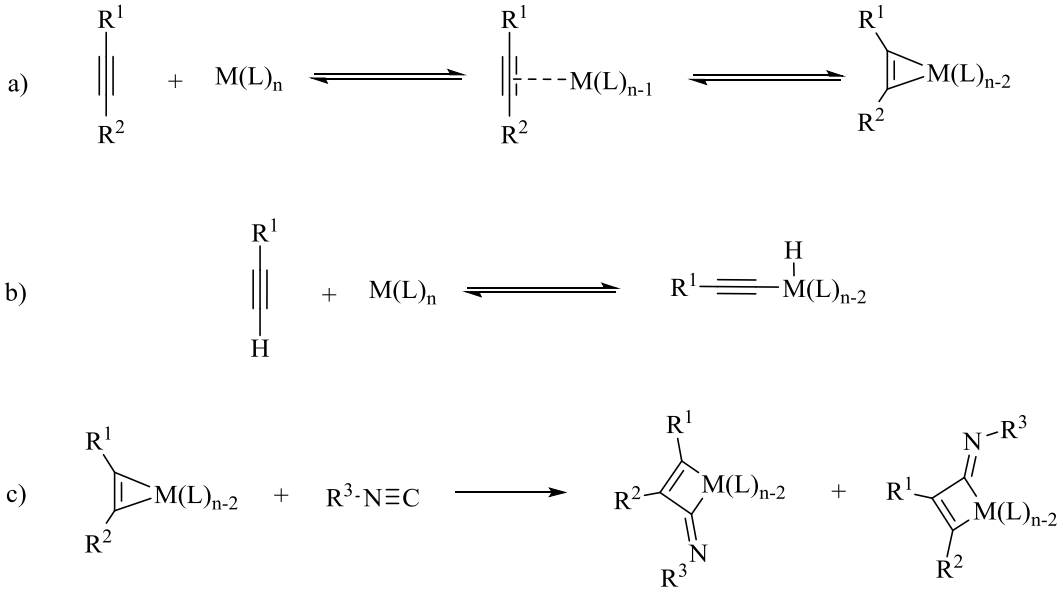
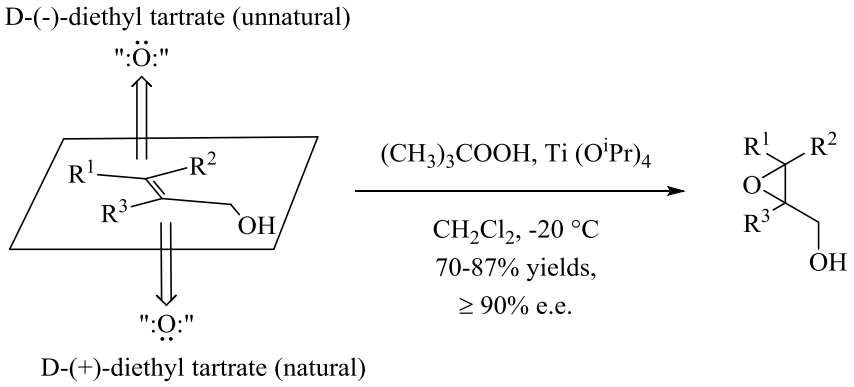


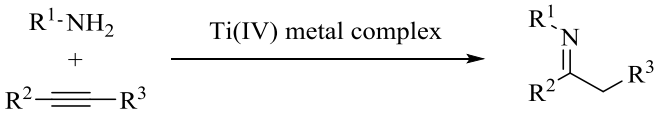
Figure 1.3 a) alkyne coordination to metal center through π-orbitals. b) 1,1-metal insertion between s-sp hybridized bond. c) Isonitrile performing 1,1-insertions between metal-carbon bonds.

1.3 Titanium catalyzed MCR and Odom Group Chemistry

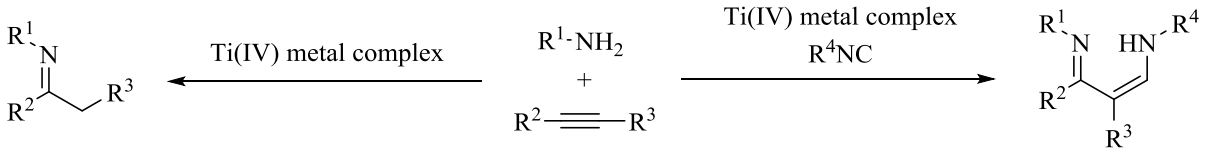
Transfiguring unreactive coupling partners into useful MCR products via earth abundant, non-toxic metal catalysis is non-trivial. Both titanium mediated and catalyzed reactions have been extensively studied with most notable example being the Sharpless asymmetric epoxidation (**Scheme 1.3**).[14] One type of reaction that has provided powerful C-N bond formation is hydroamination, with multiple examples of stoichiometric and catalytic titanium usage (**Scheme 1.4**).[15] Odom et al advanced titanium catalyzed hydroamination into a novel MCR, producing α,β-unsaturated-β-iminoamines via isonitrile insertion (**Scheme 1.5**).[16]



Scheme 1.3 Sharpless asymmetric epoxidation.[14b]



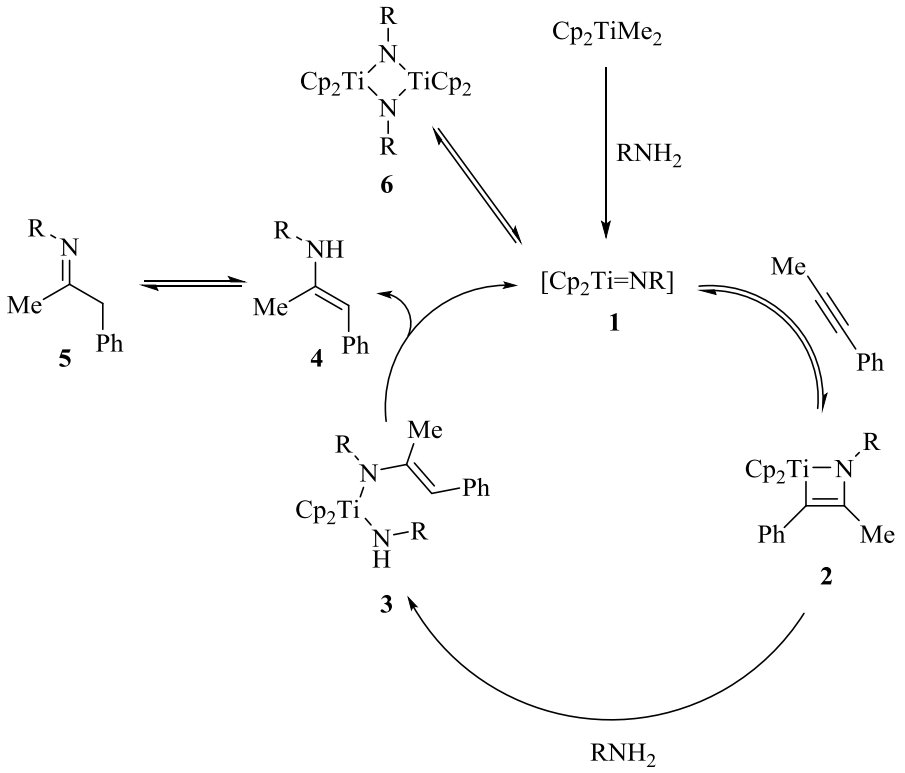
Scheme 1.4 Hydroamination of alkynes with primary amines and Ti(IV) metal complexes



Scheme 1.5 Comparison of hydroamination and iminoamination products.[16]

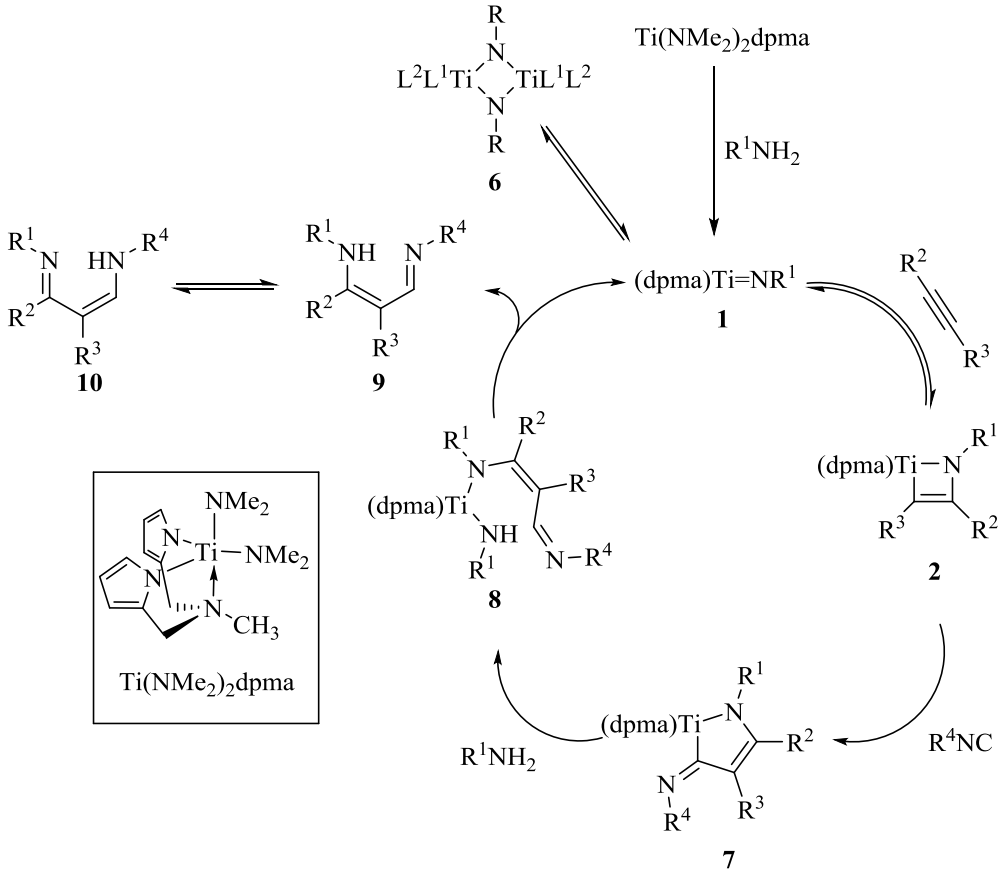
To understand the transition from hydroamination to MCR, a recount of the proposed mechanism for titanium catalyzed hydroamination is prudent. Doye et al, used kinetic studies

coupled with relatable systems (i.e. Bergman's Zirconocene system for hydroamination[17]) to identify potential intermediates and the rate determining step.[18] The initial metal complex used in their study is a precatalyst, as the active species is titanium-imido complex **1** (**Scheme 1.6**). Reaction of metal-imido complexes are well explored and offer great utility in a variety of reactions.[19] In this instance, titanium-imido complex **1** undergoes [2+2] cycloaddition with alkynes to form azatitanacyclobutene complex **2**. It is at this point that rate-determining protonolysis begins by introducing a second molecule of amine to form intermediate **3**.[18] Complete protonolysis generates enamine **4**, which tautomerizes to **5**, and regenerates complex **1**. Complex **6** is a μ-dimer that is in equilibrium with titanium-imido **1** and represents a resting state for the catalyst. Important to note, the equilibrium process forming the azatitanacyclobutene is likely operating under Curtin-Hammett conditions, which controls the product distribution of the possible regioisomers.[2a,16]



Scheme 1.6 Catalytic cycle for titanium-based hydroamination of alkynes proposed by Doye et al. that proceeds through similar Bergman zirconocene hydroamination.[17a]

As previously stated, isonitriles are a common in MCR and 1,1-insertion chemistry can be utilized in titanium based catalysis.[16] Introduction of isonitrile provides a trap for azatitanacyclobutene **2** by inserting into the titanium-carbon bond (**Scheme 1.7**). In order for this chemistry to work, the insertion of isonitrile needs to be faster than protonolysis of complex **2.** If this is the case, then pentacyclic metal complex **7** will form. Protonolysis of complex **7** leads to the formation of α,β-unsaturated-β-iminoamine tautomers **9** and **10**.



Scheme 1.7 Catalytic cycle proposed for Titanium MCR forming 1,3-diimine tautomers.

The power of this technique is the regioselective control with small modifications to catalyst and choice of primary amine. These 1,3-diimine products are useful intermediates that mimic some reactivity of 1,3-diketones, therefore, they can act as alternatives in classical heterocyclic

syntheses.[2a] As it is typically difficult to generate 1,3-diketones asymmetrically, and 1,3-dialdehydes are incredibly sensitive substrates, a 1,3-diimine synthesis that is regioselective would be quite practical.

Choice of alkyne substrate plays a role in regioselectivity through, primarily, electronic effects. Terminal alkynes with an aryl or alkenyl substituent have a strong electronic preference for 1,3-dialdimine formation (R^2 = H, R^3 = aryl or alkenyl). Aryl stabilization of the building negative charge (generated from Ti-C bond formation) accounts for the observed regioselectivity and is a common result for titanium catalyzed hydroamination (**Figure 1.4**).

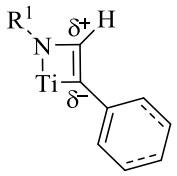
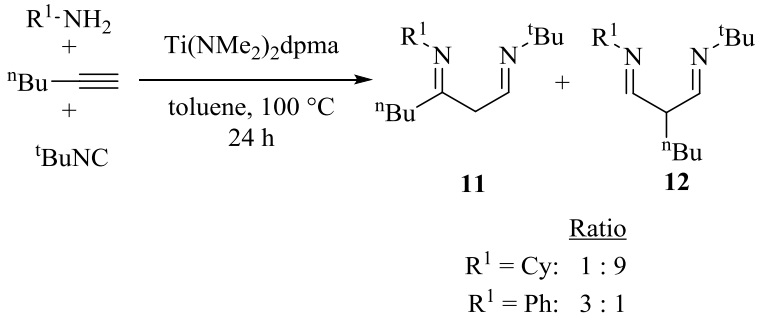


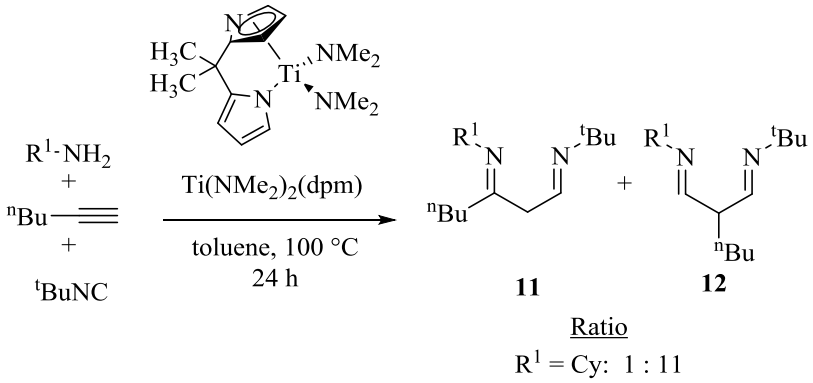
Figure 1.4 Electronic preference for aryl and alkenyl substrates

Terminal alkynes with alkyl substituents are generally considered electron donating by hyperconjugation, and can stabilize the partial positive charge that occurs on the carbon bonded to nitrogen. However, sterics and electronics from the amine source also play a large role in regioselectivity. As an example the multicomponent coupling reaction between cyclohexylamine, 1-hexyne, *tert*-butylisonitrile catalyzed by $Ti(NMe_2)_2$dpma results in 1:9 selectivity of keto-aldimine **11** and dialdimine **12** (**Scheme 1.8**).[20] Switching cyclohexylamine with aniline, while keeping all other conditions the same, the selectivity is 3:1.



Scheme 1.8 Effect of amine on regioselectivity of MCR catalyzed by $Ti(NMe_2)_2dpma$

It is important to note that precatalyst choice also impacts the selectivity. $Ti(NMe_2)_2dpma$ has a methyl group (attached to the tertiary amine) that sits in the active site sterically hindering alkyl groups, but has little to no effect on terminal aryl alkynes.[21] A second catalyst common in Odom group is $Ti(NMe_2)_2dpm$,[15m] which has no significant steric hindrance of the active site. Implementation of this catalyst provides improved regioselectivity of dialdimine **12** (**Scheme 1.9**).

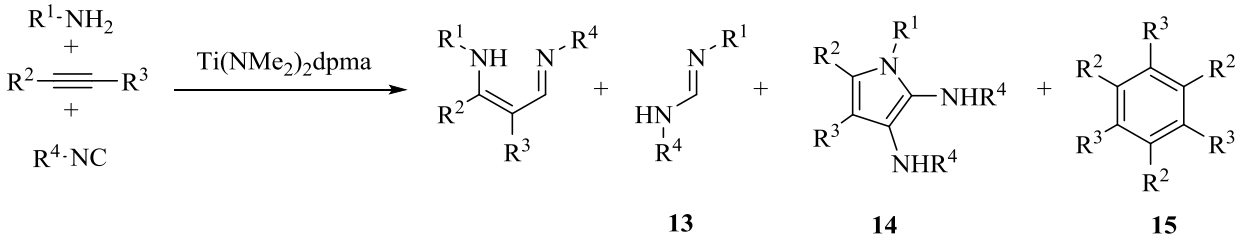


Scheme 1.9 Improved regioselectivity of dialdimine **12** using $Ti(NMe_2)_2dpm$

This second catalyst is also used for internal alkyne derivatives due to several factors, one of which is the reduction of steric hindrance at the active site. The more active of the two species, in terms of reactivity and rate, is $Ti(NMe_2)_2dpm$ due to increased Lewis acidity of the titanium metal center.[22] The titanium metal center in $Ti(NMe_2)_2dpma$ receives more donation of electron density from the bridging amine.[21]

Internal alkynes that consist of one alkyl group and one aryl group will follow the same model as terminal aryl alkynes (R^2 = alkyl, R^3 = aryl or alkenyl). If, however, unsymmetrical bi-alkyl or bi-aryl alkyne substrates are used, a mixture of products with poor selectivity is observed. Internal alkynes, bi-aryls especially, react much slower so it is common practice to have longer reaction times and heating at higher temperatures.

Byproducts of the MCR reaction are minimal, but several common ones have been identified and even optimized (**Scheme 1.10**). Often the most visible is formamide formation (**13**), which is the two component coupling of primary amine and isonitrile. Additionally, a four component coupling product whereby two insertions of isonitrile can occur to make an intermediate that cyclizes to unusual 2,3-diaminopyrroles (**14**).[23] The last and least prominent is formation of benzene (**15**) through trimerization of alkynes (typically visible with terminal aryl substrates). Hydroamination can occur but is usually completely shut down with addition of isonitrile.



Scheme 1.10 Possible byproducts of titanium catalyzed MCC

In general, the reaction exhibits a wide substrate tolerance with a few challenging functional groups that must be protected. Titanium complexes suffer from low stability in air and water due to the highly favorable formation of TiO_2. Ketones, aldehydes, alcohols, carboxylic acids and esters must be properly protected, as unfavorable side reactions occur with each functional group. Avoidance of acidic protons is also necessary to ensure catalyst stability.

The design and implementation of these 1,3-diimine skeletons as intermediates for heterocyclic syntheses is an intriguing development that has scarcely been investigate outside of Odom group. Furthermore, limited studies into the electronic nature of the 1,3-diimine provide interesting avenues for future work (i.e transimination, Grignard additions, 1,3-dipolar-cycloaddition reactions). Titanium catalyzed MCR combines inexpensive, non-toxic catalyst with amenable structure diversification that is exhibited in MCR.

REFERENCES

REFERENCES

(1) a) Moseley, J. D.; Kappe, C. O. *Green Chemistry* **2011**, *13*, 794-806. b) Sheldon, R. A. *Green Chemistry* **2005**, *7*, 267-278. c) Dunn, P. J.; Galvin, S.; Hettenbach, K. *Green Chemistry* **2004**, *6*, 43-48. d) Sheldon Roger, A. In *Pure and Applied Chemistry* 2000; Vol. 72, p 1233. e) Schreiber, S. L. *Science* **2000**, *287*, 1964-1969. f) Trost, B. M. *Angewandte Chemie International Edition in English* **1995**, *34*, 259-281.

(2) a) Odom, A. L.; McDaniel, T. J. *Accounts of Chemical Research* **2015**, *48*, 2822-2833. b) Tojino, M.; Ryu, I. In *Multicomponent Reactions*; Wiley-VCH Verlag GmbH & Co. KGaA: 2005, p 169-198. c) Banfi, L.; Riva, R.; Basso, A. *Synlett* **2010**, *2010*, 23-41. d) Angel, C.; Carlos, C.; Alberto, C. *Current Topics in Medicinal Chemistry* **2014**, *14*, 2209-2230. e) Jeena, V.; Robinson, R. S. *RSC Advances* **2014**, *4*, 40720-40739. f) Santos, M. M. M. *Tetrahedron* **2014**, *70*, 9735-9757. g) Elnagdi, M. H.; Moustafa, M. S.; Al-Mousawi, S. M.; Mekheimer, R. A.; Sadek, K. U. *Molecular Diversity* **2015**, *19*, 625-651. h) González, M. J.; López, L. A.; Vicente, R. *Tetrahedron Letters* **2015**, *56*, 1600-1608. i) Hassan, S.; Müller, T. J. J. *Advanced Synthesis & Catalysis* **2015**, *357*, 617-666. j) Prajapati, N. P.; Vekariya, R. H.; Patel, H. D. *Synthetic Communications* **2015**, *45*, 2399-2425. k) Hu, R.; Li, W.; Tang, B. Z. *Macromolecular Chemistry and Physics* **2016**, *217*, 213-224. l) Levi, L.; Muller, T. J. J. *Chemical Society Reviews* **2016**.

(3) a) Jensen, P. R.; Mincer, T. J.; Williams, P. G.; Fenical, W. *Antonie van Leeuwenhoek*, *87*, 43-48. b) Firn, R. D.; Jones, C. G. *Natural Product Reports* **2003**, *20*, 382-391. c) Cordier, C.; Morton, D.; Murrison, S.; Nelson, A.; O'Leary-Steele, C. *Natural Product Reports* **2008**, *25*, 719-737. d) Grabowski, K.; Baringhaus, K.-H.; Schneider, G. *Natural Product Reports* **2008**, *25*, 892-904.

(4) a) Ugi, I. *Angewandte Chemie* **1962**, *74*, 9-22. b) Ugi, I.; Steinbrückner, C. *Angewandte Chemie* **1960**, *72*, 267-268. c) Ugi, I., Meyr, R., Fetzer, U., Steinbruckner, C. *Angewandte Chemie* **1959**, *71*, 373-388.

(5) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *Journal of the American Chemical Society* **2002**, *124*, 6552-6554.

(6) a) Zhu, J. *European Journal of Organic Chemistry* **2003**, *2003*, 1133-1144. b) Ugi, I.; Domling, A.; Werner, B. *Journal of Heterocyclic Chemistry* **2000**, *37*, 647-658.

(7) a) Zheng, L.; Ju, J.; Bin, Y.; Hua, R. *The Journal of Organic Chemistry* **2012**, *77*, 5794-5800. b) Grondal, C.; Jeanty, M.; Enders, D. *Nat Chem* **2010**, *2*, 167-178. c) Kim, J. K.; Kim, Y. H.; Nam, H. T.; Kim, B. T.; Heo, J.-N. *Organic Letters* **2008**, *10*, 3543-3546. d) Kopecky, D. J.; Rychnovsky, S. D. *Journal of the American Chemical Society* **2001**, *123*, 8420-8421.

(8) a) Ganem, B. *Accounts of Chemical Research* **2009**, *42*, 463-472. b) Akritopoulou-Zanze, I. *Current Opinion in Chemical Biology* **2008**, *12*, 324-331. c) Ngouansavanh, T.; Zhu, J. *Angewandte Chemie International Edition* **2006**, *45*, 3495-3497. d) Dömling, A. *Chemical Reviews* **2006**, *106*, 17-89.

(9) a) Dömling, A.; Wang, W.; Wang, K. *Chemical Reviews* **2012**, *112*, 3083-3135. b) Touré, B. B.; Hall, D. G. *Chemical Reviews* **2009**, *109*, 4439-4486. c) Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angewandte Chemie International Edition* **2009**, *48*, 1304-1307. d) Lutz, W. *Current Medicinal Chemistry* **2002**, *9*, 2085-2093. e) Banfi, L.; Guanti, G.; Riva, R. *Chemical Communications* **2000**, 985-986.

(10) a) Yan, B.; Liu, Y. *Organic Letters* **2007**, *9*, 4323-4326. b) Wender, P. A.; Pedersen, T. M.; Scanio, M. J. C. *Journal of the American Chemical Society* **2002**, *124*, 15154-15155. c) Noels, A. F.; Demonceau, A.; Petiniot, N.; Hubert, A. J.; Teyssié, P. *Tetrahedron* **1982**, *38*, 2733-2739. d) Mihovilovic, M. D.; Stanetty, P. *Angewandte Chemie International Edition* **2007**, *46*, 3612-3615. e) Galliford, C. V.; Scheidt, K. A. *The Journal of Organic Chemistry* **2007**, *72*, 1811-1813. f) Biggs-Houck, J. E.; Younai, A.; Shaw, J. T. *Current Opinion in Chemical Biology* **2010**, *14*, 371-382.

(11) a) Shibata, T. *Advanced Synthesis & Catalysis* **2006**, *348*, 2328-2336. b) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *Journal of the Chemical Society, Perkin Transactions 1* **1973**, 977-981. c) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263-3283.

(12) a) Yu, Z.-X.; Cheong, P. H.-Y.; Liu, P.; Legault, C. Y.; Wender, P. A.; Houk, K. N. *Journal of the American Chemical Society* **2008**, *130*, 2378-2379. b) Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Pham, S. M.; Zhang, L. *Journal of the American Chemical Society* **2005**, *127*, 2836-2837. c) Ramón, D. J.; Yus, M. *Angewandte Chemie International Edition* **2005**, *44*, 1602-1634. d) Patel, S. J.; Jamison, T. F. *Angewandte Chemie* **2003**, *115*, 1402-1405. e) Inglesby, P. A.; Evans, P. A. *Chemical Society Reviews* **2010**, *39*, 2791-2805. f) de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chemical Society Reviews* **2012**, *41*, 3969-4009. g) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chemical Reviews* **2004**, *104*, 3079-3160.

(13) Atkins, P. W. *Shriver & Atkins' inorganic chemistry*; Oxford University Press: Oxford; New York, 2010.

(14) a) Stephenson, G. R. In *Advanced Asymmetric Synthesis*; Stephenson, G. R., Ed.; Springer Netherlands: Dordrecht, 1996, p 367-391. b) Katsuki, T.; Sharpless, K. B. *Journal of the American Chemical Society* **1980**, *102*, 5974-5976.

(15) a) Zhang, Z.; Leitch, D. C.; Lu, M.; Patrick, B. O.; Schafer, L. L. *Chemistry – A European Journal* **2007**, *13*, 2012-2022. b) Vujkovic, N.; Ward, B. D.; Maisse-François, A.; Wadepohl, H.; Mountford, P.; Gade, L. H. *Organometallics* **2007**, *26*, 5522-5534. c) Swartz, D. L.; Odom, A. L. *Organometallics* **2006**, *25*, 6125-6133. d) Lorber, C.; Choukroun, R.; Vendier, L. *Organometallics* **2004**, *23*, 1845-1850. e) Li, Y.; Shi, Y.; Odom, A. L. *Journal of the American Chemical Society* **2004**, *126*, 1794-1803. f) Zhang, Z.; Schafer, L. L. *Organic Letters* **2003**, *5*, 4733-4736. g) Shi, Y.; Hall, C.; Ciszewski, J. T.; Cao, C.; Odom, A. L. *Chemical Communications* **2003**, 586-587. h) Cao, C.; Shi, Y.; Odom, A. L. *Organic Letters* **2002**, *4*, 2853-2856. i) Ackermann, L.; Bergman, R. G. *Organic Letters* **2002**, *4*, 1475-1478. j) Straub, B. F.; Bergman, R. G. *Angewandte Chemie* **2001**, *113*, 4768-4771. k) Shi, Y.; Ciszewski, J. T.; Odom, A. L. *Organometallics* **2001**, *20*, 3967-3969. l) Nobis, M.; Drießen-Hölscher, B. *Angewandte Chemie International Edition* **2001**, *40*,

3983-3985. m) Cao, C.; Ciszewski, J. T.; Odom, A. L. *Organometallics* **2001**, *20*, 5011-5013. n) Bytschkov, I.; Doye, S. *European Journal of Organic Chemistry* **2003**, *2003*, 935-946. o) Haak, E.; Bytschkov, I.; Doye, S. *Angewandte Chemie International Edition* **1999**, *38*, 3389-3391. p) Heutling, A.; Pohlki, F.; Doye, S. *Chemistry – A European Journal* **2004**, *10*, 3059-3071.

(16) Cao, C.; Shi, Y.; Odom, A. L. *Journal of the American Chemical Society* **2003**, *125*, 2880-2881.

(17) a) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *Journal of the American Chemical Society* **1992**, *114*, 1708-1719. b) Baranger, A. M.; Walsh, P. J.; Bergman, R. G. *Journal of the American Chemical Society* **1993**, *115*, 2753-2763.

(18) Pohlki, F.; Doye, S. *Angewandte Chemie International Edition* **2001**, *40*, 2305-2308.

(19) a) Cundari, T. R.; Klinckman, T. R.; Wolczanski, P. T. *Journal of the American Chemical Society* **2002**, *124*, 1481-1487. b) Guiducci, A. E.; Boyd, C. L.; Mountford, P. *Organometallics* **2006**, *25*, 1167-1187. c) Hanna, T. E.; Keresztes, I.; Lobkovsky, E.; Bernskoetter, W. H.; Chirik, P. J. *Organometallics* **2004**, *23*, 3448-3458. d) Hazari, N.; Mountford, P. *Accounts of Chemical Research* **2005**, *38*, 839-849. e) M. McInnes, J.; J. Blake, A.; Mountford, P. *Journal of the Chemical Society, Dalton Transactions* **1998**, 3623-3628. f) Mountford, P. *Chemical Communications* **1997**, 2127-2134.

(20) Pasko, C. M.; Dissanayake, A. A.; Billow, B. S.; Odom, A. L. *Tetrahedron* **2016**, *72*, 1168-1176.

(21) Harris, S. A.; Ciszewski, J. T.; Odom, A. L. *Inorganic Chemistry* **2001**, *40*, 1987-1988.

(22) a) DiFranco, S. A.; Maciulis, N. A.; Staples, R. J.; Batrice, R. J.; Odom, A. L. *Inorganic Chemistry* **2012**, *51*, 1187-1200. b) Bemowski, R. D.; Singh, A. K.; Bajorek, B. J.; DePorre, Y.; Odom, A. L. *Dalton Transactions* **2014**, *43*, 12299-12305. c) Billow, B. S.; Bemowski, R. D.; DiFranco, S. A.; Staples, R. J.; Odom, A. L. *Organometallics* **2015**, *34*, 4567-4573.

(23) Barnea, E.; Majumder, S.; Staples, R. J.; Odom, A. L. *Organometallics* **2009**, *28*, 3876-3881.

CHAPTER 2. ONE-POT SYNTHESIS OF PYRROLES USING A TITANIUM-CATALYZED MULTICOMPONENT COUPLING PROCEDURE

2.1 Introduction

Heterocycles are a class of ring structures which contain one or more heteroatoms (e.g. oxygen, sulfur, and nitrogen). Pyrrole is a nitrogen containing five-membered aromatic ring. The pyrrole moiety appears in biological systems, natural products, and widely sold pharmaceuticals (**Figure 2.1**).[1] For biological systems, pyrrole appears as the main component of porphyrin; an organic macrocycle involved in the binding of Fe^{2+} for oxygen transportation.[2] This characteristic of pyrrole-metal binding provides a precedent for use of pyrrole derivatives as ligands.[3]

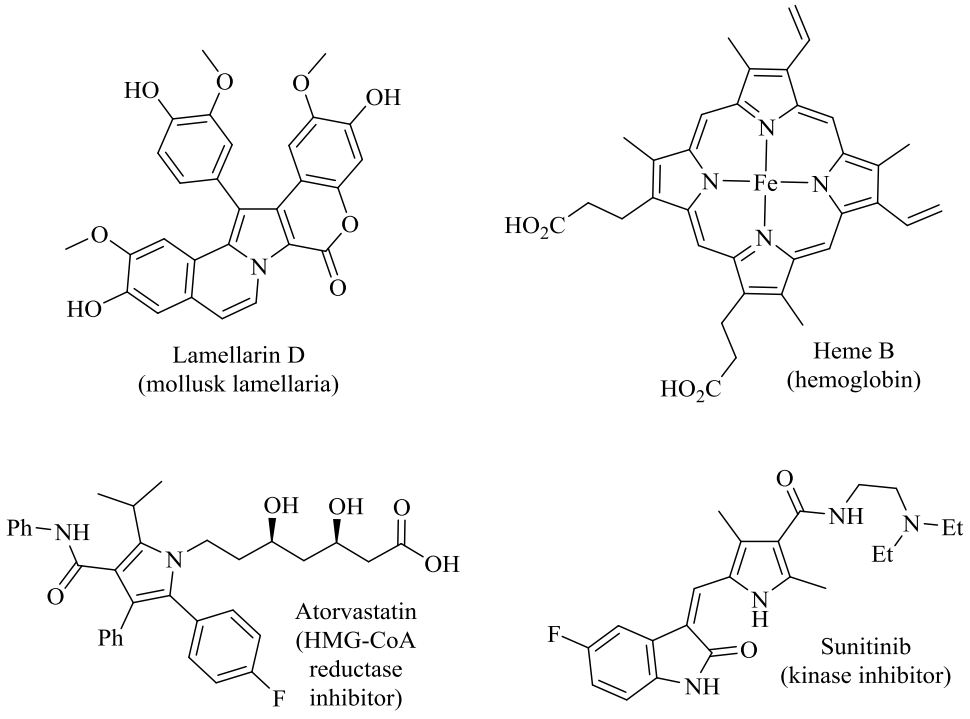
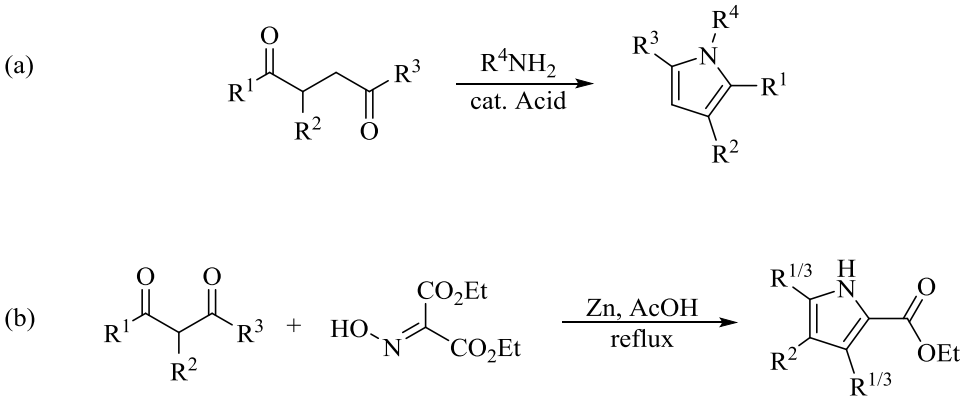


Figure 2.1 Pyrrole core structure as it appears in natural products, biological systems, and pharmaceuticals.

Over the past few decades, an increasing number of natural products containing pyrrole core structures have been isolated. For example, in 1985 pyrrole based alkaloids, known as lamellarins, were isolated from marine mollusk *lamellaria*.[4] Upon further investigation into this class of

compounds, many derivatives have been effective at combating multi-drug resistant cancer cell lines at non-cytotoxic levels.[5] Pyrrole containing drug molecules that are currently on the market are atorvastatin (Lipitor®), a cholesterol lowering drug, and sunitinib (Sutent®) used for treatment of renal cell carcinoma.[6]

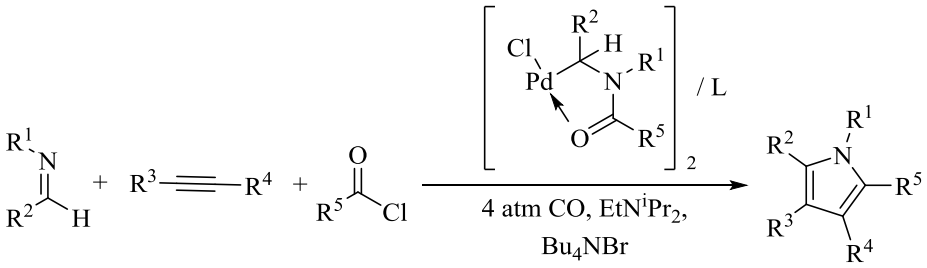
With these driving forces it is unsurprising to see many groups devising general syntheses for this particular heterocycle. In the classical synthesis, the reaction between 1,3- and 1,4-dicarbonyls with amines have been a staple of pyrrole syntheses. This is seen in the classic Paal-Knorr pyrrole synthesis (**Scheme 2.1**).[7] The amine condenses with one carbonyl, forming the imine, and then cyclizes upon nitrogen attack of the second carbonyl. This process is reversible, however, loss of water forms an aromatic molecule with a stabilization energy of 22 kcal·mol^{-1}.[8] The Fischer-Fink variation of the Paal-Knorr synthesis uses 1,3-dicarbonyls with zinc reduced oxime malonate to prepare 2-carboxylate pyrroles.[9]



Scheme 2.1 Synthetic routes to substituted pyrroles. (a) Paal-Knorr reaction. (b) Fischer-Fink variation of the Paal-Knorr.

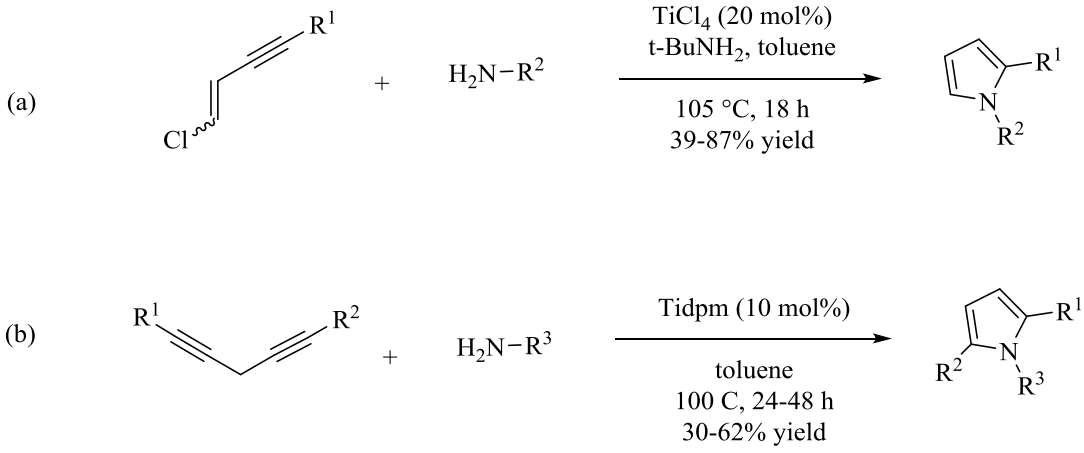
Evident draw backs to this methodology are both preparation of asymmetric starting materials and pyrrole formation is rarely regioselective leading to mixtures. A Pd-catalyzed multicomponent coupling (MCC) reaction reported by the Arndsten group (**Scheme 2.2**) produced diversified

pyrroles in good yield and regioselectively, but requires 5 mol% of palladium and the use of additives.[10]



Scheme 2.2 Arndsten palladium-catalyzed pyrroles synthesis.

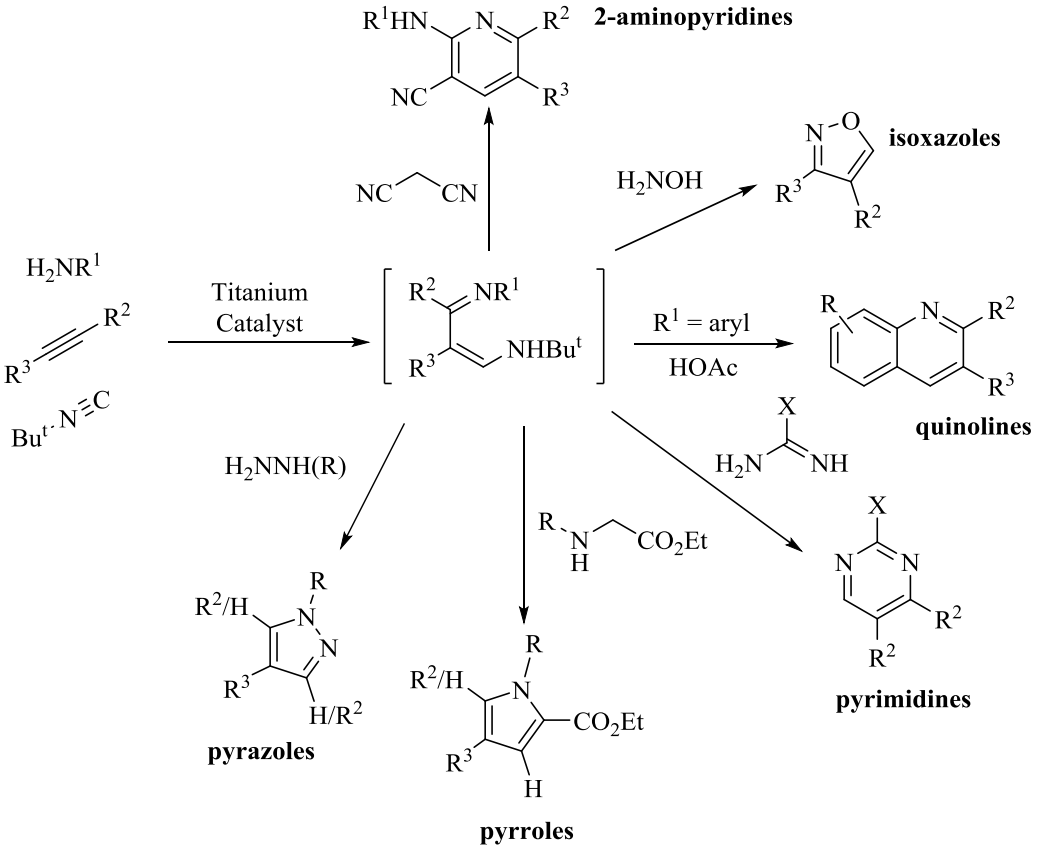
Utilization of pyrrole derivatives is highly exhibited in both current and previous investigations performed by Odom and co-workers.[11] Titanium based catalysts with pyrrolyl ancillary ligands have provided hydroamination of alkynes, diynes, and alkenes. Titanium catalyzed pyrrole syntheses have been promulgated through several times in the literature as well. Ackerman et al, published a hydroamination of vinylic chloroenyne derivatives that undergo subsequent cyclization to the pyrrole moiety (**Scheme 2.3**).[12] Similar to this work is the hydroamination of diynes to yield 1,2,5-substituted pyrroles reported by Odom et al.[11h]



Scheme 2.3 (a) Ackerman hydroamination of chloroenynes, (b) Odom hydroamination of diynes.

MCC chemistry offers efficient and cost effective routes to complex molecules that can be generated from simple starting materials. MCC is attractive for industrial applications as it can

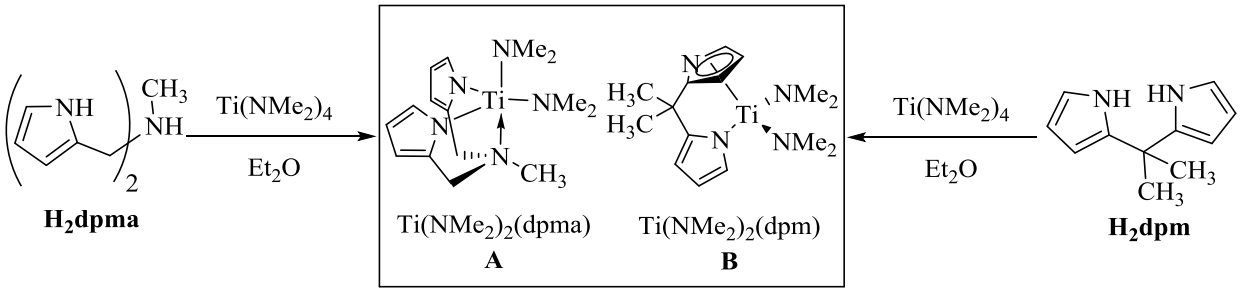
reduce the frequency of costly purifications. The Odom group has utilized titanium(IV) metal complexes to afford an expanding list of heterocycles[13] (**Scheme 2.4**) from the MCC intermediate previously described in chapter one. The α,β-unsaturated-β-iminoamine (3CC) is formed by the combination of an amine, alkyne and isonitrile in a 100% atom economical reaction.[11d] These intermediates behave similarly to 1,3-dicarbonyls, but are more stable, typically requiring higher reaction temperatures to convert to their heterocyclic counterpart. Herein, a one pot procedure to construct substituted pyrrole-2-carboxylates in modest to good yield from a titanium catalyzed MCC intermediate is described.



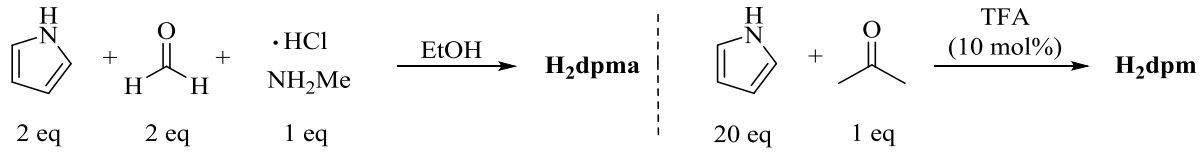
Scheme 2.4 3CC intermediate acquired from titanium MCC generates variety of heterocycles via addition of an additive.

2.2 Results and Discussion

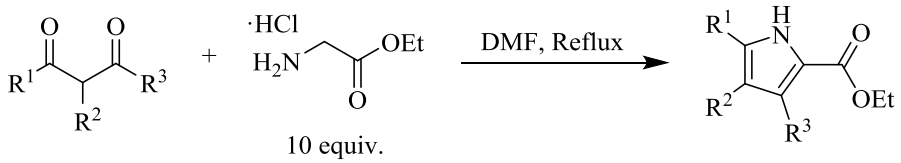
This work involved several areas of potential interest: optimizing conditions, substrate tolerance, and regioselectivity of pyrrole formation. The 3CC intermediate was formed by either Ti(NMe_2)dpma (**A**) or Ti(NMe_2)dpm (**B**). The catalysts were prepared in near quantitative yield by the addition of ancillary ligand (1 equivalent of **H_2dpma** and **H_2dpm** respectively) to a cold ethereal solution of Ti(NMe_2)$_4$ (**Scheme 2.5**).[11a,14] The ligands themselves were either prepared by a 5 componenent double Mannich reaction (H_2dpma)[11a] or pyrrole condensation reaction with acetone (H_2dpm) (**Scheme 2.6**).[15] The condensation of ethyl glycinate hydrochloride to 3CC is an extension of the work performed by Mataka et al., with 1,3-diones as successful substrates for pyrrole formation (**Scheme 2.7**).[16]



Scheme 2.5 Synthesis of titanium MCC catalyst.

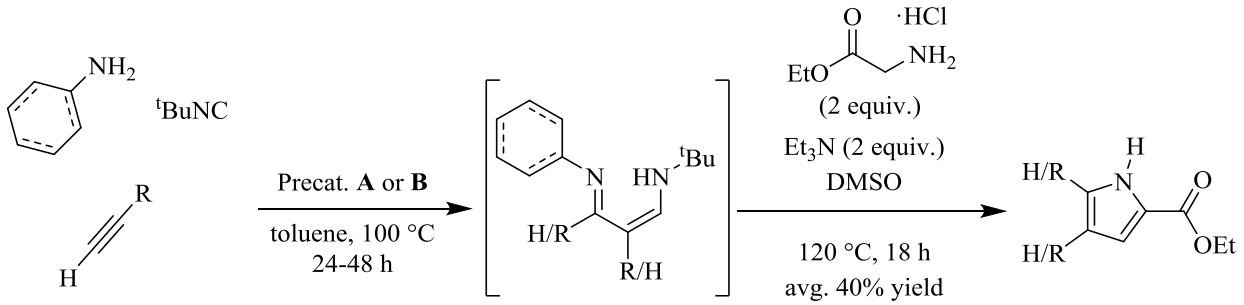


Scheme 2.6 Synthesis of pyrrole based ancillary ligands.



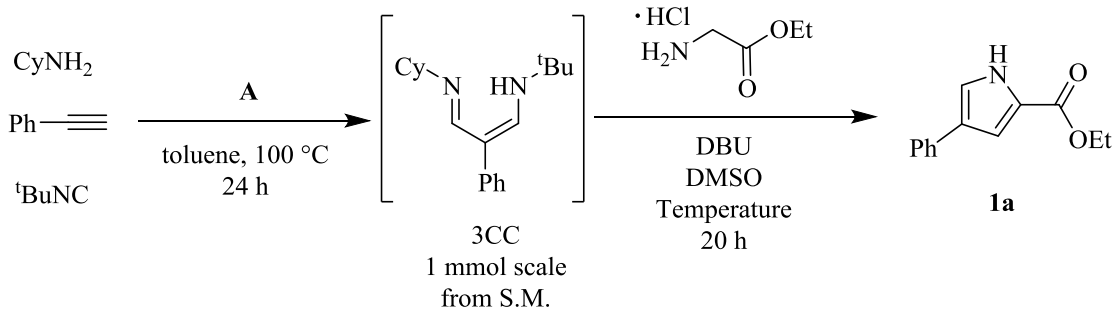
Scheme 2.7 Mataka variation of the Fischer-Fink modification.

An initial set of conditions for the pyrrole formation had been established by Amila Dissanayake, who treated the 3CC intermediate from the titanium MCC reaction with ethyl glycinate hydrochloride (2 eq), Et_3N (2 eq), and DMSO at 80 °C for 18 h (**Scheme 2.8**). Moderate yields for a variety of different substrates were observed, but the reaction was not scalable and reproducibility was low for several substrates. The conditions were optimized using the Design of Experiment (DOE) method, a statistical modeling technique that maps the experimental domain and reveals the impact of independent, as well as co-dependent, variables.



Scheme 2.8 Initial conditions for pyrrole formation from 3CC intermediate.

DOE can allow for fewer experiments to determine the experimental domain of a reaction; mapping out directions to a global maximum or in our case the optimal yield. DOE considers interaction effects between variables whereas the standard one variable at a time (OVAT) method does not. Elucidating these variable effects precludes the necessity of running an infinite number of experiments to obtain optimal yield as is the case with OVAT. After a base and solvent screening, which revealed DBU (base) and DMSO (solvent) to be the best combination, a 2-level full factorial design (2-FFD)[17] was applied to a cyclization reaction of model phenyl (3CC) derivative to pyrrole **1a** (**Scheme 2.9**).



Scheme 2.9 Model reaction for optimization of pyrrole formation.

The reaction conditions illustrated in **Scheme 2.9** includes four variables that were chosen for optimization. These four variables (**Table 2.1**) are not the only potential parameters that could be optimized, but from chemical intuition, they seemed the most likely to effect the overall yield. A minimum and maximum value were chosen to create the boundaries of the experimental domain. It is important to note that selecting a wide range can cover more of the experimental space, but problems of curvature (deviation from linear modeling) are much more prevalent. Selecting too narrow of a range results in a smaller experimental space; making it less likely that a local or global maximum is contained within the experimental space.

Table 2.1 Variables scaled to a range of -1 for minimum values and 1 for maximum values.

	VARIABLE	MIN -1	MAX 1
DMSO	X_1	1 mL	3 mL
GLYCINATE	X_2	1 eq	4 eq
DBU	X_3	1 eq	4 eq
TEMPERATURE	X_4	70 °C	120 °C

Each variables minimum value is assigned as -1 and the maximum value assigned as a +1 (e.g. a two level design has two settings). This is to scale each of the natural variables into a range, allowing for the direct comparison of individual variables without associating number bias. A 2-

FFD with 4 variables requires 16 unique experiments (e.g. 2^4) to generate a complete model with all primary, secondary, and ternary terms to describe the experimental space (**Equation 1**). The output measurement (Y) is yield of product **1a** and the coefficients (β) are the indicators for how relevant each term is to Y.

(1) $$Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_4X_4 + \beta_{12}X_1X_2 + \beta_{13}X_1X_3 + \beta_{14}X_1X_4 + \beta_{23}X_2X_3 + \beta_{24}X_2X_4 + \beta_{123}X_1X_2X_3 + \beta_{234}X_2X_3X_4 + \beta_{124}X_1X_2X_4 + \beta_{134}X_1X_3X_4$$

Table 2.2 2-FFD of all 16 possible experiments

EXPERIMENT	YIELD	X_1	X_2	X_3	X_4	ORDER
1	13.7	-1	-1	-1	-1	L
2	9.1	1	-1	-1	-1	C
3	14.4	-1	1	-1	-1	M
4	16.4	1	1	-1	-1	F
5	6	-1	-1	1	-1	K
6	5.5	1	-1	1	-1	I
7	26.3	-1	1	1	-1	E
8	30.2	1	1	1	-1	N
9	46.8	-1	-1	-1	1	O
10	50.5	1	-1	-1	1	A
11	15.8	-1	1	-1	1	J
12	20.6	1	1	-1	1	D
13	17.1	-1	-1	1	1	H
14	19.6	1	-1	1	1	G
15	40.6	-1	1	1	1	P
16	62.9	1	1	1	1	B

In order to remove experimental bias, the order in which the experiments were conducted was randomized and the same batch of reagents were used. The yields for each reaction were quantified by calibrated GC-FID using naphthalene as an internal standard. A matrix is constructed that contains all of the scaled variables shown in **Table 2.2** including a column of ones at the far left. Also in order to calculate the importance of secondary and ternary terms, nine more columns are added with the appropriate operations such as column X_1X_2 equals column X_1 multiplied by

column X_2. This model matrix will be X (**Equation 2**) will be manipulated into a final vector, b, that will contain all of the β coefficients in the order that the variables appear from left to right in the model matrix.

(2) $$(X^t \cdot X)^{-1} \cdot X^t \cdot y = b$$

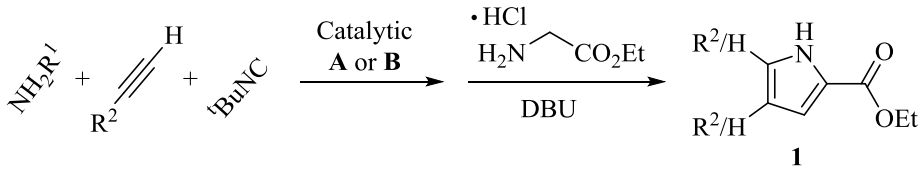
In order to obtain the vector b, the transpose of the model matrix (X^t) is multiplied by the model matrix (X). The inverse of the resulting matrix is then multiplied by X^t again. Finally this term is then multiplied by a vector which is composed of the yields (y) from each experiment in the order they appear in the model matrix. The model is then shown in the form of **equation 3** where all of the influential terms are shown.

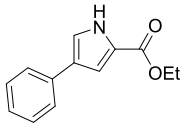
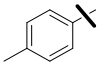
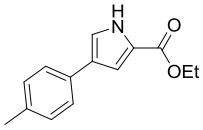
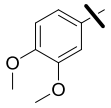
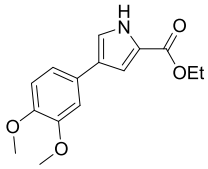
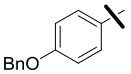
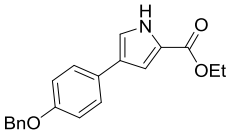
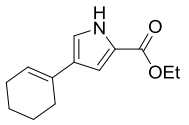
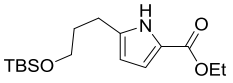
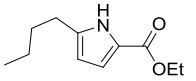
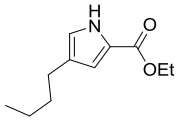
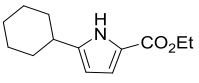
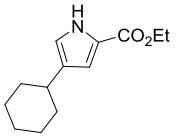
(3) $$Y = 24.8 + 2.06X_1 + 3.61X_2 + 1.23X_3 + 9.45X_4 + 1.48X_1X_2 + 1.47X_1X_3 + 2.10X_1X_4 + 10.34X_2X_3 – 2.87X_2X_4 + 0.58X_1X_2X_3 + 5.60X_2X_3X_4 + 0.55X_1X_2X_4 + 0.57X_1X_3X_4$$

Primary terms show linear correlations to the Y value. For example the β_4 which corresponds to the importance of temperature was 9.45. Compared relatively to the other primary terms, temperature is most influential on reaction yields. There is also an important secondary cross term, β_{23}, showing a correlation to the amount of glycine to the amount of dbu in the reaction. It is more difficult to ascertain reaction conditions for secondary terms and even less facile are ternary terms. Ternary terms are the result of three variables influencing each other simultaneously and in most cases are negligible to the model error. However, as shown in **equation 3** that was not the case for this experiment.

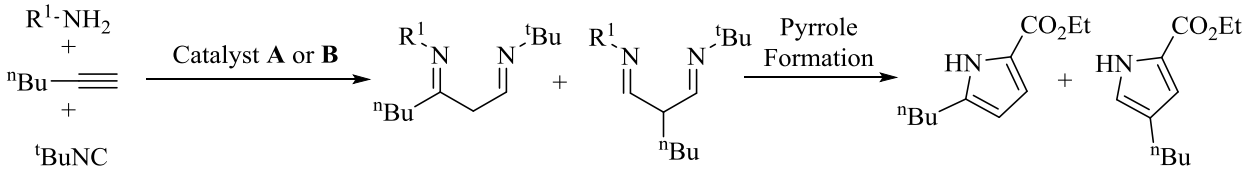
After some additional experiments to probe the region of highest yield (i.e. all variables set to the maximum level) an optimized set of conditions were obtained. The 3CC can be cyclized to a pyrrole derivative by treating the MCC intermediate with ethyl glycinate hydrochloride (3 eq), DBU (2.8 eq), DMSO (4 mL) at 120 °C for 18 h. A substrate scope was used to determine the generality of these new set of conditions.

Table 2.3 Examples of di-substituted pyrrole-2-carboxylates using the optimized conditions.



Entry	R^1	R^2	Catalyst	Product	Yield (%)
1a			**A**		50
1b			**A**		47
1c			**A**		44
1d			**A**		40
1e			**A**		27
1f			**A**		41
1g			**A**		56
1h			**B**		35
1i			**A**		47
1j			**B**		48[d]

Regioselective control for the products initially begins at the formation of the 3CC intermediate. As stated previously (chapter one), aryl groups on the alkyne show preferential positioning on the carbon atom between the two imines. This translates into only one possible isomer upon pyrrole formation. For terminal alkyl alkynes, two isomers can be distinguished via catalyst and amine combination (**Scheme 2.10**). To regioselectively obtain isomers **1f**, **1g**, and **1i**, catalyst **A** and aniline are used in combination during the 3CC formation. The other isomers, **1h** and **1j**, can be obtained by using a combination of catalyst **B** and cyclohexylamine.

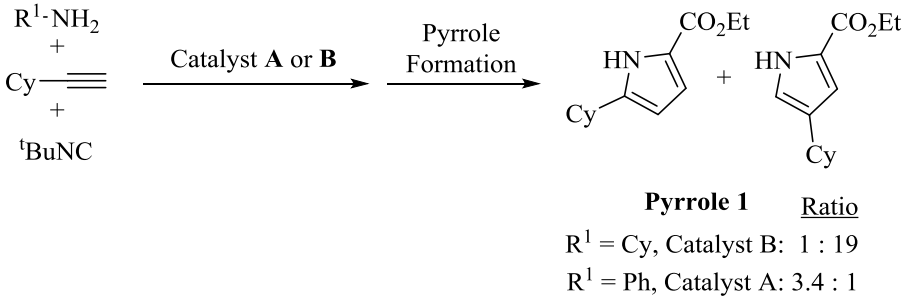


3CC	Ratio
R^1 = Cy, Catalyst A:	1 : 9
R^1 = Cy, Catalyst B:	1 : 11
R^1 = Ph, Catalyst A:	3 : 1
R^1 = Ph, Catalyst B:	1 : 1

Pyrrole 1	Ratio
R^1 = Cy, Catalyst B:	1 : 12
R^1 = Ph, Catalyst A:	6.4 : 1

Scheme 2.10 Regioselectivities for both 3CC formation and pyrrole formation.

The regioselectivities for terminal alkyl substrates were determined by comparing crude GC-FID to purified pyrrole standards. For the 1-hexyne derivative, the four possible combinations of amine and catalyst were tested to provide the optimized conditions. It becomes apparent that amine choice plays a major role in the regioselectivity; however, due to the differences in both electronics and sterics, it is difficult to pinpoint the exact reason. Regioselectivities are further enhanced by catalyst choice which is hypothesized to be caused by the increase in sterics in the active site for catalyst **A** vs catalyst **B**. However, all of this is conjecture as the alkyne is in equilibrium with the azatitanacyclobutene meaning that the trapping rates of isonitrile insertion could also be playing a role. Similar regioselectivities are observed when using cyclohexylacetylene in lieu of 1-hexyne (**Scheme 2.11**).



Scheme 2.11 Regioselectivities with cyclohexyl groups.

Although most examples involving terminal alkynes provide a single isomer, internal alkynes have the opportunity to produce two or three possible isomers. Reaction of glycinate amine could take place at either the aldimine (t-butyl imine) site or the ketimine (phenyl imine) site (**Figure 2.2**). Furthermore, if the initial transimination is reversible and fast then either the ring closure or elimination of amine to aromatize the ring would be the rate determining step (RDS). What truly makes this complicated is the almost complete lack of study on transimination of 1,3-diimines.[13b] However, several studies on transimination[18] and imine metathesis[19] have been performed on imines and 1,2-diimines.[20]

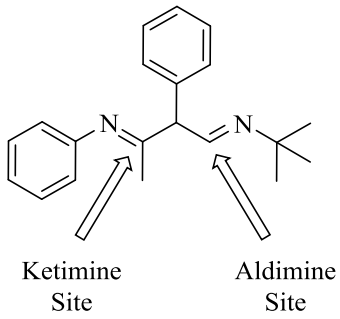
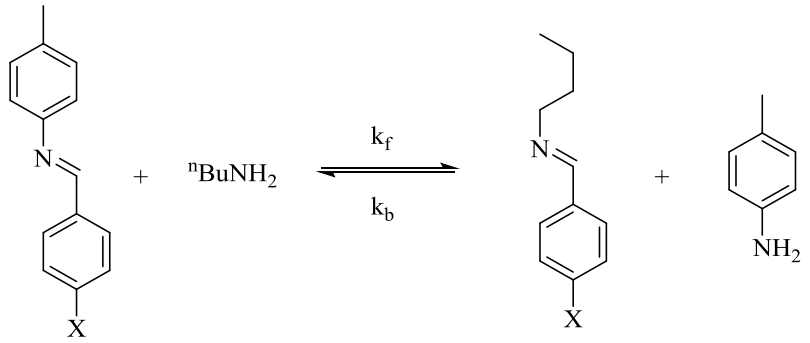


Figure 2.2 Differentiating the sites of the 3CC.

It has been well established for imines that transimination is a reversible process and can be catalyzed by Lewis acid,[18a] amino acids,[18c,21] amines,[18e] and metal complexes.[22] The equilibria typically lie with the more nucleophilic amine exchanging for a less nucleophilic amine. For example, Di Stefano and coworkers found that when reacting N-benzylidene-*p*-toluidines

derivatives with butylamine, the equilibrium in every case favored the corresponding N-benzylidenebutylamine product (**Table 2.4**).[19c] To the best of this researcher's knowledge there isn't a direct comparison between the reactivity of ketimines and aldimines to transimination. Even in our own system the ketimine carbon is an aryl imine and the aldimine carbon is an aliphatic imine.

Table 2.4 Di Stefano's and Co-workers transimination study of Aryl Aldimines with aliphatic amine equilibrium exchange.[19c]

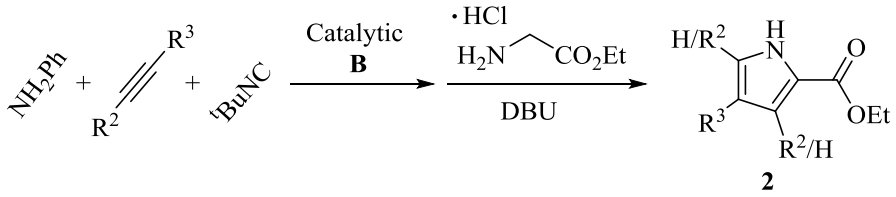


ENTRY	X	K	$K_F(M^{-1} S^{-1})$	$K_B(M^{-1} S^{-1})$	$T_{1/2}^C$ (S)
1	H	35	0.60	1.7×10^{-2}	240
2	OCH_3	23	3.3×10^{-2}	1.4×10^{-3}	1100
3	CN	120	3.4×10^{-3}	2.8×10^{-5}	11900
4	NO_2	240	7.9×10^{-4}	3.3×10^{-6}	62000

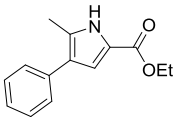
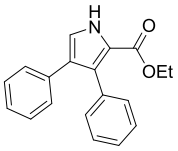
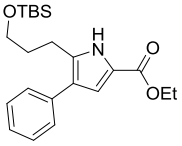
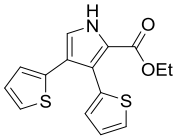
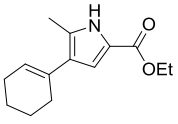
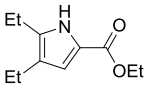
To determine if (a) there is a major isomer that is obtained from preferential transimination of the ketimine site (due to favorable equilibria for replacing aryl amines with aliphatic imines) or (b) there is a predominate product based on rate determining ring-closure, a substrate scope consisting of various internal alkynes was investigated (**Table 2.5**). The 3CC formation is predictable for all cases shown where either symmetrical or electronic bias provides predominately one product (>50:1). With the combined assistance of X-ray crystallography (**Figure 2.3**) and coupled-HSQC 2D NMR spectroscopy[23] (**Table 2.6**) the regiochemistry was assigned. All products shown are the major isomer with only trace amounts of a second isomer observed by GC-

MS. A switch in regiochemistry was observed when comparing alkyl-aryl alkynes and biaryl alkynes that was quite unexpected.

Table 2.5 Examples of tri-substituted pyrrole-2-carboxylates.



2

Entry	R^2	R^3	Product	Yield(%)
2a	Me			65
2b				51
2c				25
2d				37
2e	Me			61
2f	Et	Et		29

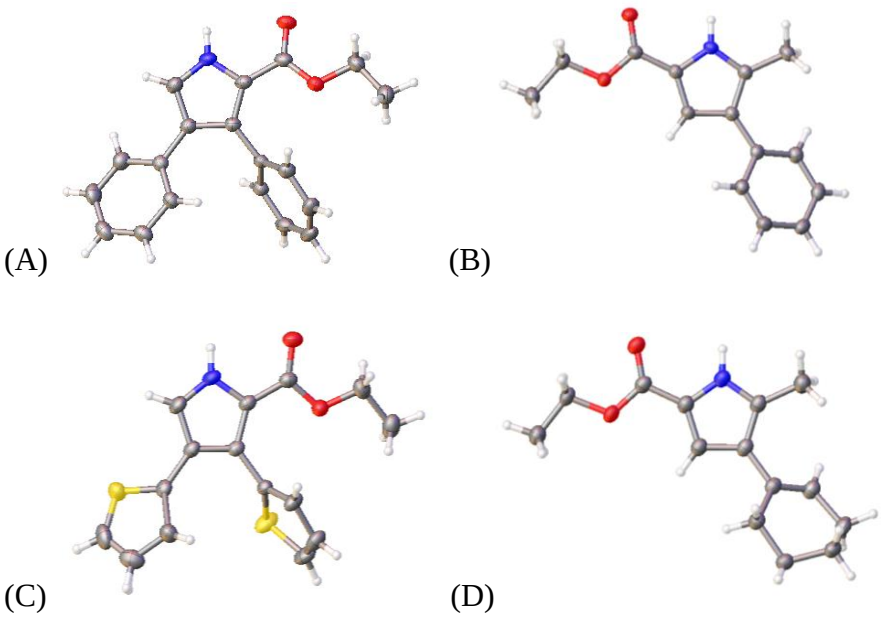


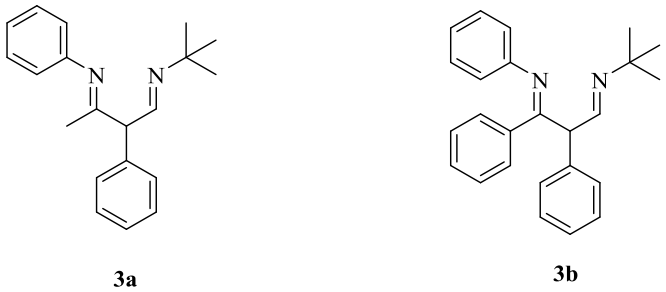
Figure 2.3 X-ray Crystal structures of (A) **2b,** (B) **2a,** (C) **2d,** (D) **2e.**

Table 2.6 C-H coupling constants for compounds **1a**, **1i**, **2a**-**2f**.

Compound	C-H pyrrole $^{1}J_{CH}$ coupling	C–H assignment (α or β)
1a	186 Hz, 175 Hz	α, β
1i	177 Hz, 173 Hz	β, β
2a	175 Hz	β*
2b	189 Hz	α*
2c	175 Hz	β
2d	189 Hz	α*
2e	175 Hz	β*
2f	172 Hz	β

A closer investigation into the mechanism revealed one plausible answer to this regiochemical model. The transimination is in this case a fast, reversible equilibria that does not determine the product distribution. According to related cyclizations, the ring closure is more commonly invoked as the rate-determining step.[8,24] To test this assertion NMR and GC-FID studies were used to follow two reactions in attempts to ascertain mechanistic details regarding potential intermediates and productive pathways. 1,3-diimines **3a** and **3b** (**Figure 2.4**), intermediate 3CC for compounds

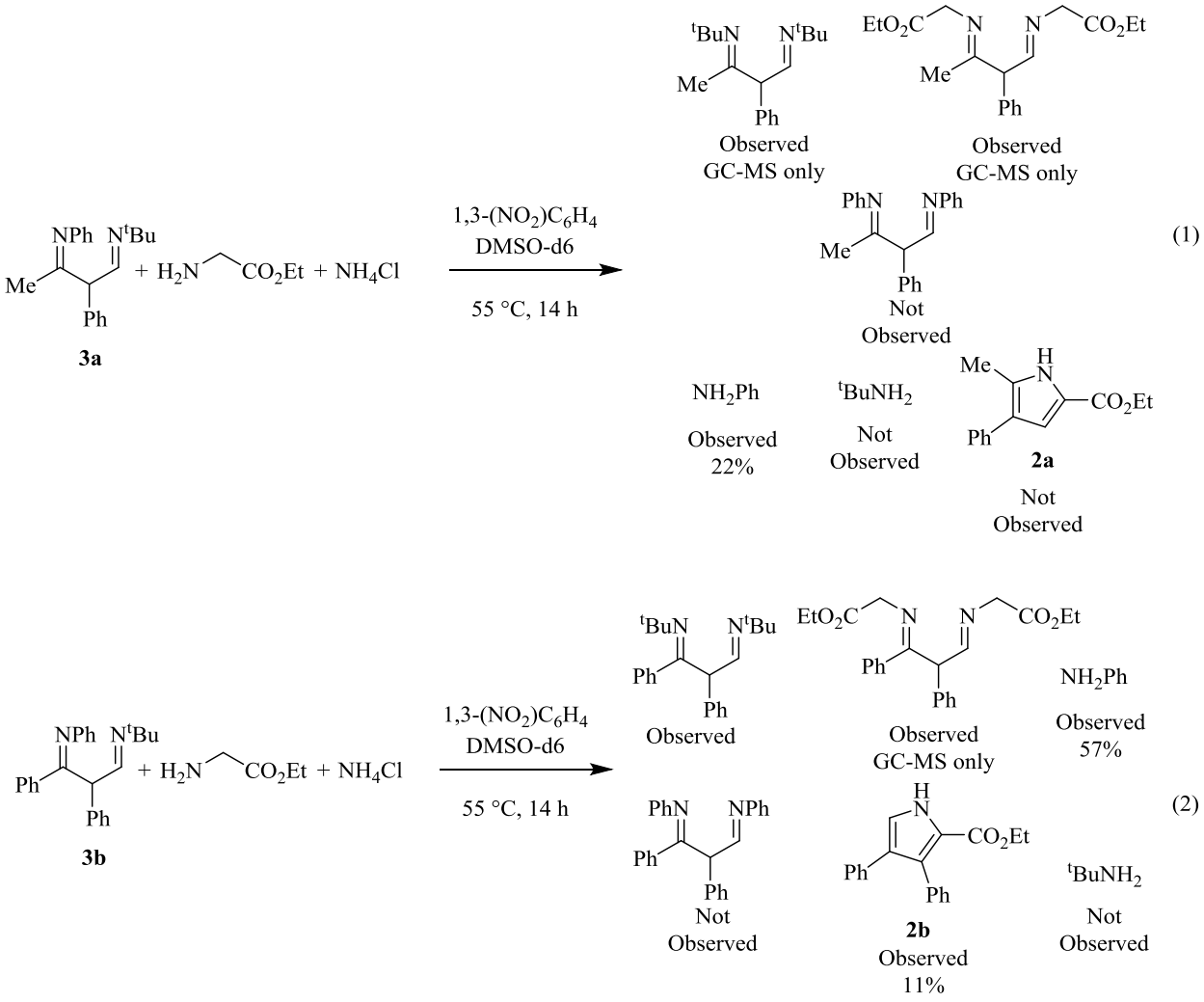
2a and **2b,** respectively, were isolated from similar MCR conditions using 1-phenylpropyne or diphenylacetylene. These isolated 3CC products were reacted each with ethylglycinate and ammonium chloride at 55 °C, a temperature that is ill-suited for pyrrole formation.



3a **3b**

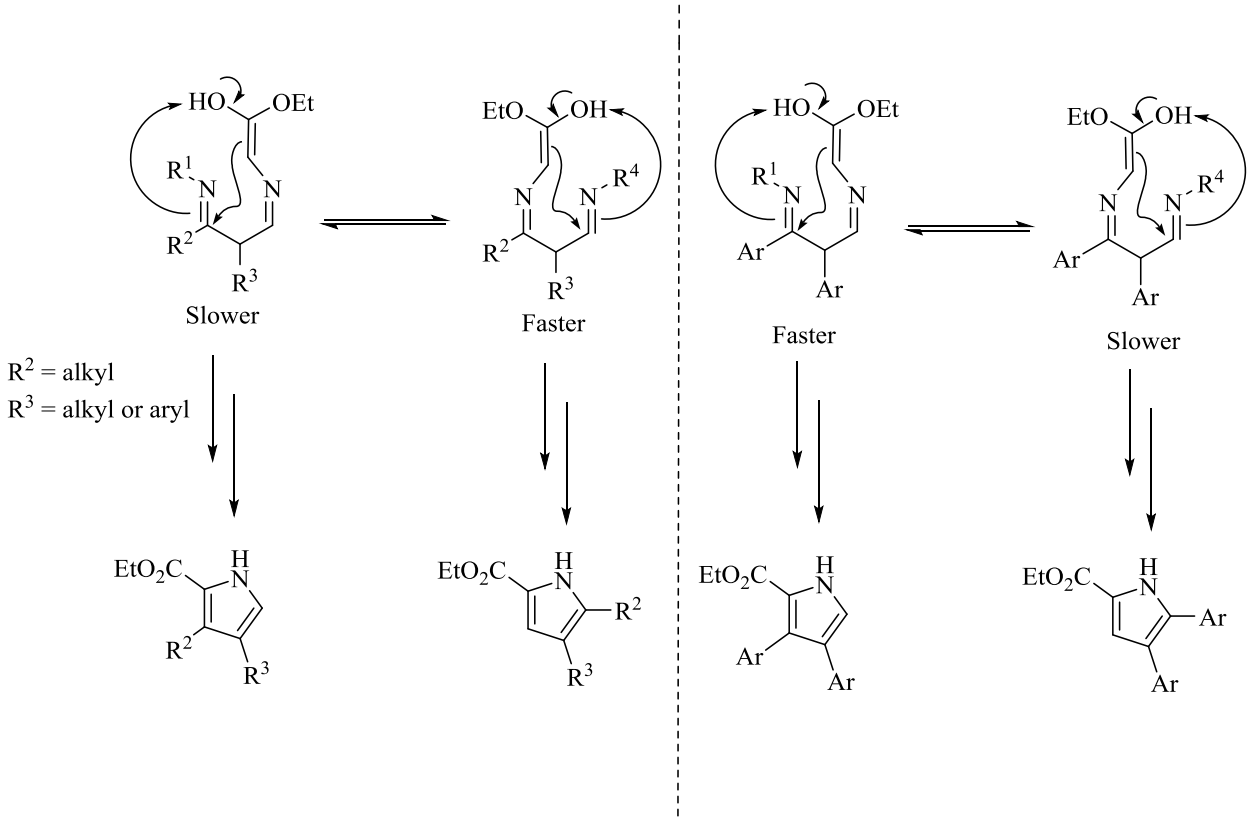
Figure 2.4 1,3-diimine isolated for mechanistic studies.

Interestingly, in both cases, the only free amine observed was aniline, which strongly implicates that transimination at the ketimine site is favored (**Scheme 2.12**).[13b] However, this observation does not necessarily prove this claim as it is possible that liberation of t-butyl amine via transimination could lead to displacement of aniline by the more nucleophilic t-butyl amine.[19c] In fact, observed in the GC-MS are several distinct 3CC isomers, except for those resulting from free aniline transimination. The striking difference between the two substrates tested is both the amount of free aniline produced (22% and 57% when starting with **3a** and **3b**, respectively) under similar conditions and the observance of pyrrole **2b**.



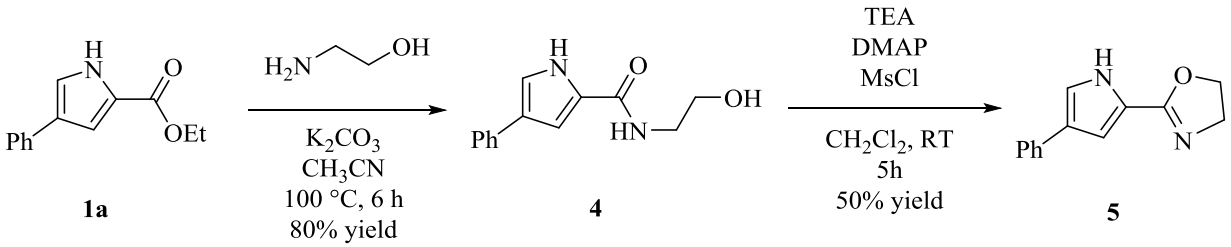
Scheme 2.12 (1) Reaction of **3a** with pyrrole formation conditions (2) Reaction of **3b** with pyrrole formation conditions.

The latter provides some insight as to the nature of the ring closure step. If the product determining step is the ring closure and not transimination, then the stabilization of positive charge by the aromatic group at the ketimine carbon would increase the rate of carbon-carbon bond formation, thus providing pyrrole **2b** even at reduced temperatures (**Scheme 2.13**).

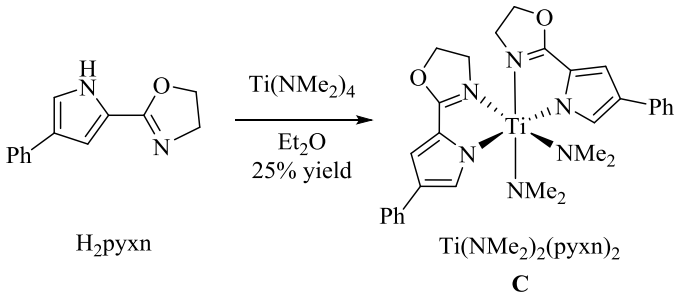


Scheme 2.13 Model depicting relative rates for pyrrole formation.

Pyrrole **1a** was utilized in the synthesis of an asymmetric ligand, pyrrole **5**, that provided incentive to continue study on a catalyst previously reported to perform MCR; producing pyrazoles in a single step.[11q] The ligand was prepared by transamidation of ethyl-carboxylate with 2-aminoethanol,[25] followed by ring closure to produce an oxazoline (**Scheme 2.14**).[26] Addition of 2 eq of ligand to $Ti(NMe_2)_4$ afforded catalyst **C** in 25% yield (**Scheme 2.15**). The metal complex is 6-coordinate with two ancillary ligands and two dimethylamide groups. The oxazoline is nitrogen bound and is trans to the dimethylamide, while the two pyrrolyl groups are also trans, which is similar to the aforementioned catalyst.



Scheme 2.14 Synthesis of asymmetric ligand H_2pyxn.



Scheme 2.15 Synthesis of titanium catalyst **C**.

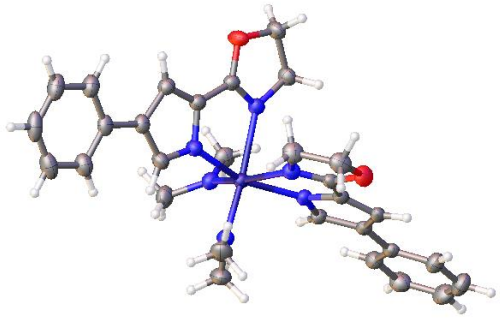
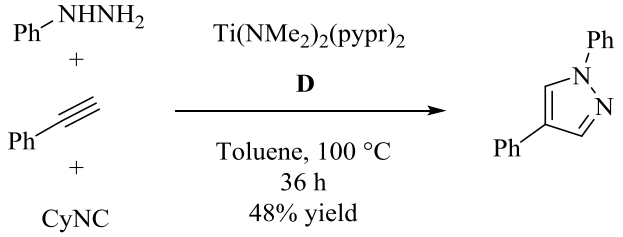


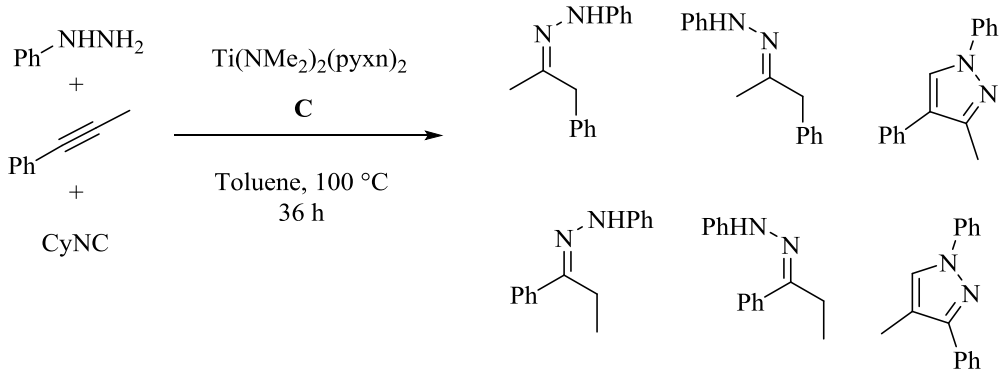
Figure 2.5 X-ray crystallographic data on $Ti(NMe_2)_2pyxn_2$ **(C).**

A MCR between mono-substituted hydrazines, terminal alkynes, and isonitriles catalyzed by titanium complex **D** was reported in 2012 and produced 1,3-disubstituted pyrazoles as the only isomer (**Scheme 2.16**).[11q] A limitation of this catalysis was the exclusion of internal alkynes. It was hypothesized that the methyl group on the 2-position of the ancillary ligand blocked the necessary conformation for effective catalysis. As titanium complex **C** does not have such restrictive groups at the two position, it was believed that internal alkynes would react to form pyrazoles using this new catalyst. A reaction of phenylhydrazine, 1-phenylpropyne, and

cyclohexylisonitrile catalyzed by **C** at 100 °C for 36 hours provided a mixture of four hydrazination products and two pyrazole isomers (**Scheme 2.17**). Judging by GC-MS, hydrohydrazination was the dominate product followed by pyrazole formation.



Scheme 2.16 One-step pyrrole synthesis from titanium MCR



Scheme 2.17 Expansion of substrate scope using **C** results in four hydrazination isomers and two pyrazole isomers.

2.3 Conclusion

The successful adaptation of a classical heterocyclic synthesis using 1,3-diimines in lieu of 1,3-diones has been described. The advantages of this methodology are the facile construction of asymmetric products, the use of commercially inexpensive materials, and the operational simplicity of the reaction. The pyrrole formation shows a unique switch in regioselectivity depending on initial alkyne. Aryl stabilization of positive charge at the ketimine carbon provides one possible answer to this peculiar anomaly. It is unclear as to why such regioselective switches haven't occurred in similar systems such as Gupton's vinylogous amidates[27] or other heterocyclic synthesis reported by Odom group.[13a]

Pyrroles have shown widespread usage as ancillary ligands for late and early transition metal catalysis. It is therefore advantageous to investigate economical routes for constructing these types of molecules. The synthesis of a pyrrolyl oxazoline based titanium catalyst is described and has shown expansion of the current available substrate scope of the previously reported catalyst **D**. However, the large amount of hydrazination product makes this catalyst far from viable. As will be described in later chapters this methodology has potential to adapt well to the total synthesis of natural products containing core pyrrole subunits.

2.4 Experimental

General Considerations: All manipulations of air-sensitive compounds were carried out in an MBraun drybox under a purified nitrogen atmosphere. All glassware was heated at 150 °C for 4 h and stored in a drybox under nitrogen. Toluene was purified by first sparging with dry nitrogen to remove oxygen and then ran through activated alumina to remove water. ^{1}H and ^{13}C NMR spectra were recorded on a VXR-500 spectrometer in $CDCl_3$. Regiochemistry of compounds **1a**, **1i**, and **2a-2f** were determined by coupled-HSQC. Melting points were measured on a Mel-Temp II apparatus (Laboratory Devices Inc, USA) with a mercury thermometer in an open capillary tube. Single crystal X-ray diffraction data was collected in the Center for Crystallographic Research at MSU and structures deposited in the Cambridge Crystallographic Data Centre.

Ligands H_2dpma[11a] and H_2dpm[15] were prepared by literature methods. Ti$(NMe_2)_2$(dpma)[11a] (**A**) and Ti$(NMe_2)_2$(dpm)[14] (**B**) were made following literature procedures. Alkynes were purchased either from Sigma-Aldrich or GFS chemicals and distilled from CaO under dry nitrogen or prepared using Sonogashira coupling.[28] Amines were purchased from Sigma-Aldrich and were distilled from KOH under dry nitrogen. Triethylamine (TEA) and glycine ethyl ester hydrochloride were both purchased from Sigma-Aldrich and used as received. *tert*-Butylisonitrile was prepared from *tert*-butylamine, $CHCl_3$, and aqueous base according to the literature procedure and purified by distillation under dry nitrogen.[29] *tert*-Butyldimethylsilyl chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were purchased from Oakwood Chemicals and used as received. Dimethylsulfoxide (DMSO) was purchased from Fisher Scientific and used as received. Hexanes and ethyl acetate were purchased from Mallinckrodt Chemicals and used as received.

Ethyl glycinate was prepared for Methods B and C below by dissolving ethyl glycinate hydrochloride in water and adding 2 equivalents of K_2CO_3. The solution was extracted with

dichloromethane in three portions. The combined organic layers were dried and filtered; then, the volatiles were removed by rotary evaporation to give the ethyl glycinate as a clear to pale yellow oil.

General Procedure for 1,3-diimine Synthesis

A pressure tube was charged with a magnetic stir bar and Ti precatalyst **A** or **B** (10 mol%) in toluene (2 mL), amine (2 mmol), alkyne (1 mmol), and t-butylisonitrile (1.2 mmol) were added. The pressure tube was sealed, removed from the drybox, and placed into an oil bath preheated to 100-120 °C for 24-48 h. The reaction was removed from the bath, and volatiles were removed in vacuo.

General Procedures for 2-carboxylpyrroles

Method A

The pressure tube from 1,3 diimine formation was charged with glycine ethyl ester hydrochloride (420 mg, 3 mmol), DBU (420 μL, 2.8 mmol), and DMSO (4 mL). The pressure tube was resealed and heated for 18 h at 120 °C in an oil bath. The reaction was removed from the bath and extracted with DCM (40 mL). The organic layer was washed with 10 % $NaHCO_3$ (30 mL) and with brine (30 mL). The aqueous layers were combined and washed with DCM (40 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, and filtered. Volatiles were removed, and the crude was purified by flash column chromatography on silica gel with hexanes:ethyl acetate (4:1) and 1% TEA to afford the desired product.

Method B

The pressure tube from 1,3 diimine formation was charged with glycine ethyl ester (309 mg, 3 mmol), NH_4Cl (22 mg, 0.4 mmol), and DMSO (4 mL). The pressure tube was resealed and heated for 18 h at 120 °C in an oil bath. The reaction was removed from the bath, and extracted

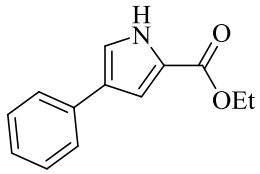
with DCM (40 mL). The organic layer was washed with 10% $NaHCO_3$ (30 mL) and with brine (30 mL). The aqueous layers were combined and washed with DCM (40 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, and filtered. Volatiles were removed, and the crude was purified by flash column chromatography on silica gel with hexanes:ethyl acetate (4:1) and 1% TEA to afford desired product.

Method C

All materials from method B were scaled to alkyne (20 mmol).

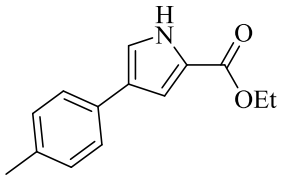
Preparative Details

Synthesis of ethyl 4-phenyl-pyrrole-2-carboxylate (Table 2.3, 1a)



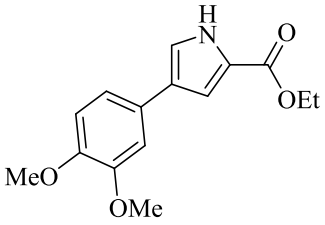
1,3-diimine synthesis followed general procedure using Ti precatalyst **A** (32.4 mg, 10 mol%), cyclohexylamine (230 μL, 2 mmol), phenylacetylene (110 μL, 1 mmol) and heating at 100 °C for 24 h. Method A: The pyrrole was afforded (108 mg, 50%) as a light brown solid. Method B: The pyrrole was afforded (104 mg, 48%) as a light brown solid. Method C: The pyrrole was afforded (1.8 g, 42%) as a light brown solid. M.p. 97-99 °C (lit.[30] Mp: 98-99 °C). ^{1}H NMR ($CDCl_3$): δ 9.25 (1H, br s, N-H pyrrole), 7.44-7.46 (2H, m, Ar-H), 7.27-7.30 (2H, m, Ar-H), 7.14-7.18 (3H, m, Ar-H and C-H pyrrole), 4.28 (2H, q, J_{HH} = 7.2 Hz, CH2), 1.31 (3H, t, J_{HH} = 7.2 Hz, CH3). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 161.2, 134.5, 128.7, 126.5, 125.3, 123.7, 119.4, 112.4, 60.5, 14.4. Elemental analysis: found %C 72.45, %H 6.46, %N 6.59; calcd.; %C 72.54, %H 6.09, %N 6.51.

Synthesis of ethyl 4-(p-tolyl)-pyrrole-2-carboxylate (Table 2.3, 1b)



1,3-diimine synthesis followed general procedure using Ti precatalyst **A** (32.4 mg, 10 mol%) , cyclohexylamine (230 μL, 2 mmol), 1-ethynyl-4-methylbenzene (127 μL, 1 mmol) and heating at 100 °C for 24 h. Method A: The pyrrole was afforded (108 mg, 47%) as a light orange solid. M.p. 166-167 °C (lit.[30] Mp: 165-166 °C). ^{1}H NMR ($CDCl_3$) δ 9.27 (1H, br s, N-H pyrrole), 7.43 (2H, d, J_{HH} = 3.1 Hz, Ar-H), 7.18-7.22 (m, 4H, Ar-H and C-H pyrrole), 4.36 (2H, q, J_{HH} = 7.2 Hz, CH2), 1.40 (3H, t, J_{HH} = 7.2 Hz, CH3); ^{13}C {^{1}H} NMR ($CDCl_3$) δ 161.2, 135.9, 131.7, 129.5, 126.8, 125.2, 123.6, 119.1, 112.3, 60.5, 21.1, 14.5; elemental analysis: found %C 73.42, %H 6.49, %N 6.19; calcd. %C 73.34, %H 6.59, %N 6.11.

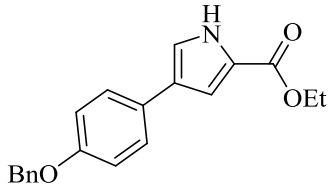
Synthesis of ethyl 4-(3,4-dimethoxy)phenyl-pyrrole-2-carboxylate (Table 2.3, 1c)



1,3-diimine synthesis followed general procedure using Ti precatalyst **A** (32.4 mg, 10 mol%), cyclohexylamine (230 μL, 2 mmol), 1-ethynyl-3,4-dimethoxybenzene (162 mg, 1 mmol) and heating at 100 °C for 24 h. Method A: The pyrrole was afforded (121 mg, 44%) as a light yellow solid. M.p. 141-142 °C (lit.[31] Mp: 136.3-137.5 °C). ^{1}H NMR ($CDCl_3$) δ 9.18 (1H, br s, N-H pyrrole), 7.15-7.18 (2H, m, C-H pyrrole), 7.08 (1H, dd, J_{HH} = 8.4 Hz, 2.1 Hz, Ar-H), 7.04 (1H, d, J_{HH} = 2.1 Hz, Ar-H), 6.89 (1H, d, J_{HH} = 8.4 Hz, Ar-H), 4.36 (2H, q, J_{HH} = 7.2 Hz, CH_2), 3.94 (3H, s, CH_3), 3.90 (3H, s, CH_3), 1.39 (3H, t, J_{HH} = 7.2 Hz, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$) δ 161.1, 149.2

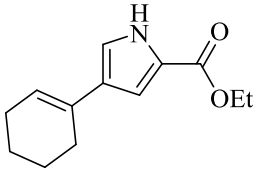
147.8, 127.7, 126.8, 123.6, 118.8, 117.6, 112.2, 111.6, 108.9, 60.5, 56.0, 59.9, 14.5. HRMS (ES) m/z calcd. for $C_{15}H_{16}NO_4$ 274.1079, found 274.1089.

Synthesis of ethyl 4-(4-benzyloxy)phenyl-pyrrole-2-carboxylate (Table 2.3, 1d)



1,3-diimine synthesis followed general procedure using Ti precatalyst **A** (32.4 mg, 10 mol%), cyclohexylamine (230 μL, 2 mmol), 1-ethynyl-4-benzyloxybenzene (208 mg, 1 mmol) and heating at 100 °C for 24 h. Method A: The pyrrole was afforded (128 mg, 40%) as a red solid. M.p. 146-147 °C. ^{1}H NMR ($CDCl_3$) δ 9.22 (1H, br s, N-H pyrrole), 7.29-7.44 (7H, m, Ar-H), 7.12-7.13 (2H, m, Ar-H and C-H pyrrole), 6.92-6.98 (2H, m, Ar-H and C-H pyrrole), 5.06 (2H, s, CH_2), 4.33 (2H, q, J_{HH} = 7.1 Hz, CH_2), 1.37 (3H, t, J_{HH} = 7.1 Hz, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$) δ 161.2, 157.5, 137.1, 128.5, 127.9, 127.6, 127.4, 126.5, 126.4, 123.5, 118.7, 115.2, 112.1, 70.1, 60.3, 14.4. Elemental analysis: found %C 74.64, %H 5.89, %N 4.42; calcd. %C 74.75, %H 5.96, %N 4.36.

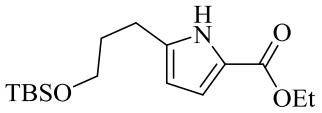
Synthesis of ethyl 4-(cyclohexen-1-yl)-pyrrole-2-carboxylate (Table 2.3, 1e)



1,3-diimine synthesis followed general procedure using Ti precatalyst **A** (32.4 mg, 10 mol%), cyclohexylamine (230 μL, 2 mmol), 1-cyclohexenylacetylene (123 μL, 1 mmol) and heating at 100 °C for 24 h. Method A: The pyrrole was afforded (59 mg, 27%) as a brown solid. M.p. 56-59 °C. ^{1}H NMR ($CDCl_3$) δ 9.28 (1H, br s, N-H pyrrole), 6.95 (1H, d, J_{HH} = 1.7 Hz, C-H pyrrole), 6.88 (1H, d, J_{HH} = 1.7 Hz, C-H pyrrole), 5.98-6.00 (1H, m, C-H alkene), 4.28 (2H, q, J_{HH} = 7.2 Hz, CH_2), 2.24-2.27 (2H, m, CH_2), 2.10-2.14 (2H, m, CH_2), 1.68-1.73 (2H, m, CH_2), 1.58-1.63 (2H,

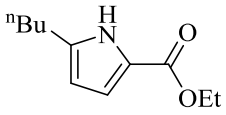
m, CH_2), 1.31-1.39 (3H, t, J_{HH} = 7.2 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 161.4, 129.9, 122.8, 120.6, 118.4, 110.9, 60.3, 27.0, 25.3, 22.7, 22.3, 14.4. Elemental analysis: found %C 71.29, %H 7.64, %N 6.30; calcd. %C 71.29, %H 7.81, %N 6.39.

Synthesis of ethyl 5-(3-tertbutyldimethylsilyloxy)propyl-pyrrole-2-carboxylate (Table 2.3, 1f)



1,3-diimine synthesis followed general procedure using Ti precatalyst **A** (32.4 mg, 10 mol%), cyclohexylamine (230 μL, 2 mmol), 1-*t*-butyldimethylsilyloxy-pent-4-yne (236 μL, 1 mmol) and heating at 100 °C for 24 h. Method A: The pyrrole was afforded (128 mg, 41%) as a light brown solid. M.p. 63-64 °C. ^1H NMR ($CDCl_3$): δ 9.31 (1H, br s, N-H pyrrole), 6.81 (1H, d, J_{HH} = 3.3 Hz, C-H pyrrole), 5.94 (1H, d, J_{HH} = 3.3 Hz, C-H pyrrole), 4.27 (2H, q, J_{HH} = 7.2 Hz, CH_2), 3.62 (2H, t, J_{HH} = 5.9 Hz, CH_2), 2.69 (2H, t, J_{HH} = 7.3 Hz, CH_2) 1.79-1.85 (2H, quin, J_{HH} = 7.3 Hz, 6.7 Hz, CH_2), 1.31-1.40 (3H, t, J_{HH} = 7.2 Hz, CH_3), 0.89 (9H, s), δ 0.03 (6H, s, CH_3-Si). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 161.2, 138.1, 121.3, 115.8, 108.0, 61.9, 59.9, 31.9, 25.9, 24.1, 18.3, 14.5, –5.3. Elemental analysis: found %C 61.82, %H 9.13, %N 4.78; calcd. %C 61.69, %H 9.38, %N 4.50.

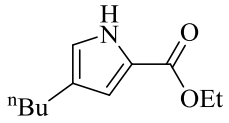
Synthesis of ethyl 5-butyl-pyrrole-2-carboxylate (Table 2.3, 1g)



1,3-diimine synthesis followed general procedure using Ti precatalyst **A** (32.4 mg, 10 mol%), aniline (180 μL, 2 mmol), 1-hexyne (115 μL, 1 mmol) and heating at 100 °C for 24 h. Method A: The pyrrole was formed after heating at 80 °C for 18 h and afforded (109 mg, 56%) as a brown oil. ^1H NMR ($CDCl_3$): δ 9.40 (1H, br s, N-H pyrrole), 6.80 (1H, d, J_{HH} = 2.6 Hz, C-H pyrrole), 5.94 (1H, d, J_{HH} = 2.6 Hz, CH-pyrrole), 4.28 (2H, q, J_{HH} = 7.2 Hz, CH_2), 2.61 (2H, t, J_{HH} = 7.5 Hz,

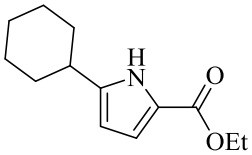
CH_2), 1.57-1.63 (2H, quin, J_{HH} = 7.5 Hz, 7.0 Hz, CH_2), 1.31-1.35 (5H, m, CH_2 and CH_3), 0.89 (3H, t, J_{HH} = 7.5 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 161.5, 139.0, 121.0, 115.8, 107.8, 60.0, 31.4, 27.5, 22.2, 14.5, 13.7. Elemental analysis: found %C 67.74, %H 8.70, %N 7.24; calcd. %C 67.66, %H 8.78, %N 7.17.

Synthesis of ethyl 4-butyl-pyrrole-2-carboxylate (Table 2.3, 1h)



1,3-diimine synthesis followed general procedure using Ti precatalyst **B** (30.8 mg, 10 mol%), cyclohexylamine (230 μL, 2 mmol), 1-hexyne (115 μL, 1 mmol) and heating at 100 °C for 24 h. Method A: The pyrrole was afforded (68 mg, 35%) as a brown oil. ^1H NMR ($CDCl_3$): δ 8.91 (1H, br s, N-H pyrrole), 6.77 (1H, d, J_{HH} = 1.9 Hz, C-H pyrrole), 6.74 (1H, d, J_{HH} = 1.9 Hz, C-H pyrrole), 4.31 (2H, q, J_{HH} = 7.1 Hz, CH_2), 2.46 (2H, t, J_{HH} = 7.5 Hz, CH_2), 1.52-1.58 (2H, m, CH_2), 1.34-1.38 (5H, m, CH_2 and CH_3), 0.91 (3H, t, J_{HH} = 7.3 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 161.2, 134.5, 128.7, 126.5, 125.3, 123.7, 119.4, 112.4, 60.5, 14.4. Elemental analysis: found %C 67.07, %H 8.66, %N 7.25; calcd. %C 67.66, %H 8.76, %N 7.17. HRMS (ES) m/z calcd. for $C_{11}H_{16}NO_2$ 194.1181, found 194.1185.

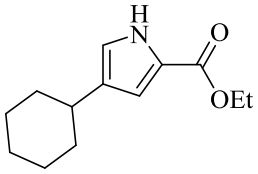
Synthesis of ethyl 5-cyclohexyl-pyrrole-2-carboxylate (Table 2.3, 1i)



1,3-diimine synthesis followed general procedure using Ti precatalyst **A** (32.4 mg, 10 mol%), aniline (180 μL, 2 mmol), cyclohexylacetylene (131 μL, 1 mmol) and heating at 100 °C for 24 h. Method A: The pyrrole was afforded (104 mg, 47%) as a light orange solid. M.p. 106-107 °C. ^1H NMR ($CDCl_3$): δ 8.78 (1H, br s, N-H pyrrole), 6.82 (1H, t, J_{HH} = 2.9 Hz, C-H pyrrole), 5.97 (1H,

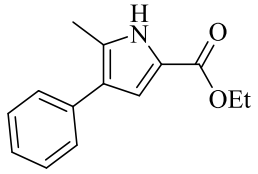
t, J_{HH} = 2.9 Hz, C-H pyrrole), 4.29 (2H, q, J_{HH} = 7.3 Hz, CH_2), 2.57-261 (1H, m, C-H cyclohexyl), 1.98-2.00 (2H, m, C-H cyclohexyl), 1.80-1.83 (2H, m, C-H cyclohexyl), 1.71-1.74 (1H, m, C-H cyclohexyl), 1.21-1.43 (8H, m, C-H cyclohexyl, CH_3). ^{13}C {^1H} NMR ($CDCl_3$) δ 161.4, 143.8, 120.9, 115.6, 106.1, 60.0, 36.9, 32.8, 26.1, 25.9, 14.6. HRMS (ES) m/z calcd. for $C_{13}H_{19}NO_2$ 221.1416, found 221.1417.

Synthesis of ethyl 4-cyclohexyl-pyrrole-2-carboxylate (Table 2.3, 1j)



1,3-diimine synthesis followed general procedure using Ti precatalyst **B** (30.8 mg, 10 mol%), cyclohexylamine (230 μL, 2 mmol), cyclohexylacetylene (131 μL, 1 mmol) and heating at 100 °C for 24 h. Method A: The pyrrole was afforded (106 mg, 48%) as a bright orange solid. M.p. 68-69 °C. ^1H NMR ($CDCl_3$): δ 8.86 (1H, br s, N-H pyrrole), 6.80 (1H, t, J_{HH} = 2.4 Hz, C-H pyrrole), 6.75 (1H, t, J_{HH} = 2.4 Hz, C-H pyrrole), 4.30 (2H, q, J_{HH} = 7.2 Hz, CH_2), 2.43-249 (1H, m, C-H cyclohexyl), 1.93-1.95 (2H, m, C-H cyclohexyl), 1.77-1.82 (2H, m, C-H cyclohexyl), 1.66-1.74 (1H, m, C-H cyclohexyl), 1.21-1.43 (8H, m, C-H cyclohexyl, CH_3). ^{13}C {^1H} NMR ($CDCl_3$) δ 161.3, 133.0, 122.4, 119.0, 113.2, 60.2, 36.0, 34.5, 26.5, 26.2, 14.5. HRMS (ES) m/z calcd. for $C_{13}H_{19}NO_2$ 221.1416, found 221.1425.

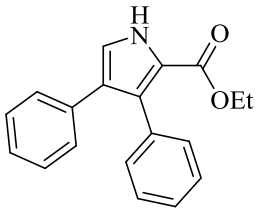
Synthesis of ethyl 4-phenyl-5-methyl-pyrrole-2-carboxylate (Table 2.5, 2a)



1,3-diimine synthesis followed general procedure using Ti precatalyst **B** (30.8 mg, 10 mol%), aniline (180 μL, 2 mmol), 1-phenylpropyne (125 μL, 1 mmol) and heating at 100 °C for 48 h.

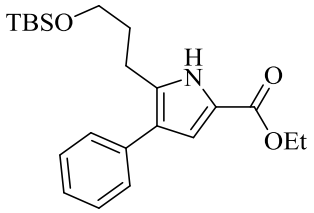
Method A: The pyrrole was afforded (149 mg, 65%) as a pale yellow solid. M.p. 124-126 °C (lit. Mp: 125.5 °C); ^{1}H NMR ($CDCl_3$) δ 9.63 (1H, br s, N-H pyrrole), 7.41-7.46 (4H, m, Ar-H), 7.26-7.30 (1H, m, Ar-H), 7.07 (1H, d, J_{HH} = 2.6 Hz, C-H pyrrole), 4.39 (2H, q, J_{HH} = 7.2 Hz, CH_2), 2.49 (3H, s, CH_3), 1.41 (3H, t, J_{HH} = 7.2 Hz, CH_3); ^{13}C {^{1}H} NMR ($CDCl_3$) δ 161.5, 135.8 130.4, 128.4, 127.6, 125.8, 123.7, 120.6, 115.3, 60.2, 14.4, 12.8; elemental analysis: found %C 73.38, %H 6.52, %N 6.04; calcd. %C 73.34, %H 6.59, %N 6.11. This compound was also characterized by single crystal X-ray diffraction: CCDC #1405632.

Synthesis of ethyl 3,4-diphenyl-pyrrole-2-carboxylate (Table 2.5, 2b)



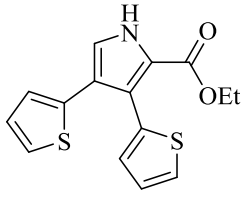
1,3-diimine synthesis followed general procedure using Ti precatalyst **B** (30.8 mg, 10 mol%), aniline (180 μL, 2 mmol), diphenylacetylene (178 mg, 1 mmol) and heating at 120 °C for 60 h. Method A: The pyrrole was afforded (148 mg, 51%) as a pale yellow solid. M.p. 120-122 °C (lit.[27] Mp: 118-119 °C). ^{1}H NMR ($CDCl_3$): δ 9.32 (1H, br s, N-H pyrrole), 7.24-7.27 (5H, m, Ar-H), 7.14-7.18 (3H, m, Ar-H), 7.07-7.13 (3H, m, Ar- H and C-H pyrrole), 4.16 (2H, q, J_{HH} = 7.2 Hz, CH_2), 1.11-1.14 (3H, t, J_{HH} = 7.2 Hz, CH_3); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 161.2, 134.5, 132.9, 130.8, 129.6, 129.3, 128.3, 128.2, 128.1, 127.4, 126.8, 120.2, 60.2, 14.0. Elemental analysis: found %C 78.39, %H 5.81, %N 4.88; calcd. %C 78.33, %H 5.88, %N 4.81. This compound was also characterized by single crystal X-ray diffraction: CCDC #1405634.

Synthesis of ethyl 4-phenyl-5-(3-tert-butyldimethylsilyloxy)propyl-pyrrole-2-carboxylate (Table 2.5, 2c)



1,3-diimine synthesis followed general procedure using Ti precatalyst **B** (30.8 mg, 10 mol%), aniline (180 μL, 2 mmol), 1-(*tert*-butyldimethylsilyloxy)-5-phenylprop-4-yne (274 mg, 1 mmol) and heating at 100 °C for 48 h. Method A: The pyrrole was afforded (97 mg, 25%) as a red solid. M.p. 79-81 °C. ^{1}H NMR ($CDCl_3$): δ 9.35 (1H, br s, N-H pyrrole), 7.36-7.40 (3H, m, Ar-H), 7.01-7.27 (2H, m, Ar-H), 7.01 (1H, d, J_{HH} = 2.9 Hz, C-H pyrrole), 4.34 (2H, q, J_{HH} = 7.1 Hz, CH_2), 3.69 (2H, t, J_{HH} = 6.1 Hz, CH_2), 2.89-2.92 (2H, t, J_{HH} = 7.3 Hz, CH_2), 1.87 (2H, pent, J_{HH} = 7.3 Hz, CH_2), 1.37 (3H, t, J_{HH} = 7.1 Hz, CH_3), 0.91 (9H, s, CH_3), 0.06 (6H, s, CH_3-silyl). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 161.1, 135.9, 134.1, 128.5, 127.9, 125.9, 123.7, 120.9, 115.3, 62.1 60.1, 31.7, 26.0, 22.9, 18.4, 14.6, -5.3. Elemental analysis: found %C 67.97, %H 8.81, %N 3.62; calcd. %C 68.17, %H 8.58, %N 3.61.

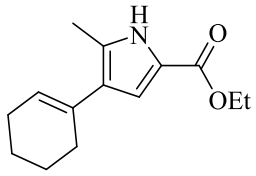
Synthesis of ethyl 3,4-di(thiophen-2-yl)-pyrrole-2-carboxylate (Table 2.5, 2d)



1,3-diimine synthesis followed general procedure using Ti precatalyst **B** (30.8 mg, 10 mol%), aniline (180 μL, 2 mmol), 1,2-di(thiophene-2-yl)ethyne (190 mg, 1 mmol) and heating at 100 °C for 48 h. Method A: The pyrrole was afforded (112 mg, 37%) as a yellow solid. M.p. 109-111 °C. ^{1}H NMR ($CDCl_3$) δ 9.33 (1H, br s, N-H pyrrole), 7.38 (1H, dd, J_{HH} = 5.1 Hz, 1.1 Hz, C-H

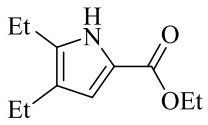
thiophene), 7.15 (1H, d, J_{HH} = 3.3 Hz, C-H pyrrole), 7.11 (1H, dd, J_{HH} = 5.1 Hz, 1.1 Hz, C-H thiophene), 7.07 (1H, dd, J_{HH} = 5.1 Hz, 3.3 Hz, C-H thiophene), 7.02 (1H, dd, J_{HH} = 3.3 Hz, 1.1 Hz, C-H thiophene), 6.91 (1H, dd, J_{HH} = 5.1 Hz, 3.3 Hz, C-H thiophene), 6.78 (1H, dd, J_{HH} = 3.3 Hz, 1.1 Hz, C-H thiophene), 4.22 (2H, q, J_{HH} = 7.2 Hz, CH_2), 1.19 (3H, t, J_{HH} = 7.2 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 160.7, 136.0, 134.3, 128.6, 127.0, 126.6, 126.1, 124.2, 123.8, 121.7, 121.6, 120.8, 119.7, 60.5, 14.0. Elemental analysis: found %C 59.16, %H 4.68, %N 4.51; calcd. %C 59.38, %H 4.32, %N 4.62. This compound was also characterized by single crystal X-ray diffraction: CCDC #1417571.

Synthesis of ethyl 4-(cyclohexen-1-yl)-5-methyl-pyrrole-2-carboxylate (Table 2.5, 2e)



1,3-diimine synthesis followed general procedure using Ti precatalyst **B** (30.8 mg, 10 mol%), aniline (180 μL, 2 mmol), 1-(cyclohex-1-enyl)propyne (135 μL, 1 mmol) and heating at 100 °C for 48 h. Method A: The pyrrole was afforded (142 mg, 61%) as a light brown solid. M.p. 99-100 °C. ^1H NMR ($CDCl_3$) δ 8.94 (1H, br s, N-H pyrrole), 6.78 (1H, d, J_{HH} = 2.8 Hz, C-H pyrrole), 5.67-5.69 (1H, m, C-H alkene), δ 4.27 (2H, q, J_{HH} = 7.2 Hz, CH_2), 2.32 (3H, s, CH_3), 2.24-2.27 (2H, m, CH_2), 2.12-2.16 (2H, m, CH_2), 1.69-1.73 (2H, m, CH_2), 1.59-1.63 (2H, m, CH_2), 1.32 (3H, t, J_{HH} = 7.2 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 161.2, 134.5, 128.7, 126.5, 125.3, 123.7, 119.4, 112.4, 60.5, 14.4. Elemental analysis: found %C 72.13, %H 8.13, %N 6.08; calcd. %C 72.07, %H 8.21, %N 6.00. This compound was also characterized by single crystal X-ray diffraction: CCDC #1417570.

Synthesis of ethyl 4,5-diethyl-pyrrole-2-carboxylate (Table 2.5, 2f)



1,3-diimine synthesis followed general procedure using Ti precatalyst **B** (30.8 mg, 10 mol%), aniline (180 μL, 2 mmol), 3-hexyne (114 μL, 1 mmol) and heating at 100 °C for 48 h. Method A: The pyrrole was afforded (57 mg, 29%) as a brown solid. M.p. 53-54 °C (lit.[32] Mp: 60-62 °C). ^{1}H NMR ($CDCl_3$): δ 8.99 (1H, br s, N-H pyrrole), 6.75 (1H, d, J_{HH} = 2.9 Hz, C-H pyrrole), 4.30 (2H, q, J_{HH} = 7.2 Hz, CH_2), 2.61 (2H, q, J_{HH} = 7.7 Hz, CH_2), 2.40 (2H, q, J_{HH} = 7.5 Hz, CH_2), 1.35 (3H, t, J_{HH} = 7.2 Hz, CH_3), 1.22 (3H, t, J_{HH} = 7.7 Hz, CH_3), 1.17 (3H, t, J_{HH} = 7.5 Hz, CH_3). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 161.3, 135.8, 123.6, 119.7, 115.1, 59.9, 19.2, 18.7, 15.4, 14.6, 13.8. Elemental analysis: found %C 67.85, %H 8.75, %N 7.40; calcd. %C 67.66, %H 8.78, %N 7.17.

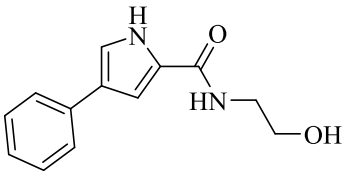
Design of Experiment

The series of experiments reported in **Table 2.2** were conducted using the natural variable setting that corresponds to the scaled valuable shown (i.e. temperature of 70 °C for scaled variable of -1). The yield was determined by a calibrated GC-FID with naphthalene as internal standard. All three component coupling reactions were performed with the same batch of starting materials and the series of experiments were conducted in a random order to remove experimental bias. To assess the experimental bias in the experimental design, a center point (e.g. all scaled variables set to zero) was conducted in triplicate and provided a deviation of less than 2%. A least squares fit model was used to describe the experimental domain and the resulting coefficients can be seen in **equation 3**.

The center points that were performed provide an estimated variance of error (s_i^2) of 0.052. Calculating the error for the coefficients at the 95% confidence level (i.e. t_{crit} = 4.23 for 2 degrees of freedom) using the s_i^2 results in an approximate error of ± 0.22. This is a reasonable error to obtain for coefficients of this magnitude and considering the minimal error shown in the center points.

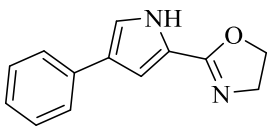
Synthesis of Asymmetric ligand and Catalyst C

N-(2-hydroxyethyl)-4-phenyl-1H-pyrrole-2-carboxamide (4)



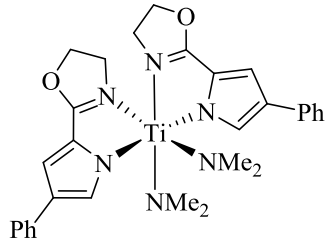
In an oven-dried flask, purged with nitrogen, was added a magnetic stir bar, pyrrole **1a** (333 mg, 1.55 mmol), K_2CO_3 (353 mg, 2.56 mmol), ethanolamine (28 mL, 300 eq), and CH_3CN (14 mL). The solution was refluxed at 105 °C for 6 hours and the resulting solution was added to H_2O (60 mL) and product extracted with three portions of ethyl acetate (20 mL). The organic layers were collected and washed with water and a brine solution. The organic layer was dried with Na_2SO_4, filtered, and volatiles were removed via rotary evaporation to yield product as off white solid (0.284 g, 79%). M.p. 167-169 °C. ^{1}H NMR (MeOH-d^4): δ 7.52 (d, 2H, J = 8.6 Hz, Ar-H), 7.32 (t, 2 H, J = 8.6 Hz, Ar-H), 7.27 (d, 1H, J = 1.8 Hz, C-H pyrrole), 7.18 (app. t, 1H, J = 7.7 Hz, Ar-H), 7.13 (app. d, 1H, J = 1.5 Hz, C-H pyrrole), 3.70 (t, 2H, J = 5.2 Hz, CH_2), 3.48 (t, 2H, J = 5.2 Hz, CH_2).

2-(4-phenyl-1H-pyrrol-2-yl)-4,5-dihydrooxazole (5)



In an oven dried Schlenk flask, purged with nitrogen, was added magnetic stir bar, pyrrole **4** (332 mg, 1.44 mmol), TEA (1.6 mL, 11.5 mmol), DMAP, (36 mg, 0.30 mmol) and CH_2Cl_2 (15 mL). The solution was stirred for 5 minutes, then methanesulfonyl chloride (280 μL, 3.62 mmol) was added drop-wise. After 5 hours at room of stirring at room temperature the reaction is quenched with water, and the product was extracted with 2 portions of CH_2Cl_2. The organic layers were collected and washed sequentially with water and brine solution. The organic layer was dried using Na_2SO_4, filtered, and the volatiles removed via rotary evaporation. The solid was recrystallized in methanol producing yellow solid (152 mg, 50%). M.p. decomp. 230 °C. ^{1}H NMR ($CDCl_3$): δ 10.71 (br s, 1H, N-H pyrrole), 7.53 (dd, 2H, J = 1.5 Hz, 8.4 Hz, Ar-H), 7.36 (t, 2 H, J = 6.9 Hz, Ar-H), 7.23 (app. s, 1H, C-H pyrrole), 7.21 (app. t, 1H, Ar-H), 7.06 (d, 1H, J = 1.5 Hz, C-H pyrrole), 4.47 (t, 2H, J = 9.9 Hz, CH_2), 4.09 (t, 2H, J = 9.9 Hz, CH_2). ^{13}C NMR ($CDCl_3$): δ 159.5, 134.9, 128.7, 126.2, 126.0, 125.2, 120.8, 119.0, 110.4, 67.7, 54.1.

Titanium catalyst (C)



In an Mbraun glovebox, a vial containing $Ti(NMe)_4$ (245 mg, 1.1 mmol) and ether (9 mL) was chilled in a cold well. This solution was added dropwise to a filter flask containing ligand **5** and ether (30 mL). The reaction was stirred for 16 h at room temperature and volatiles were removed. The crude oil product was recrystallized by ether layered with pentane producing brick red colored crystals (300 mg, 25%). ^{1}H NMR ($CDCl_3$): δ 7.71 (s, 2H, C-H pyrrole), 7.62 (d, 4H, J = 7.8 Hz, Ar-H), 7.34 (t, 4 H, J = 7.8 Hz, Ar-H), 7.14 (t, 2H, J = 7.8 Hz, Ar-H), 6.91 (d, 2H, J = 1.4 Hz, C-H pyrrole), 4.45 (m, 4H, CH_2), 3.58 (m, 2H, C-H), 3.47 (s, 12H, CH_3), 3.15 (q, 2H, J =

9.5 Hz, C-H). ^{13}C NMR ($CDCl_3$): δ 166.6, 136.5, 131.3, 128.6, 126.3, 125.6, 124.8, 124.8, 107.4, 70.8, 50.0, 47.3. This compound was also characterized by single crystal X-ray diffraction: un-submitted.

General Procedure for Pyrazole Synthesis

In an Mbraun glovebox, a pressure tube was charged with Ti-catalyst **C** (15 mol%, 83.7 mg) solution in toluene (2 mL). Phenylhydrazine (98 μL, 1 mmol), 1-phenylpropyne (125 μL, 1 mmol), and cyclohexylisonitrile (186 μL, 1.5 mmol) were then added in that sequence. The pressure tube was sealed, removed from the glovebox, and heated in an oil bath at 100 °C for 36 hours. The resulting solution was analyzed by GC-MS and revealed masses corresponding to hydrohydrazination (224 m/z) and pyrazole (234 m/z) formation.

REFERENCES

REFERENCES

(1) a) Woodward, R. B.; Ayer, W. A.; Beaton, J. M.; Bickelhaupt, F.; Bonnett, R.; Buchschacher, P.; Closs, G. L.; Dutler, H.; Hannah, J.; Hauck, F. P.; Ito, S.; Langemann, A.; Legoff, E.; Leimgruber, W.; Lwowski, W.; Sauer, J.; Valenta, Z.; Volz, H. *Journal of the American Chemical Society* **1960**, *82*, 3800-3802. b) Fleming, I. A. N. *Nature* **1967**, *216*, 151-152. c) Murshudov, G. N.; Grebenko, A. I.; Barynin, V.; Dauter, Z.; Wilson, K. S.; Vainshtein, B. K.; Melik-Adamyan, W.; Bravo, J.; Ferrán, J. M.; Ferrer, J. C.; Switala, J.; Loewen, P. C.; Fita, I. *Journal of Biological Chemistry* **1996**, *271*, 8863-8868. d) Rae, T. D.; Goff, H. M. *Journal of Biological Chemistry* **1998**, *273*, 27968-27977. e) Roth, B. D. In *Progress in Medicinal Chemistry*; F.D. King, A. W. O. A. B. R., Scott, L. D., Eds.; Elsevier: 2002; Vol. Volume 40, p 1-22. f) Young, I. S.; Thornton, P. D.; Thompson, A. *Natural Product Reports* **2010**, *27*, 1801-1839. g) Mal, D.; Shome, B.; Dinda, B. K. In *Heterocycles in Natural Product Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: 2011, p 187-220. h) Seiple, I. B.; Su, S.; Young, I. S.; Nakamura, A.; Yamaguchi, J.; Jørgensen, L.; Rodriguez, R. A.; O'Malley, D. P.; Gaich, T.; Köck, M.; Baran, P. S. *Journal of the American Chemical Society* **2011**, *133*, 14710-14726. i) Bhardwaj, V.; Gumber, D.; Abbot, V.; Dhiman, S.; Sharma, P. *RSC Advances* **2015**, *5*, 15233-15266. j) Namba, K.; Takeuchi, K.; Kaihara, Y.; Oda, M.; Nakayama, A.; Nakayama, A.; Yoshida, M.; Tanino, K. *Nat Commun* **2015**, *6*.

(2) Kim, H. J.; Khalimonchuk, O.; Smith, P. M.; Winge, D. R. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research* **2012**, *1823*, 1604-1616.

(3) a) Su, B.; Wang, X.; Wang, J.; Li, X. *Journal of Coordination Chemistry* **2015**, *68*, 4212-4223. b) Liu, J.-Y.; Tao, P.; Wang, Y.-X.; Li, Y.-S. *RSC Advances* **2014**, *4*, 19433-19439. c) Gao, L.; Deligonul, N.; Gray, T. G. *Inorganic Chemistry* **2012**, *51*, 7682-7688. d) Qiao, S.; Ma, W.-A.; Wang, Z.-X. *Journal of Organometallic Chemistry* **2011**, *696*, 2746-2753. e) Bachmann, J.; Nocera, D. G. *Journal of the American Chemical Society* **2004**, *126*, 2829-2837.

(4) Andersen, R. J.; Faulkner, D. J.; He, C. H.; Van Duyne, G. D.; Clardy, J. *Journal of the American Chemical Society* **1985**, *107*, 5492-5495.

(5) a) Vanhuyse, M.; Kluza, J.; Tardy, C.; Otero, G.; Cuevas, C.; Bailly, C.; Lansiaux, A. *Cancer Letters* **2005**, *221*, 165-175. b) Kluza, J.; Marchetti, P.; Bailly, C. In *Modern Alkaloids*; Wiley-VCH Verlag GmbH & Co. KGaA: 2007, p 171-187. c) Yamaguchi, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *Tetrahedron Letters* **2006**, *47*, 3755-3757.

(6) a) Motzer , R. J.; Hutson , T. E.; Tomczak , P.; Michaelson , M. D.; Bukowski , R. M.; Rixe , O.; Oudard , S.; Negrier , S.; Szczylik , C.; Kim , S. T.; Chen , I.; Bycott , P. W.; Baum , C. M.; Figlin , R. A. *New England Journal of Medicine* **2007**, *356*, 115-124. b) Demetri, G. D.; van Oosterom, A. T.; Garrett, C. R.; Blackstein, M. E.; Shah, M. H.; Verweij, J.; McArthur, G.; Judson, I. R.; Heinrich, M. C.; Morgan, J. A.; Desai, J.; Fletcher, C. D.; George, S.; Bello, C. L.; Huang, X.; Baum, C. M.; Casali, P. G. *The Lancet*, *368*, 1329-1338. c) Quek, R.; George, S. *Hematology/Oncology Clinics of North America* **2009**, *23*, 69-78.

(7) a) Knorr, L. *Berichte der deutschen chemischen Gesellschaft* **1884**, *17*, 2863-2870. b) Paal, C. *Berichte der deutschen chemischen Gesellschaft* **1884**, *17*, 2756-2767.

(8) Amarnath, V.; Anthony, D. C.; Amarnath, K.; Valentine, W. M.; Wetterau, L. A.; Graham, D. G. *The Journal of Organic Chemistry* **1991**, *56*, 6924-6931.

(9) Kleinspehn, G. G. *Journal of the American Chemical Society* **1955**, *77*, 1546-1548.

(10) Dhawan, R.; Arndtsen, B. A. *Journal of the American Chemical Society* **2004**, *126*, 468-469.

(11) a) Harris, S. A.; Ciszewski, J. T.; Odom, A. L. *Inorganic Chemistry* **2001**, *40*, 1987-1988. b) Cao, C.; Ciszewski, J. T.; Odom, A. L. *Organometallics* **2001**, *20*, 5011-5013. c) Cao, C.; Shi, Y.; Odom, A. L. *Organic Letters* **2002**, *4*, 2853-2856. d) Cao, C.; Shi, Y.; Odom, A. L. *Journal of the American Chemical Society* **2003**, *125*, 2880-2881. e) Cao, C.; Li, Y.; Shi, Y.; Odom, A. L. *Chemical Communications* **2004**, 2002-2003. f) Li, Y.; Shi, Y.; Odom, A. L. *Journal of the American Chemical Society* **2004**, *126*, 1794-1803. g) Shi, Y.; Cao, C.; Odom, A. L. *Inorganic Chemistry* **2004**, *43*, 275-281. h) Ramanathan, B.; Keith, A. J.; Armstrong, D.; Odom, A. L. *Organic Letters* **2004**, *6*, 2957-2960. i) Banerjee, S.; Shi, Y.; Cao, C.; Odom, A. L. *Journal of Organometallic Chemistry* **2005**, *690*, 5066-5077. j) Banerjee, S.; Odom, A. L. *Organometallics* **2006**, *25*, 3099-3101. k) Swartz, D. L.; Odom, A. L. *Organometallics* **2006**, *25*, 6125-6133. l) Patel, S.; Li, Y.; Odom, A. L. *Inorganic Chemistry* **2007**, *46*, 6373-6381. m) Majumder, S.; Odom, A. L. *Organometallics* **2008**, *27*, 1174-1177. n) Banerjee, S.; Barnea, E.; Odom, A. L. *Organometallics* **2008**, *27*, 1005-1014. o) Swartz Ii, D. L.; Odom, A. L. *Dalton Transactions* **2008**, 4254-4258. p) Swartz Ii, D. L.; Spencer, L. P.; Scott, B. L.; Odom, A. L.; Boncella, J. M. *Dalton Transactions* **2010**, *39*, 6841-6846. q) Dissanayake, A. A.; Odom, A. L. *Chemical Communications* **2012**, *48*, 440-442.

(12) Ackermann, L.; Sandmann, R.; Kaspar, L. T. *Organic Letters* **2009**, *11*, 2031-2034.

(13) a) Odom, A. L.; McDaniel, T. J. *Accounts of Chemical Research* **2015**, *48*, 2822-2833. b) Pasko, C. M.; Dissanayake, A. A.; Billow, B. S.; Odom, A. L. *Tetrahedron* **2016**, *72*, 1168-1176.

(14) a) Shi, Y.; Hall, C.; Ciszewski, J. T.; Cao, C.; Odom, A. L. *Chemical Communications* **2003**, 586-587. b) Novak, A.; Blake, A. J.; Wilson, C.; Love, J. B. *Chemical Communications* **2002**, 2796-2797.

(15) Littler, B. J.; Miller, M. A.; Hung, C.-H.; Wagner, R. W.; O'Shea, D. F.; Boyle, P. D.; Lindsey, J. S. *The Journal of Organic Chemistry* **1999**, *64*, 1391-1396.

(16) Mataka, S.; Takahashi, K.; Tsuda, Y.; Tashiro, M. *Synthesis* **1982**, *1982*, 157-159.

(17) Carlson, R.; Carlson, J. E. In *Data Handling in Science and Technology*; Rolf, C., Johan, E. C., Eds.; Elsevier: 2005; Vol. Volume 24, p ix-x.

(18) a) Giuseppone, N.; Schmitt, J.-L.; Schwartz, E.; Lehn, J.-M. *Journal of the American Chemical Society* **2005**, *127*, 5528-5539. b) Chen, C.-W.; Tseng, M.-C.; Hsiao, S.-K.; Chen, W.-

H.; Chu, Y.-H. *Organic & Biomolecular Chemistry* **2011**, *9*, 4188-4193. c) Wilhelms, N.; Kulchat, S.; Lehn, J.-M. *Helvetica Chimica Acta* **2012**, *95*, 2635-2651. d) Gökcan, H.; Konuklar, F. A. S. *Journal of Molecular Graphics and Modelling* **2014**, *51*, 173-183. e) Ciaccia, M.; Cacciapaglia, R.; Mencarelli, P.; Mandolini, L.; Di Stefano, S. *Chemical Science* **2013**, *4*, 2253-2261.

(19) a) Tóth, G.; Pintér, I.; Messmer, A. *Tetrahedron Letters* **1974**, *15*, 735-738. b) Ciaccia, M.; Di Stefano, S. *Organic & Biomolecular Chemistry* **2015**, *13*, 646-654. c) Ciaccia, M.; Pilati, S.; Cacciapaglia, R.; Mandolini, L.; Di Stefano, S. *Organic & Biomolecular Chemistry* **2014**, *12*, 3282-3287.

(20) M. McInnes, J.; J. Blake, A.; Mountford, P. *Journal of the Chemical Society, Dalton Transactions* **1998**, 3623-3628.

(21) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chemical Reviews* **2007**, *107*, 5416-5470.

(22) a) Meyer, K. E.; Walsh, P. J.; Bergman, R. G. *Journal of the American Chemical Society* **1995**, *117*, 974-985. b) Cantrell, G. K.; Meyer, T. Y. *Organometallics* **1997**, *16*, 5381-5383. c) J. Blake, A.; E. Collier, P.; C. Dunn, S.; Li, W.-S.; Mountford, P.; V. Shishkin, O. *Journal of the Chemical Society, Dalton Transactions* **1997**, 1549-1558. d) Cantrell, G. K.; Meyer, T. Y. *Journal of the American Chemical Society* **1998**, *120*, 8035-8042. e) McInnes, J. M.; Mountford, P. *Chemical Communications* **1998**, 1669-1670. f) Burland, M. C.; Pontz, T. W.; Meyer, T. Y. *Organometallics* **2002**, *21*, 1933-1941.

(23) a) Pretsch, E. œ.; B©*hlmann, P.; Badertscher, M.; 4th, rev. and enl. ed.; Springer,: Berlin, 2009, p xv, 433 p. b) Page, T. F.; Alger, T.; Grant, D. M. *Journal of the American Chemical Society* **1965**, *87*, 5333-5339.

(24) a) Katritzky, A. R.; Ostercamp, D. L.; Yousaf, T. I. *Tetrahedron* **1987**, *43*, 5171-5186. b) Agosta, W. C. *The Journal of Organic Chemistry* **1961**, *26*, 1724-1728. c) Mothana, B.; Boyd, R. J. *Journal of Molecular Structure: THEOCHEM* **2007**, *811*, 97-107. d) Snyder, S. A.; Kontes, F.; ElSohly, A. M. *Heterocycles* **2012**, *84*, 265-274.

(25) Bouérat, L.; Fensholdt, J.; Liang, X.; Havez, S.; Nielsen, S. F.; Hansen, J. R.; Bolvig, S.; Andersson, C. *Journal of Medicinal Chemistry* **2005**, *48*, 5412-5414.

(26) Kuuloja, N.; Tois, J.; Franzén, R. *Tetrahedron: Asymmetry* **2011**, *22*, 468-475.

(27) Gupton, J. T.; Krumpe, K. E.; Burnham, B. S.; Dwornik, K. A.; Petrich, S. A.; Du, K. X.; Bruce, M. A.; Vu, P.; Vargas, M.; Keertikar, K. M.; Hosein, K. N.; Jones, C. R.; Sikorski, J. A. *Tetrahedron* **1998**, *54*, 5075-5088.

(28) a) Mujkic, M.; Lentz, D. *Dalton Transactions* **2012**, *41*, 839-849. b) Aksın-Artok, Ö.; Krause, N. *Advanced Synthesis & Catalysis* **2011**, *353*, 385-391. c) Ban, H. S.; Minegishi, H.; Shimizu, K.; Maruyama, M.; Yasui, Y.; Nakamura, H. *ChemMedChem* **2010**, *5*, 1236-1241. d) Mio, M. J.; Kopel, L. C.; Braun, J. B.; Gadzikwa, T. L.; Hull, K. L.; Brisbois, R. G.; Markworth,

C. J.; Grieco, P. A. *Organic Letters* **2002**, *4*, 3199-3202. e) Marshall, J. A.; Cleary, D. G. *The Journal of Organic Chemistry* **1986**, *51*, 858-863.

(29) Weber, W. P.; Gokel, G. W.; SpringerLink (Online service) In *Reactivity and Structure: Concepts in Organic Chemistry,*; Springer Berlin Heidelberg,: Berlin, Heidelberg, 1977.

(30) Gupton, J. T.; Krolikowski, D. A.; Yu, R. H.; Riesinger, S. W.; Sikorski, J. A. *The Journal of Organic Chemistry* **1990**, *55*, 4735-4740.

(31) Handy, S. T.; Zhang, Y.; Bregman, H. *The Journal of Organic Chemistry* **2004**, *69*, 2362-2366.

(32) Chapman, R. A.; Roomi, M. W.; Morton, T. C.; Krajcarski, D. T.; MacDonald, S. F. *Canadian Journal of Chemistry* **1971**, *49*, 3544-3564.

CHAPTER 3. N-ALKYLATED PYRROLES FROM TITANIUM CATALYZED MCR AND APPLICATION TO NATURAL PRODUCT DERIVATIVES

3.1 Introduction

Nature is uniquely qualified at supplying early formulations of biologically active (BA) compounds and active pharmaceutical ingredients (API). Upon rigorous isolation of these natural products (NP), biological testing is performed to ascertain activity for compounds against bacteria,[1] funguses,[2] viruses,[3] and cancers.[4] A frequent motif in these BA compounds is a heterocycle moiety; for example, pyrroles.[5] As was discussed briefly in the previous chapter, several classes of marine based NP's such as lukianols,[6] lamellarins,[7] storniamide,[8] and rhazinilam[9] have been discovered over the past few decades (**Figure 3.1**).

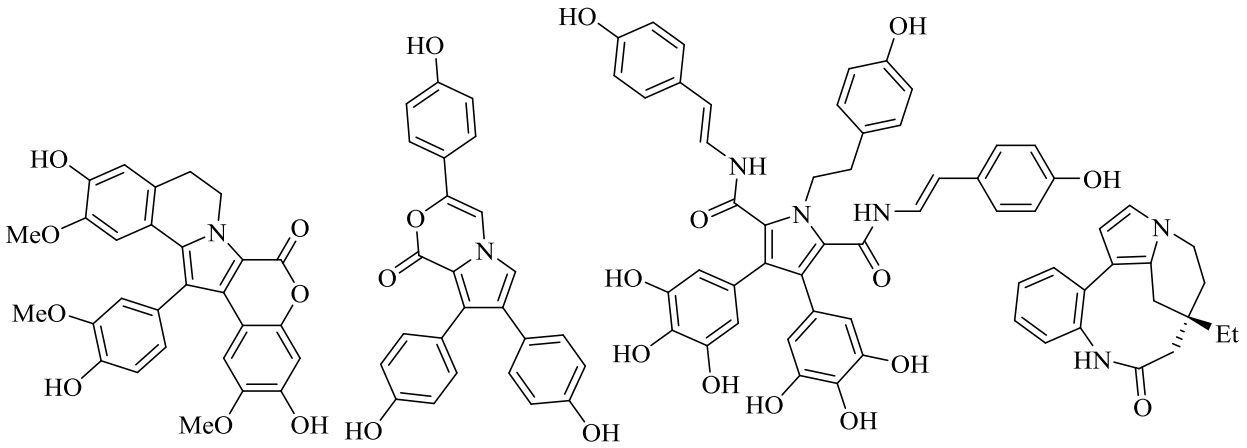


Figure 3.1 Marine based natural products isolated from sponges, tunicates, and plants.

Marine based NP's, and lamellarins in particular, have exhibited exciting levels of biological activity towards drug-resistant strains of cancer.[10] This important area of study is retarded by the low-abundance of material that often plagues isolation from natural sources. Several groups have proposed unique paths to synthesize the BA NP's that follow two distinct philosophies. Either (a) the pyrrole moiety is modified via couplings of alkyl halides and electrophilic aromatic

substitutions reactions or (b) the pyrrole is formed through a cyclo addition/condensation type reaction (**Figure 3.2**).

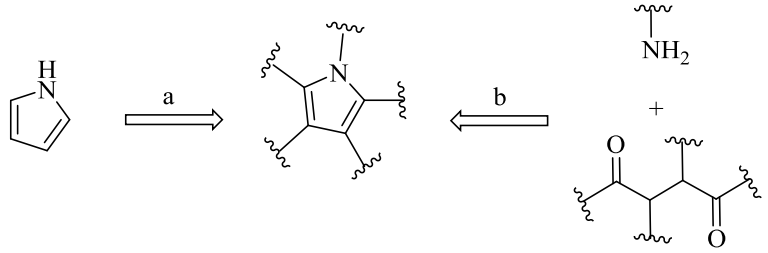
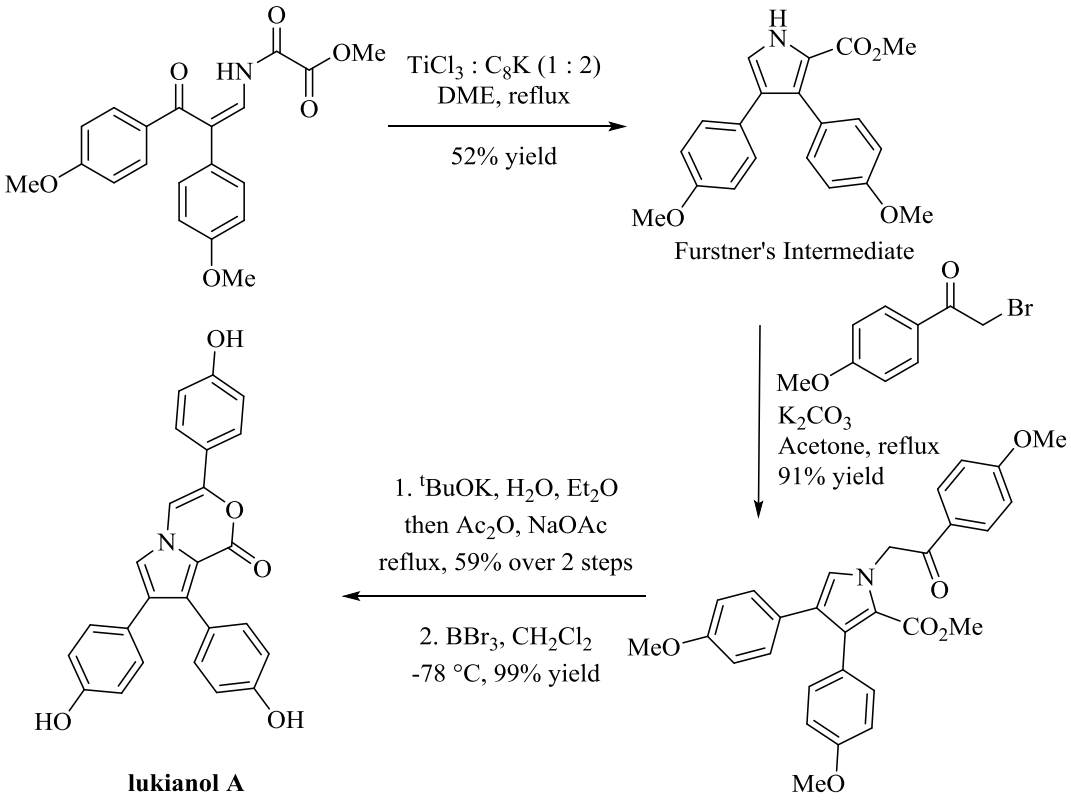


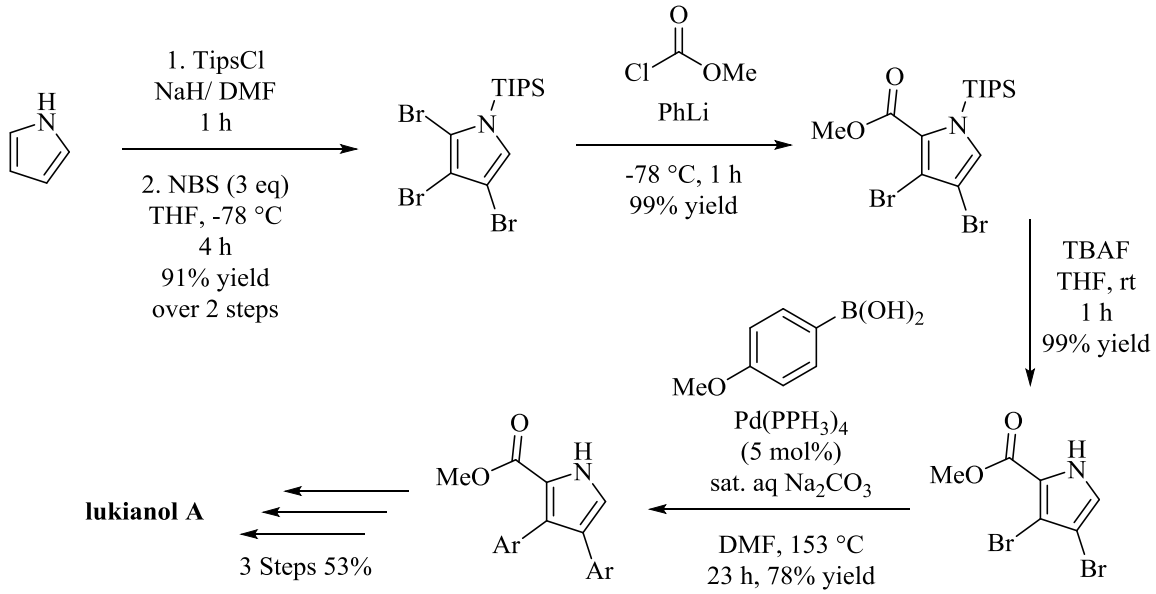
Figure 3.2 Construction of pyrrole containing compounds via two distinct paths.

The juxtaposition between these two procedures is best shown through the synthesis of a single natural product. The total synthesis of lukianol A was first performed by Furstner and co-workers in 1995 using an intriguing chemoselective reductive coupling, mediated by Ti-graphite, as the key step (**Scheme 3.1**).[11]

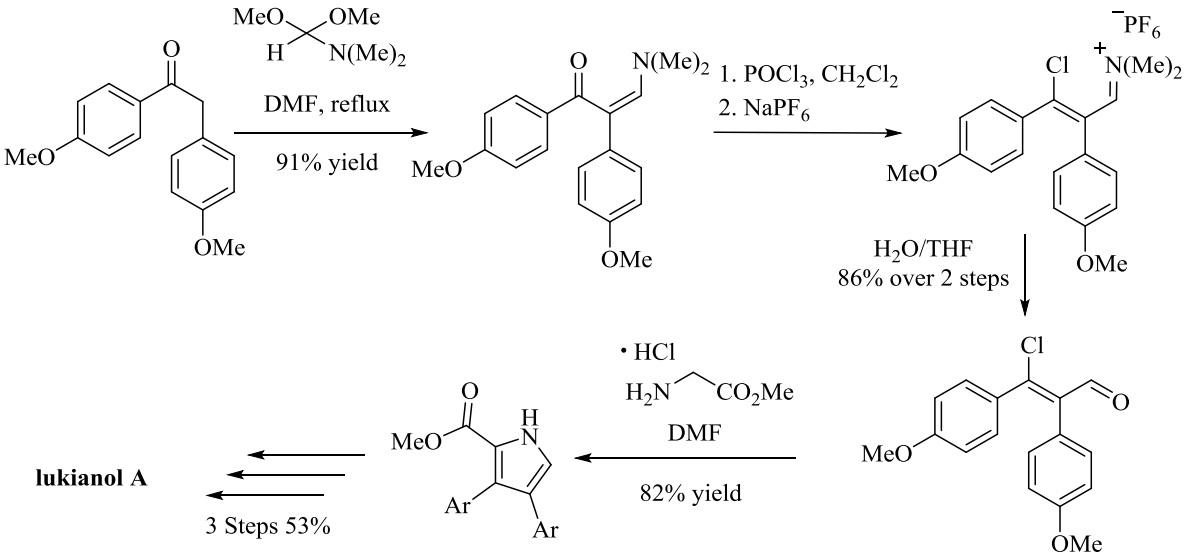


Scheme 3.1 Furstner's synthesis of lukianol A[11]

Since Furstener's publication, the key 3,4-biaryl intermediate has been a popular synthetic target.[5] Banwell et al., synthesized Furstner's intermediate in a sequential manor, starting from pyrrole, using multiple cross coupling reactions (**Scheme 3.2**).[6a] Through a strategy of selective bromination at the 3,4-positions using triisopropylsilylchloride; the general 3,4-biaryl pyrrole intermediate was formed and lukianol A was formed at 37% yield over 8 steps. Gupton and co-workers provided a different route reacting β-chloroenealdehydes with methylglycinate hydrochloride (**Scheme 3.3**).[12] This alternate route provides the same 3,4-biaryl intermediate that can be transformed using Fuerstner's synthesis to lukianol A, offering the NP in 36% yield over 7 steps.



Scheme 3.2 Banwell's synthesis of lukianol A from pyrrole starting material[6a]

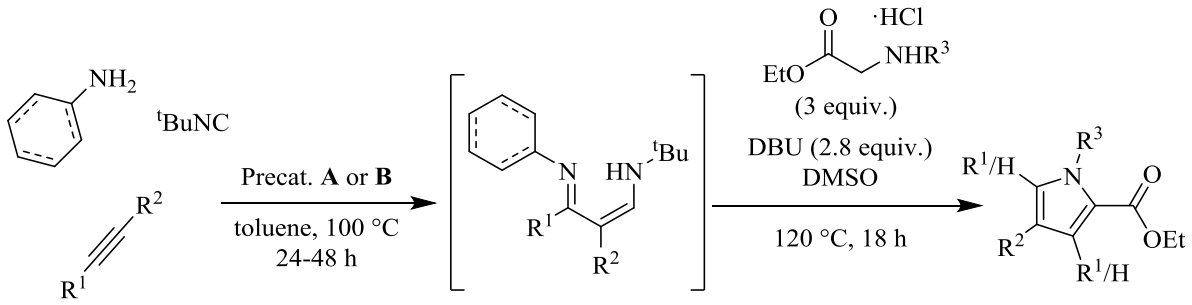


Scheme 3.3 Gupton's synthesis of Furstner's intermediate.

Intermediates that can be generated in the fewest amounts of steps from commercially available materials pose a great advantage to lengthy sequential type syntheses. Therefore, a strategy using MCC is ideal for conserving steps, enhancing efficiency of producing key intermediates, and improves atom economy. Herein, the synthesis of N-alkylated pyrroles from MCR intermediates is described along with the current progress to key natural product motifs.

3.2 Results and Discussion

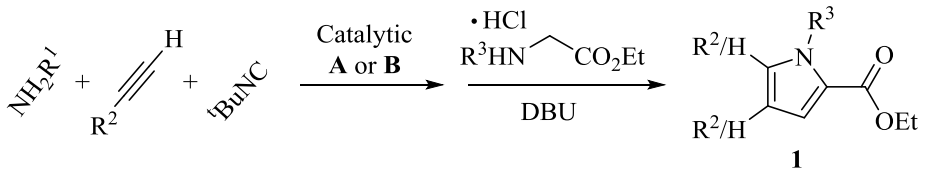
This investigation was identified as unique from Chapter 2, as observed regioselectivities for several derivatives deviate from the model proposed for glycine condensation on to 3CC intermediates. Also, the appearance of a byproduct in certain substrates reveals a competition between two reactions. Several N-substituted glycine derivatives (R^2 = Me, Bn, Ph, Cy, ^{t}Bu) were investigated for possible generation of N-alkylated pyrroles (**Scheme 3.4**).

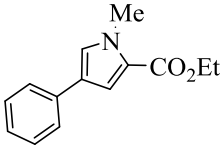
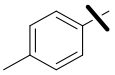
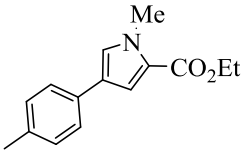
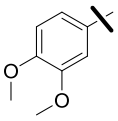
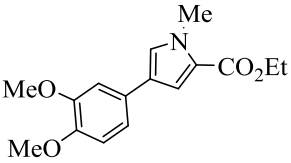
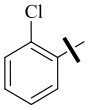
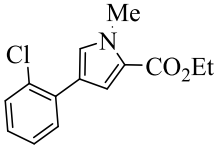
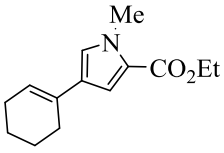
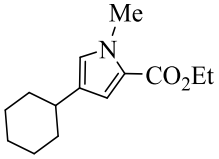
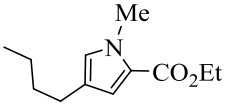
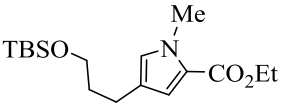


Scheme 3.4 Conditions for forming N-alkylated pyrroles from 3CC intermediate.

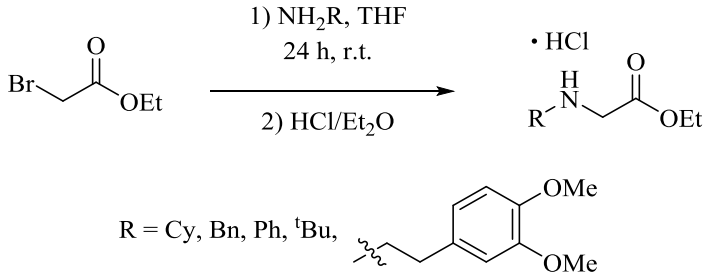
The catalysts implemented for MCC used in this study are the same as those previously described (Chapter 2) with the same designations, $Ti(NMe_2)_2$dpma (**A**) and $Ti(NMe_2)_2$dpm (**B**). The optimized conditions for the ethyl glycinate pyrrole formation reaction were mimicked for all ethyl sarcosinate derivatives. A similar substrate scope was carried out to identify the generality for this reaction (**Table 3.1**).

Table 3.1 Examples of tri-substituted pyrrole-2-carboxylates using the optimized conditions.



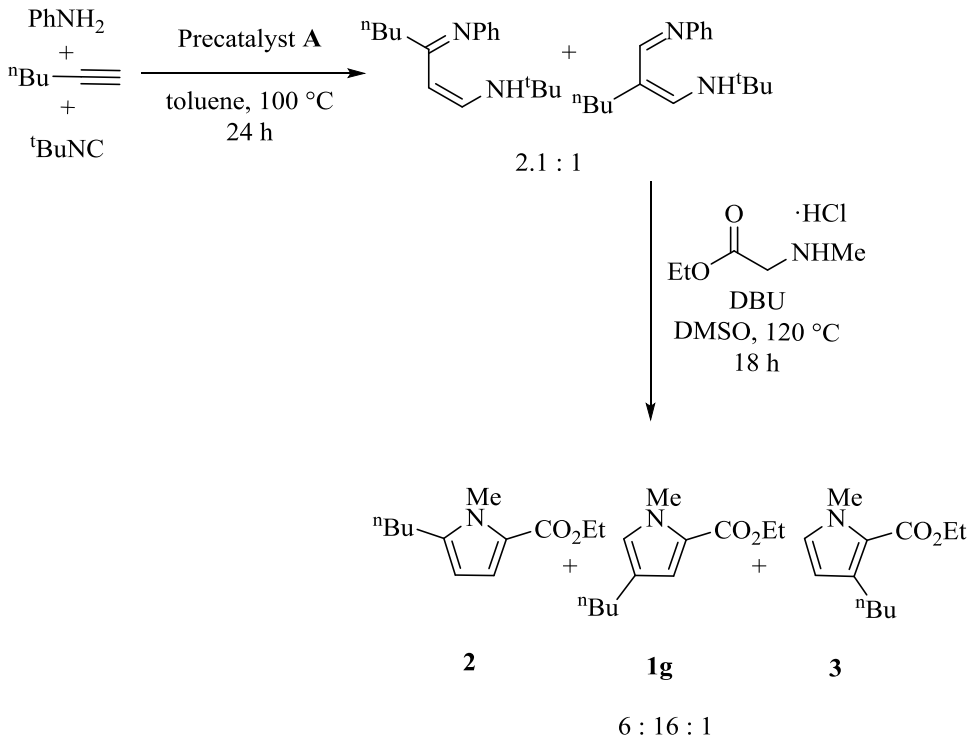
Entry	R^1	R^2	R^3	Catalyst	Product	Yield (%)
1a	Cy		Me	**A**		64
1b	Cy		Me	**A**		68
1c	Cy		Me	**A**		64
1d	Cy		Me	**A**		63
1e	Cy		Me	**A**		30
1f	Cy		Me	**B**		35
1g	Cy		Me	**B**		22
1h	Ph		Me	**B**		13

Glycinate derivatives can be made in gram quantities with relative ease (**Scheme 3.5**).[13] Unfortunately, it became abundantly clear early on that N-alkylated glycinate compounds with substitutions larger than methyl preferred unfavorable side reactions. In other words, ethyl sarcosinate was the only glycine derivative that supplied pyrroles in modest to good yields. In all other cases it is believed that either the nitrogen is too sterically hindered (i.e. R^3 = Cy or ^{t}Bu) or electronically less nucleophilic (i.e. R^3 = Ph). It is unclear as to why the benzyl glycinate derivative is also incapable of pyrrole formation as it is fairly similar to methyl and ethyl in terms of both sterics and electronics.



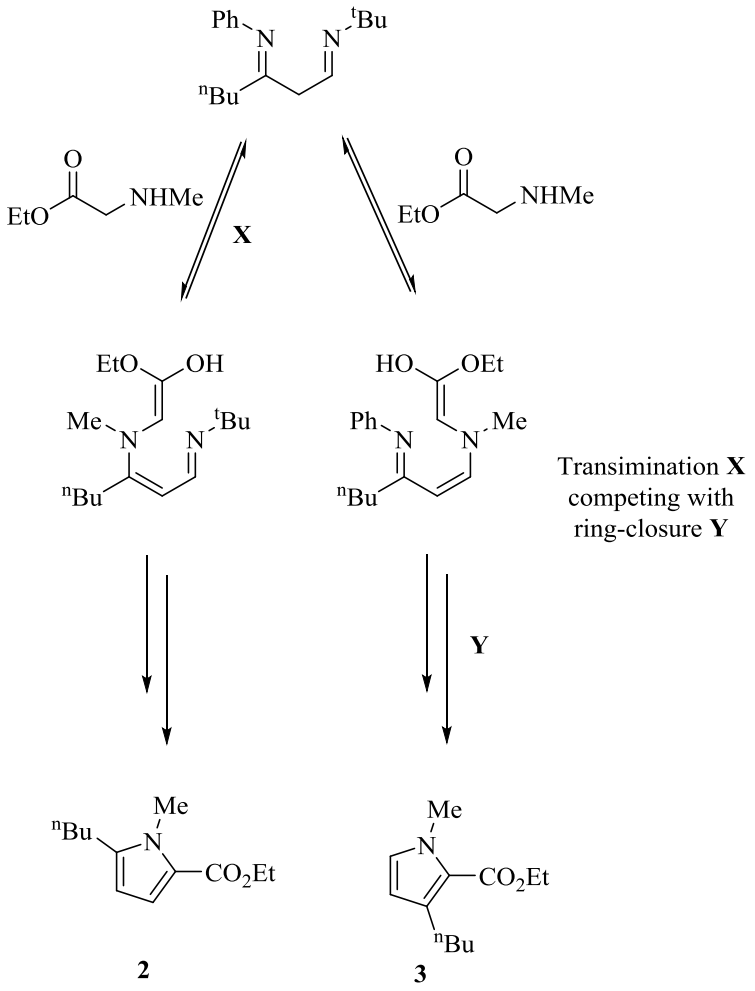
Scheme 3.5 Synthesis of ethyl glycinate derivatives.[13]

An interesting observation is the appearance of 3 isomers for 1-hexyne derived product **1g** (**Scheme 3.6**). A mixture of 2 isomers is obtained in the 3CC formation reaction, which leads to the possibility of a 1,2,5- (**2**), 1,2,4- (**1g**), and 1,2,3-substituted pyrrole (**3**). Products **2** and **3** result from the condensation of ethyl sarcosinate on to keto-aldimine 3CC. To assess the extent of regioselectivity, 3CC conditions that promote keto-aldimine product where used. The distribution of products was determined by GC-FID and compounds verified via comparison to methylation of ethyl 5-butyl-pyrrole-2-carboxylate using sodium hydride and methyl iodide (**2**).



Scheme 3.6 Regioselectivities using ethyl sarcosinate.

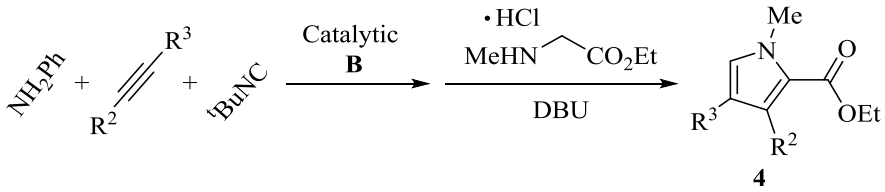
This is the first appearance of isomer **3**, which was not observed when using ethyl glycinate. This is believed to be caused by the slow cyclization of glycinate methylene to ketimine carbon (see Chapter 2). If the *N*-methyl group on sarcosinate is increasing sterics, it may mean that transimination at the ketimine site may now be in competition with the cyclization of methylene carbon (**Scheme 3.7**).



Scheme 3.7 Competition between transimination **X** and ring-closure **Y**.

This chemistry was extended to internal alkynes that have the potential to exhibit multiple isomers, which was previously unobserved. All substrates exhibited a 1,2,3,4-tetrasubstituted pyrrole scaffold as the major isomer, including those substrates that previously held the 3-position unsubstituted (**Table 3.2**). Regiochemistry was confirmed by coupled-HSQC of compounds **4a-4c** (**Table 3.3**), and X-ray crystal data of compound **4b** (**Figure 3.3**).

Table 3.2 Examples of 1,2,3,4-tetrasubstituted pyrrole-2-carboxylates in poor yields.



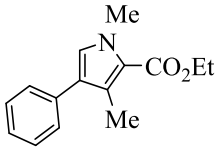
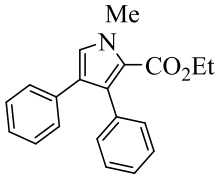
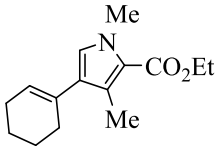
Entry	R^2	R^3	Product	Yield(%)[a]
4a	Me			32
4b				27
4c	Me			25

Table 3.3 C-H coupling constants for compounds **4a**-**4c**.

Compound	C-H pyrrole $^1J_{CH}$ coupling	C–H assignment (α or β)
4a	189 Hz	β
4b	189 Hz	β*
4c	187 Hz	β

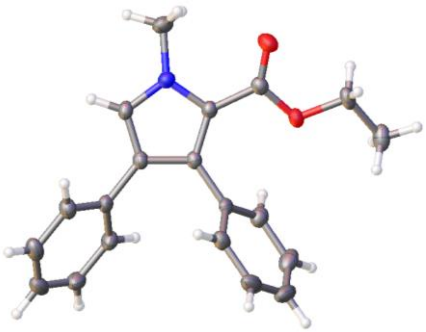
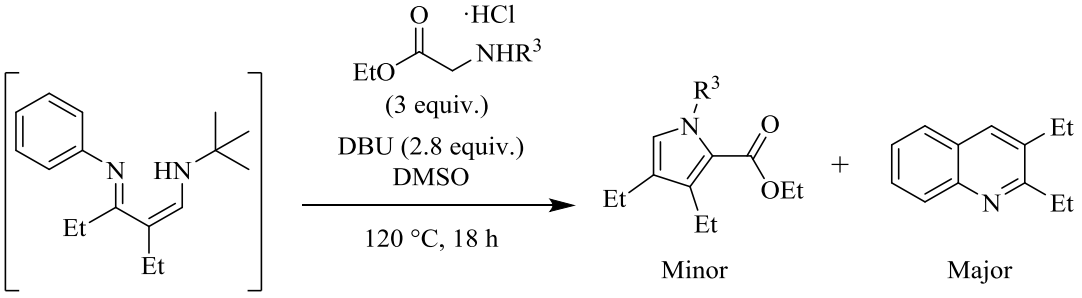


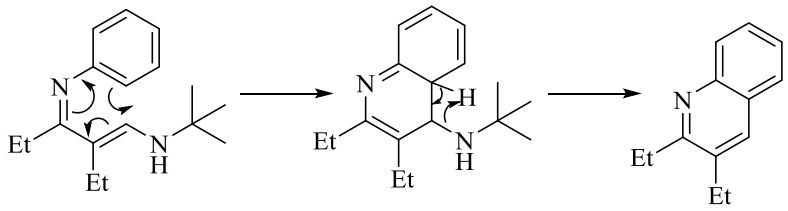
Figure 3.3 Xray-crystal structure of compound **4b**

Other internal alkynes were evaluated, but produced a byproduct that was quite surprising. Quinoline formation is a well precedented reaction for *N*-aryl 1,3-diimines.[14] Conditions previously reported were harsh, using concentrated acetic acid at 150 °C for 16 h or more for complete conversion. It was first noticed when substrate 3-hexyne was used, resulting in quinoline being the major product (**Scheme 3.8**).



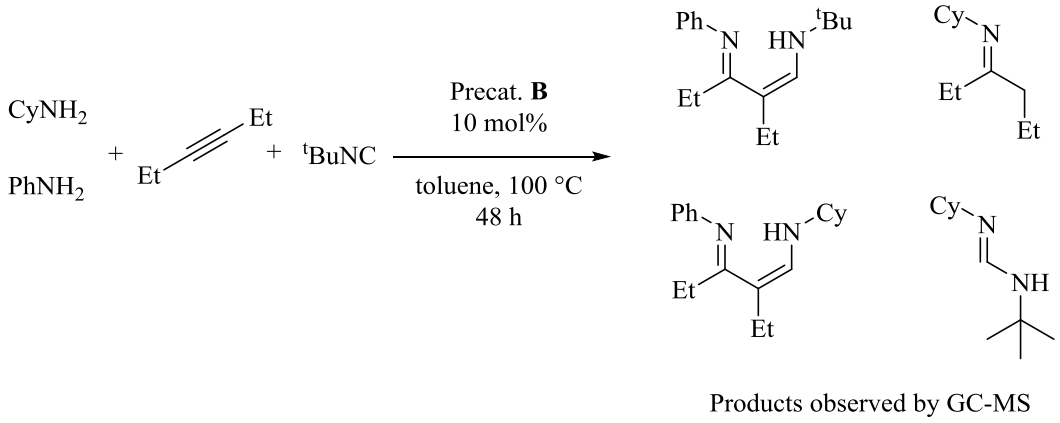
Scheme 3.8 Quinoline formation over pyrrole formation

Formation of quinoline occurs via a 6π electron cyclization followed by elimination of *tert*-butylamine to aromatize the molecule (**Scheme 3.9**).[15] This is an intramolecular reaction that is in direct competition with transimination of sarcosine. It is unclear why particular derivatives have higher observable quantities of quinoline formation. To obviate this problem, several strategies were attempted. The amine choice was the most obvious place to start so aniline was replaced with a host of potential candidates. Unfortunately, use of a non-arylamines produced poor conversion to 3CC and increased byproducts of the MCC (hydroamination). Aniline derivatives that blocked both the 2- and 6-position suffered the same problems as non-arylamines. All other aniline derivatives provided quinoline as the major product.



Scheme 3.9 6π electrocyclization to form quinolines.

Next, attempts were made to transiminate the arylamine with an amine source incapable of performing quinoline formation (i.e. alkyl amines). Several experiments were conducted that involved adding two amines, aniline and cyclohexylamine, in to the initial 3CC reaction. The amount of aniline was reduced in each experiment while cyclohexylamine was consistently added as a full equivalent to alkyne (**Scheme 3.10**).

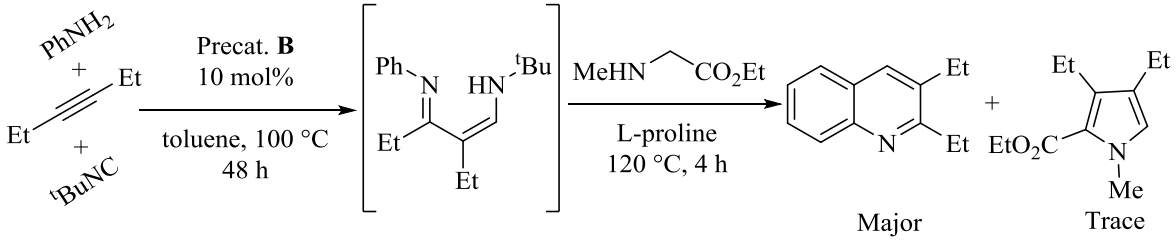


Scheme 3.10 in situ Transimination of 3CC with observable products

The expectation was for aniline to form the 3CC, as it is more efficient in doing so with internal alkynes; then, cyclohexylamine would transiminate with the arylamine due to differences in nucleophilicity.[16] However, such transimination was not observed and only replacement of *tert*-butylamine by cyclohexylamine could be seen in the GC-MS. Even more dissatisfying is when aniline equivalents were decreased, less 3CC product was formed and more hydroamination with cyclohexylamine occurred. To completely eliminate this strategy as a feasible alternative to

general reaction conditions, the 3CC was formed using only aniline, 3-hexyne, and *tert*-butylisonitrile in one step, followed by subsequent addition of cyclohexylamine. The effective transimination did not take place at the ketimine site and only replacement of *tert*-butylamine was observed as in the previous cases. This deviation from Di Stefano's findings on transimination of imines maybe a unique feature of asymmetric 1,3-diimines.

The last attempt was to use a known transimination catalyst to encourage replacement of aniline with ethyl sarcosinate. L-proline has a rich history as an organocatalysis for asymmetric induction in enolate alkylation chemistry.[17] Lehn and co-workers discovered that L-proline also functions as an effective transimination catalyst for mono-imines.[18] Therefore diethyl 3CC intermediate was reacted with the free base of sarcosinate (3 equivalents) and L-proline (1 equivalent) (**Scheme 3.11**). Interestingly, after only 4 h, all 3CC was consumed and the major product was quinoline formation. It seems that transimination at the aldimine sight, by L-proline, occurs readily and this catalyzes the 6π electrocyclization.



Scheme 3.11 Organocatalyzed 3CC transformation to Quinoline

Although improvements to this method are required, this chemistry can be adapted to the total synthesis of NP lamellarins. As a model compound, lamellarin G trimethyl ether was analyzed for a convenient and short total synthesis (**Figure 3.4**). The key steps in this analysis are the pyrrole formation utilizing this methodology and a dual biaryl-coupling that can be accomplished through hypervalent iodides.[8b,19] All starting materials are commercially available; however, for practical

purposes, the glycinate[13] and alkyne[20] were synthesized using literature procedures. If this methodology works, and that is the famous last words of a chemist, then this will be the shortest synthesis of lamellarin G trimethyl ether from commercially available materials to date. Additional benefits of this route is the high level of modularity, which will allow access to multiple lamellarin NP's for expedient structure activity relationships, and high atom economy.

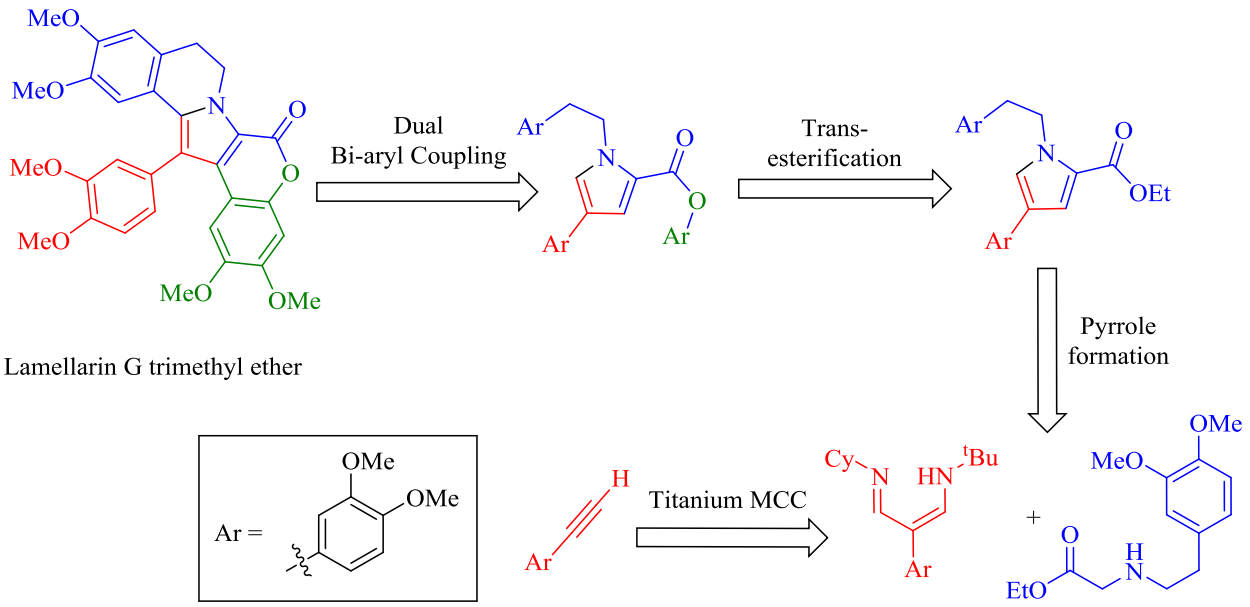
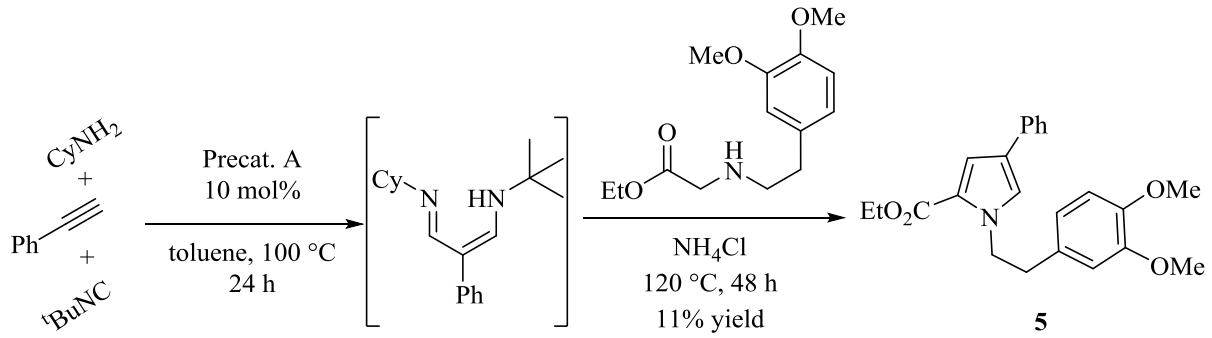


Figure 3.4 Retrosynthetic analysis of lamellarin G trimethyl ether.

Before attempting this synthesis with 3,4-dimethoxyphenylacetylene, phenylacetylene (less expensive alkyne) was used to test the efficacy of the method. The 3CC forms well with minimal formation of common byproducts (i.e. formamide, hydroamination, 4CC). Condensation of glycinate derivative shown above occurs sluggishly with 3CC as was observed previously, *de qua supra*. After 48 h the 3CC is consumed and multiple unidentified byproducts have appeared over the course of the reaction. Pyrrole **5** was isolated in only 11% yield and the reaction had low levels

of reproducibility (**Scheme 3.12**). Attempts with starting alkyne 3,4-dimethoxyphenylacetlyene provided product observable by GC-MS as trace amount.



Scheme 3.12 Synthesis of N-alkylated pyrrole **5**

3.3 Conclusion

Modification of glycinate derivative occurs with distinct regioselectivities that were unobserved for most substrates in previous investigations (see Chapter 2). For internal alkynes, this regioselectivity matches observations by Gupton et al.[12] Gupton sites the increased steric at the middle carbon of the vinylogous amidates as the source of regioselectivity, but that explanation was complete conjecture based on the experimental results with no attempts to elucidate underlying causes for the switch. Competing transimination and cyclocondensation reactions is more likely the cause for this observed regioselectivity, but it is difficult to delineate influences for promoting either reaction (**Scheme 3.6**). *N*-methyl pyrroles can be prepared in poor to good yields depending on starting alkyne (i.e. aryl alkynes provided average 65% yield) using this methodology.

As discussed multiple times, transimination plays a vital role in the reactions of 1,3-diimines and a thorough investigation is currently underway. A greater understanding of this area of chemistry will help promote the mainstream use of 1,3-diimine alternatives to classic heterocycle syntheses. The difficulties that occurred during this investigation will be mitigated and will lead to improved yields for key intermediates to the synthesis of lamellarin G trimethyl ether.

3.4 Experimental

General Considerations: All manipulations of air-sensitive compounds were carried out in an MBraun drybox under a purified nitrogen atmosphere. All glassware was heated at 150 °C for 4 h and stored in a drybox under nitrogen. Toluene was purified by first sparging with dry nitrogen to remove oxygen and then running through activated alumina to remove water. ^{1}H and ^{13}C NMR spectra were recorded on a VXR-500 spectrometer in $CDCl_3$. Regiochemistry of compounds **4a-4c** were determined by coupled-HSQC. Melting points were measured on a Mel-Temp II apparatus (Laboratory Devices Inc, USA) with a mercury thermometer in an open capillary tube. Single crystal X-ray diffraction data was collected in the Center for Crystallographic Research at MSU and structures deposited in the Cambridge Crystallographic Data Centre.

Ligands H_2dpma and H_2dpm were prepared by literature methods.[21] $Ti(NMe_2)_2$(dpma) (**A**) and $Ti(NMe_2)_2$(dpm) (**B**) were made following literature procedures.[21a,22] Alkynes were purchased either from Sigma-Aldrich or GFS chemicals and distilled from CaO under dry nitrogen or prepared using Sonogashira coupling.[20,23] Amines were purchased from Sigma-Aldrich and were distilled from KOH under dry nitrogen. Triethylamine (TEA) and ethyl sarcosinate hydrochloride were both purchased from Sigma-Aldrich and used as received. *tert*-Butylisonitrile was prepared from *tert*-butylamine, $CHCl_3$, and aqueous base according to the literature procedure and purified by distillation under dry nitrogen. *tert*-Butyldimethylsilyl chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were purchased from Oakwood Chemicals and used as received. Dimethylsulfoxide (DMSO) was purchased from Fisher Scientific and used as received. Hexanes and ethyl acetate were purchased from Mallinckrodt Chemicals and used as received.

Ethyl sarcosinate was prepared for Methods B and C below by dissolving ethyl sarcosinate hydrochloride in water and adding 2 equivalents of K_2CO_3. The solution was extracted with

dichloromethane in three portions. The combined organic layers were dried and filtered; then, the volatiles were removed by rotary evaporation to give the ethyl sarcosinate as a clear to pale yellow oil.

General Procedure for 1,3-diimine Synthesis

A pressure tube was charged with a magnetic stir bar and Ti precatalyst **A** or **B** (10 mol%) in toluene (2 mL), amine (2 mmol), alkyne (1 mmol), and *tert*-butylisonitrile (1.2 mmol) were added. The pressure tube was sealed, removed from the drybox, and placed into an oil bath preheated to 100-120 °C for 24-48 h. The reaction was removed from the bath, and volatiles were removed in vacuo.

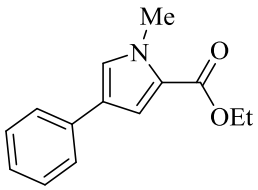
General Procedures for 2-carboxylpyrroles

Method A

The pressure tube from 1,3-diimine formation was charged with ethyl sarcosinate hydrochloride (460 mg, 3 mmol), DBU (420 μL, 2.8 mmol), and DMSO (5 mL). The pressure tube was resealed and heated for 18 h at 120 °C in an oil bath. The reaction was removed from the bath and extracted with DCM (40 mL). The organic layer was washed with 10 % $NaHCO_3$ (30 mL) and with brine (30 mL). The aqueous layers were combined and washed with DCM (40 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, and filtered. Volatiles were removed, and the crude was purified by flash column chromatography on silica gel with hexanes:ethyl acetate (4:1) and 1% TEA to afford the desired product.

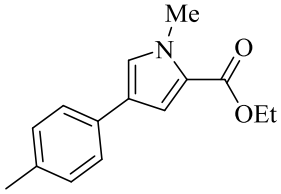
Preparative Details

Synthesis of ethyl 4-phenyl-pyrrole-2-carboxylate (Table 3.1, 1a)



1,3-diimine synthesis followed general procedure using Ti precatalyst **A** (32.4 mg, 10 mol%), cyclohexylamine (230 μL, 2 mmol), phenylacetylene (110 μL, 1 mmol) and heating at 100 °C for 24 h. Method A: The pyrrole was afforded (147 mg, 64%) as a light brown solid. M.p. 51-52 °C (lit.[24] Mp: 52-53 °C). ^{1}H NMR ($CDCl_3$): δ 7.50 (2H, d, 8.8 Hz, Ar-H), 7.35 (2H, t, 7.8 Hz, Ar-H), 7.23 (1H, d, 2.2 Hz, C-H pyrrole), 7.22 (1H, t, 7.8 Hz, Ar-H), 7.08 (1H, d, 2.2 Hz, C-H pyrrole), 4.32 (2H, q, J_{HH} = 7.3 Hz, CH_2), 3.96 (3H, s, CH_3), 1.38 (3H, t, J_{HH} = 7.3 Hz, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 161.3, 134.5, 128.7, 126.1, 126.0, 125.1, 123.9, 123.4, 114.7, 60.0, 37.0, 14.5. Elemental analysis: found %C 73.20, %H 6.92, %N 6.26; calcd. %C 73.34, %H 6.59, %N 6.11.

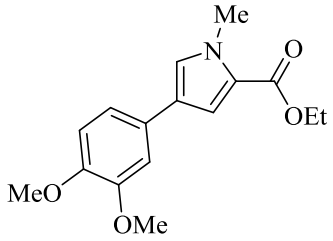
Synthesis of ethyl 4-(p-tolyl)-pyrrole-2-carboxylate (Table 3.1, 1b)



1,3-diimine synthesis followed general procedure using Ti precatalyst **A** (32.4 mg, 10 mol%), cyclohexylamine (230 μL, 2 mmol), 1-ethynyl-4-methylbenzene (127 μL, 1 mmol) and heating at 100 °C for 24 h. Method A: The pyrrole was afforded (165 mg, 68%) as a light orange solid. M.p. 72-74 °C (lit.[24] Mp: 78-79 °C). ^{1}H NMR ($CDCl_3$): δ 7.40 (2H, d, J_{HH} = 8.7 Hz, Ar-H), 7.20 (1H, d, J_{HH} = 2.6 Hz, C-H pyrrole), 7.16 (2H, d, J_{HH} = 8.1 Hz, Ar-H), 7.05 (1H, d, J_{HH} = 2.6 Hz), 4.32 (2H, q, J_{HH} = 7.9 Hz, CH_2), 3.96 (3H, s, CH_3), 2.35 (3H, s, CH_3), 1.38 (3H, t, J_{HH} = 7.9 Hz, CH_3);

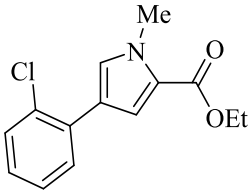
^{13}C {^{1}H} NMR ($CDCl_3$) δ 161.3, 135.7, 131.6, 129.4, 125.9, 125.0, 123.9, 123.3, 114.6, 59.9, 37.0, 21.1, 14.5. HRMS (ES) m/z calcd. for $C_{15}H_{17}NO_2$ 243.1259, found 243.1258.

Synthesis of ethyl 4-(3,4-dimethoxy)phenyl-pyrrole-2-carboxylate (Table 3.1, 1c)



1,3-diimine synthesis followed general procedure using Ti precatalyst **A** (32.4 mg, 10 mol%), cyclohexylamine (230 μL, 2 mmol), 1-ethynyl-3,4-dimethoxybenzene (162 mg, 1 mmol) and heating at 100 °C for 24 h. Method A: The pyrrole was afforded (185 mg, 64%) as a light yellow solid. M.p. 74-75 °C (lit.[24] Mp: 81-82 °C). ^{1}H NMR ($CDCl_3$): δ 7.18 (1H, d, J_{HH} = 2 Hz, C-H pyrrole), 7.05 (1H, dd, J_{HH} = 2 Hz, 7 Hz, Ar-H), 7.02 (2H, dd, J_{HH} = 2 Hz, 5 Hz, Ar-H and C-H pyrrole), 6.88 (1H, d, J_{HH} = 7 Hz, C-H pyrrole), 4.32 (2H, q, J_{HH} = 7.3 Hz, CH_2), 3.97 (3H, s, CH_3), 3.94 (3H, s, CH_3), 3.90 (3H, s, CH_3), 1.39 (3H, t, J_{HH} = 7.3 Hz, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$) δ 161.3, 149.1, 147.6, 127.7, 125.7, 123.9, 123.3, 117.3, 114.5, 111.5, 108.7, 60.0, 56.0, 55.9, 37.0, 14.5. HRMS (ES) m/z calcd. for $C_{16}H_{19}NO_4$ 289.1314, found 289.1310.

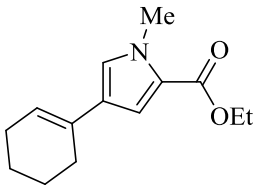
Synthesis of ethyl 4-(3,4-dimethoxy)phenyl-pyrrole-2-carboxylate (Table 3.1, 1d)



1,3-diimine synthesis followed general procedure using Ti precatalyst **A** (32.4 mg, 10 mol%), cyclohexylamine (230 μL, 2 mmol), 1-ethynyl-3,4-dimethoxybenzene (162 mg, 1 mmol) and heating at 100 °C for 24 h. Method A: The pyrrole was afforded (166 mg, 63%) as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.44 (1H, dd, J_{HH} = 1.7 Hz, 8.0 Hz, Ar-H), 7.42 (1H, dd, J_{HH} = 1.2 Hz, 8.0

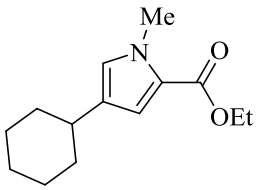
Hz, Ar-H), 7.26 (1H, app. dd, J_{HH} = 1.2 Hz, 8.0 Hz, Ar-H), 7.22 (1H, app. dd, J_{HH} = 1.7 Hz, 8.0 Hz, Ar-H) 7.23 (1H, app. s, C-H pyrrole), 7.17 (1H, dd, J_{HH} = 1.7 Hz, 8.0 Hz, Ar-H), 7.14 (1H, d, J_{HH} = 1.7 Hz), C-H pyrrole), 4.31 (2H, q, J_{HH} = 8.4 Hz, CH_2), 3.98 (3H, s, CH_3), 1.37 (3H, t, J_{HH} = 8.4 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 161.3, 133.4, 131.7, 130.3, 130.1, 129.1, 127.3, 126.9, 122.6, 120.8, 117.7, 60.0, 37.1, 14.5.

Synthesis of ethyl 4-(cyclohexen-1-yl)-pyrrole-2-carboxylate (Table 3.1, 1e)



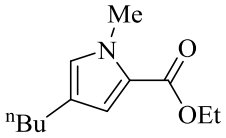
1,3-diimine synthesis followed general procedure using Ti precatalyst **A** (32.4 mg, 10 mol%), cyclohexylamine (230 μL, 2 mmol), 1-cyclohexenylacetylene (123 μL, 1 mmol) and heating at 100 °C for 24 h. Method A: The pyrrole was afforded (70 mg, 30%) as a brown solid. M.p. 53-54 °C. ^1H NMR ($CDCl_3$) δ 7.00 (1H, d, J_{HH} = 1.9 Hz, C-H pyrrole), 6.76 (1H, d, J_{HH} = 1.9 Hz, C-H pyrrole), 5.98-6.00 (1H, m, C-H alkene), 4.28 (2H, q, J_{HH} = 7.5 Hz, CH_2), 3.90 (3H, s, CH_3), 2.24-2.27 (2H, m, CH_2), 2.10-2.15 (2H, m, CH_2), 1.68-1.73 (2H, m, CH_2), 1.58-1.63 (2H, m, CH_2), 1.36 (3H, t, J_{HH} = 7.5 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 161.4, 129.9, 125.8, 125.2, 122.6, 120.3, 113.3, 59.8, 36.8, 27.0, 25.4, 22.8, 22.4, 14.5. HRMS (ES) m/z calcd. for $C_{14}H_{19}NO_2$ 233.1416, found 233.1426.

Synthesis of ethyl 4-cyclohexyl-pyrrole-2-carboxylate (Table 3.1, 1f)



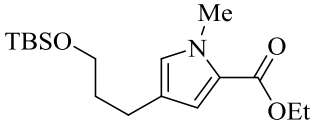
1,3-diimine synthesis followed general procedure using Ti precatalyst **B** (30.8 mg, 10 mol%), cyclohexylamine (230 μL, 2 mmol), cyclohexylacetylene (131 μL, 1 mmol) and heating at 100 °C for 24 h. Method A: The pyrrole was afforded (82 mg, 35%) as a brown oil. ^{1}H NMR ($CDCl_3$): δ 6.81 (1H, d, J_{HH} = 2.3 Hz, C-H pyrrole), 6.59 (1H,d, J_{HH} = 2.3 Hz, C-H pyrrole), 4.27 (2H, q, J_{HH} = 7.0 Hz, CH_2), 3.88 (3H, s, CH_3), 2.39-241 (1H, m, C-H cyclohexyl), 1.90-1.95 (2H, m, C-H cyclohexyl), 1.76-1.80 (2H, m, C-H cyclohexyl), 1.66-1.74 (1H, m, C-H cyclohexyl), 1.21-1.43 (8H, m, C-H cyclohexyl, CH_3). ^{13}C {^{1}H} NMR ($CDCl_3$) δ 161.4, 130.2, 126.2, 121.9, 115.4, 59.6, 36.6, 35.9, 34.6, 26.5, 26.2, 14.5. HRMS (ES) m/z calcd. for $C_{14}H_{21}NO_2$ 235.1572, found 235.1563.

Synthesis of ethyl 4-butyl-pyrrole-2-carboxylate (Table 3.1, 1g)



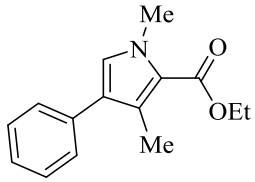
1,3-diimine synthesis followed general procedure using Ti precatalyst **B** (30.8 mg, 10 mol%), cyclohexylamine (230 μL, 2 mmol), 1-hexyne (115 μL, 1 mmol) and heating at 100 °C for 24 h. Method A: The pyrrole was afforded (46 mg, 22%) as a brown oil. ^{1}H NMR ($CDCl_3$): δ 6.77 (1H, d, J_{HH} = 2.1 Hz, C-H pyrrole), 6.58 (1H, d, J_{HH} = 2.1 Hz, C-H pyrrole), 4.27 (2H, q, J_{HH} = 7.1 Hz, CH_2), 3.87 (3H, s, CH_3), 2.42 (2H, t, J_{HH} = 7.7 Hz, CH_2), 1.52-1.58 (2H, m, CH_2), 1.33-1.38 (5H, m, CH_2 and CH_3), 0.91 (3H, t, J_{HH} = 7.1 Hz, CH_3). ^{13}C {^{1}H} NMR ($CDCl_3$) δ 161.4, 127.5, 124.0, 122.0, 117.1, 59.6, 36.6, 33.2, 26.2, 22.4, 14.5, 13.9. HRMS (ES) m/z calcd. for $C_{12}H_{19}NO_2$ 209.1416, found 209.1419.

Synthesis of ethyl 5-(3-tertbutyldimethylsilyloxy)propyl-pyrrole-2-carboxylate (Table 3.1, 1h)



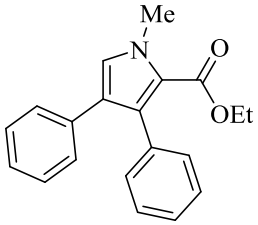
1,3-diimine synthesis followed general procedure using Ti precatalyst **A** (32.4 mg, 10 mol%), cyclohexylamine (230 μL, 2 mmol), 1-*t*-butyldimethylsilyloxy-pent-4-yne (236 μL, 1 mmol) and heating at 100 °C for 24 h. Method A: The pyrrole was afforded (42 mg, 13%) as a light brown oil. ^{1}H NMR ($CDCl_3$): δ 6.79 (1H, d, J_{HH} = 2.0 Hz, C-H pyrrole), 6.58 (1H, d, J_{HH} = 2.0 Hz, C-H pyrrole), 4.27 (2H, q, J_{HH} = 7.0 Hz, CH_2), 3.87 (3H, s, CH_3), 3.62 (2H, t, J_{HH} = 6.5 Hz, CH_2), 2.49 (2H, t, J_{HH} = 7.0 Hz, CH_2) 1.75-1.79 (2H, m, CH_2), 1.34 (3H, t, J_{HH} = 7.0 Hz, CH_3), 0.90 (9H, s), δ 0.05 (6H, s, CH_3-Si). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 161.4, 127.6, 123.3, 122.1, 62.5, 59.6, 36.6, 34.0, 26.0, 22.7, 18.4, 14.5, -5.3. HRMS (ES) m/z calcd. for $C_{17}H_{31}NO_2$ 325.2073, found 325.2060.

Synthesis of ethyl 4-phenyl-5-methyl-pyrrole-2-carboxylate (Table 3.2, 4a)



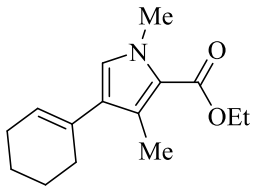
1,3-diimine synthesis followed general procedure using Ti precatalyst **B** (30.8 mg, 10 mol%), aniline (180 μL, 2 mmol), 1-phenylpropyne (125 μL, 1 mmol) and heating at 100 °C for 48 h. Method A: The pyrrole was afforded (78 mg, 32%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 7.38-7.41 (2H, m, Ar-H), 7.34-7.35 (2H, m, Ar-H), 7.26-7.29 (1H, m, Ar-H), 6.81 (1H, s, C-H pyrrole), 4.35 (2H, q, J_{HH} = 6.7 Hz, CH_2), 3.93 (3H, s, CH_3), 2.40 (3H, s, CH_3), 1.41 (3H, t, J_{HH} = 6.7 Hz, CH_3); ^{13}C {^{1}H} NMR ($CDCl_3$) δ 162.3, 135.2, 128.6, 128.4, 127.1, 126.7, 126.1, 124.9, 120.6, 59.7, 37.7, 14.5, 12.4.

Synthesis of ethyl 3,4-diphenyl-pyrrole-2-carboxylate (Table 3.2, 4b)



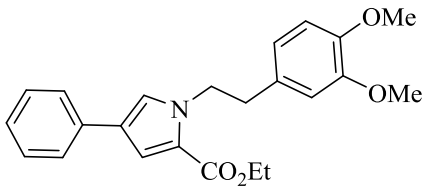
1,3-diimine synthesis followed general procedure using Ti precatalyst **B** (30.8 mg, 10 mol%), aniline (180 μL, 2 mmol), diphenylacetylene (178 mg, 1 mmol) and heating at 120 °C for 60 h. Method A: The pyrrole was afforded (82 mg, 27%) as a bright yellow solid. M.p. 89-91 °C (lit.[12] Mp: 84-86 °C). ^{1}H NMR ($CDCl_3$): δ 7.06-7.28 (10H, m, Ar-H), 6.97 (1H, s, C-H pyrrole), 4.04 (2H, q, J_{HH} = 7.2 Hz, CH_2), 4.00 (3H, s, CH_3), 0.95 (3H, t, J_{HH} = 7.2 Hz, CH_3); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 161.8, 136.0, 134.5, 131.0, 130.7, 128.1, 127.4, 126.8, 126.5, 125.8, 125.5, 124.0, 120.1, 59.7, 37.6, 13.6. Elemental analysis: found %C 78.72, %H 6.08, %N 4.65; calcd. %C 78.66, %H 6.27, %N 4.59. This compound was also characterized by single crystal X-ray diffraction: CCDC #1405633.

Synthesis of ethyl 4-(cyclohexen-1-yl)-5-methyl-pyrrole-2-carboxylate (Table 3.2, 4c)



1,3-diimine synthesis followed general procedure using Ti precatalyst **B** (30.8 mg, 10 mol%), aniline (180 μL, 2 mmol), 1-(cyclohex-1-enyl)propyne (135 μL, 1 mmol) and heating at 100 °C for 48 h. Method A: The pyrrole was afforded (62 mg, 25%) as a light brown oil. ^{1}H NMR ($CDCl_3$) δ 6.61 (1H, s, C-H pyrrole), 5.68 (1H, septet, J_{HH} = 2.0 Hz, C-H alkene), δ 4.31 (2H, q, J_{HH} = 7.3 Hz, CH_2), 3.84 (3H, s, CH_3), 2.34 (3H, s, CH_3), 2.20-2.22 (2H, m, CH_2), 2.15-2.17 (2H, m, CH_2), 1.72-1.76 (2H, m, CH_2), 1.63-1.65 (2H, m, CH_2), 1.37 (3H, t, J_{HH} = 7.3 Hz, CH_3). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 162.3, 130.9, 126.6, 126.5, 126.3, 124.9, 120.2, 59.6, 37.6, 29.8, 25.6, 23.1, 22.2, 14.5, 12.9 HRMS (ES) m/z calcd. for $C_{15}H_{21}NO_2$ 247.1572, found 247.1560.

Synthesis of ethyl 1-(3,4-dimethoxyphenethyl)-4-phenyl-pyrrole-2-carboxylate (5)



1,3-diimine synthesis followed general procedure using Ti precatalyst **A** (32.4 mg, 10 mol%), cyclohexylamine (230 μL, 2 mmol), phenylacetylene (110 μL, 1 mmol) and heating at 100 °C for 24 h. Volatiles were removed and ethyl (3,4-dimethoxyphenethyl)glycinate (0.801g, 3 mmol), NH_4Cl (40 mg, 0.75 mmol), DMSO (5 mL) were added to the pressure tube. The reaction was heated at 120 °C for 18 h. Isolation followed same procedure in method A. The pyrrole was afforded (42 mg, 11%) as a light brown oil. ^{1}H NMR ($CDCl_3$): δ 7.43 (2H, d, J_{HH} = 7.8 Hz, Ar-H), 7.33 (2H, t, 7.8 Hz, Ar-H), 7.26 (1H, d, J_{HH} = 1.7 Hz, C-H pyrrole), 7.19 (1H, t, J_{HH} = 7.8 Hz, Ar-H), 6.89 (1H, d, J_{HH} = 1.7 Hz, C-H pyrrole), 6.78 (1H, d, J_{HH} = 8.0 Hz, Ar-H), 6.70 (1H, dd, J_{HH} = 1.8 Hz, 8.0 Hz, Ar-H), 6.55 (1H, d, J_{HH} = 1.7 Hz, C-H pyrrole), 4.53 (2H, t, J_{HH} = 7.2 Hz, CH_2), 4.34 (2H, q, J_{HH} = 7.2 Hz, CH_2), 3.86 (3H, s, CH_3), 3.79 (3H, s, CH_3), 3.04 (2H, t, J_{HH} = 7.2 Hz, CH_2), 1.39 (3H, t, J_{HH} = 7.2 Hz, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 161.1, 148.8, 147.7, 134.5, 131.0, 128.7, 126.1, 125.7, 125.1, 123.8, 122.4, 121.0, 115.4, 112.0, 111.2, 60.0, 55.9, 55.8, 51.3, 37.8, 14.5.

REFERENCES

REFERENCES

(1) a) Brown, D. G.; Lister, T.; May-Dracka, T. L. *Bioorganic & Medicinal Chemistry Letters* **2014**, *24*, 413-418. b) Lin, C.-C.; Tantisantisom, W.; McAlpine, S. R. *Organic Letters* **2013**, *15*, 3574-3577. c) von Nussbaum, F.; Brands, M.; Hinzen, B.; Weigand, S.; Häbich, D. *Angewandte Chemie International Edition* **2006**, *45*, 5072-5129. d) Singh, S. B.; Barrett, J. F. *Biochemical Pharmacology* **2006**, *71*, 1006-1015. e) Butler, M. S.; Buss, A. D. *Biochemical Pharmacology* **2006**, *71*, 919-929. f) Gibbons, S. *Natural Product Reports* **2004**, *21*, 263-277. g) Faulkner, D. J. *Natural Product Reports* **2001**, *18*, 1R-49R. h) Cragg, G. M.; Newman, D. J.; Snader, K. M. *Journal of Natural Products* **1997**, *60*, 52-60.

(2) a) Overy, D.; Calati, K.; Kahn, J. N.; Hsu, M.-J.; Martín, J.; Collado, J.; Roemer, T.; Harris, G.; Parish, C. A. *Bioorganic & Medicinal Chemistry Letters* **2009**, *19*, 1224-1227. b) Arif, T.; Bhosale, J. D.; Kumar, N.; Mandal, T. K.; Bendre, R. S.; Lavekar, G. S.; Dabur, R. *Journal of Asian Natural Products Research* **2009**, *11*, 621-638. c) Parish, C. A.; Smith, S. K.; Calati, K.; Zink, D.; Wilson, K.; Roemer, T.; Jiang, B.; Xu, D.; Bills, G.; Platas, G.; Peláez, F.; Díez, M. T.; Tsou, N.; McKeown, A. E.; Ball, R. G.; Powles, M. A.; Yeung, L.; Liberator, P.; Harris, G. *Journal of the American Chemical Society* **2008**, *130*, 7060-7066. d) Ramana, C. V.; Srinivas, B.; Puranik, V. G.; Gurjar, M. K. *The Journal of Organic Chemistry* **2005**, *70*, 8216-8219. e) Donia, M.; Hamann, M. T. *The Lancet Infectious Diseases* **2003**, *3*, 338-348. f) Ligon, J. M.; Hill, D. S.; Hammer, P. E.; Torkewitz, N. R.; Hofmann, D.; Kempf, H.-J.; Pée, K.-H. v. *Pest Management Science* **2000**, *56*, 688-695.

(3) a) De Clercq, E. *Medicinal Research Reviews* **2000**, *20*, 323-349. b) Molinski, T. F.; Dalisay, D. S.; Lievens, S. L.; Saludes, J. P. *Nat Rev Drug Discov* **2009**, *8*, 69-85. c) Laille, M.; Gerald, F.; Debitus, C. *Cellular and Molecular Life Sciences CMLS* **2014**, *54*, 167-170. d) Newman, D. J.; Cragg, G. M. *Journal of Natural Products* **2012**, *75*, 311-335. e) Ng, T. B.; Huang, B.; Fong, W. P.; Yeung, H. W. *Life Sciences* **1997**, *61*, 933-949. f) Rinehart, K. L.; Shaw, P. D.; Shield, L. S.; Gloer, J. B.; Harbour, G. C.; Koker, M. E. S.; Samain, D.; Schwartz, R. E.; Tymiak, A. A.; Weller, D. L.; Carter, G. T.; Munro, M. H. G.; Hughes, R. G.; Renis, H. E.; Swynenberg, E. B.; Stringfellow, D. A.; Vavra, J. J.; Coats, J. H.; Zurenko, G. E.; Kuentzel, S. L.; Li, L. H.; Bakus, G. J.; Brusca, R. C.; Craft, L. L.; Young, D. N.; Connor, J. L. In *Pure and Applied Chemistry* 1981; Vol. 53, p 795. g) Patterson, G. M. L.; Larsen, L. K.; Moore, R. E. *Journal of Applied Phycology*, *6*, 151-157.

(4) a) Pezzuto, J. M. *Biochemical Pharmacology* **1997**, *53*, 121-133. b) Cragg, G. M.; Kingston, D. G.; Newman, D. J. *Anticancer agents from natural products*; CRC press, 2011. c) Gordaliza, M. *Clinical and Translational Oncology* **2008**, *9*, 767-776. d) Altmann, K.-H.; Gertsch, J. *Natural Product Reports* **2007**, *24*, 327-357. e) Simmons, T. L.; Andrianasolo, E.; McPhail, K.; Flatt, P.; Gerwick, W. H. *Molecular Cancer Therapeutics* **2005**, *4*, 333-342. f) da Rocha, A. B.; Lopes, R. M.; Schwartsmann, G. *Current Opinion in Pharmacology* **2001**, *1*, 364-369.

(5) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213-7256.

(6) a) G. Banwell, M.; L. Flynn, B.; Hamel, E.; C. R. Hockless, D. *Chemical Communications* **1997**, 207-208. b) Yoshida, W. Y.; Lee, K. K.; Carroll, A. R.; Scheuer, P. J. *Helvetica Chimica Acta* **1992**, *75*, 1721-1725.

(7) a) Andersen, R. J.; Faulkner, D. J.; He, C. H.; Van Duyne, G. D.; Clardy, J. *Journal of the American Chemical Society* **1985**, *107*, 5492-5495. b) Pla, D.; Albericio, F.; Alvarez, M. *MedChemComm* **2011**, *2*, 689-697.

(8) a) Palermo, J. A.; Rodríguez Brasco, M. F.; Seldes, A. M. *Tetrahedron* **1996**, *52*, 2727-2734. b) Iwao, M.; Takeuchi, T.; Fujikawa, N.; Fukuda, T.; Ishibashi, F. *Tetrahedron Letters* **2003**, *44*, 4443-4446.

(9) a) Linde, H. H. A. *Helvetica Chimica Acta* **1965**, *48*, 1822-1842. b) Ratcliffe, A. H.; Smith, G. F.; Smith, G. N. *Tetrahedron Letters* **1973**, *14*, 5179-5184.

(10) a) Kluza, J.; Marchetti, P.; Bailly, C. In *Modern Alkaloids*; Wiley-VCH Verlag GmbH & Co. KGaA: 2007, p 171-187. b) Vanhuyse, M.; Kluza, J.; Tardy, C.; Otero, G.; Cuevas, C.; Bailly, C.; Lansiaux, A. *Cancer Letters* **2005**, *221*, 165-175. c) Plisson, F.; Huang, X.-C.; Zhang, H.; Khalil, Z.; Capon, R. J. *Chemistry – An Asian Journal* **2012**, *7*, 1616-1623.

(11) Fuerstner, A.; Weintritt, H.; Hupperts, A. *The Journal of Organic Chemistry* **1995**, *60*, 6637-6641.

(12) Gupton, J. T.; Krumpe, K. E.; Burnham, B. S.; Dwornik, K. A.; Petrich, S. A.; Du, K. X.; Bruce, M. A.; Vu, P.; Vargas, M.; Keertikar, K. M.; Hosein, K. N.; Jones, C. R.; Sikorski, J. A. *Tetrahedron* **1998**, *54*, 5075-5088.

(13) Gupton, J. T.; Giglio, B. C.; Eaton, J. E.; Rieck, E. A.; Smith, K. L.; Keough, M. J.; Barelli, P. J.; Firich, L. T.; Hempel, J. E.; Smith, T. M.; Kanters, R. P. F. *Tetrahedron* **2009**, *65*, 4283-4292.

(14) Majumder, S.; Gipson, K. R.; Odom, A. L. *Organic Letters* **2009**, *11*, 4720-4723.

(15) Yamashkin, S. A.; Yudin, L. G.; Kost, A. N. *Chemistry of Heterocyclic Compounds*, *28*, 845-855.

(16) Ciaccia, M.; Pilati, S.; Cacciapaglia, R.; Mandolini, L.; Di Stefano, S. *Organic & Biomolecular Chemistry* **2014**, *12*, 3282-3287.

(17) a) Notz, W.; Tanaka, F.; Barbas, C. F. *Accounts of Chemical Research* **2004**, *37*, 580-591. b) Bisai, V.; Bisai, A.; Singh, V. K. *Tetrahedron* **2012**, *68*, 4541-4580. c) Chandrasekhara Rao, L.; Meshram, H. M.; Satish Kumar, N.; Nageswara Rao, N.; Jagadeesh Babu, N. *Tetrahedron Letters* **2014**, *55*, 1127-1131.

(18) Wilhelms, N.; Kulchat, S.; Lehn, J.-M. *Helvetica Chimica Acta* **2012**, *95*, 2635-2651.

(19) a) Pingaew, R.; Ruchirawat, S. *Synlett* **2007**, *2007*, 2363-2366. b) Tang, C.; Li, Z.; Wang, Y.; Xu, J.; Kong, L.; Yao, H.; Wu, X. *Tetrahedron Letters* **2011**, *52*, 3275-3278. c) De, S.; Mishra, S.; Kakde, B. N.; Dey, D.; Bisai, A. *The Journal of Organic Chemistry* **2013**, *78*, 7823-7844.

(20) Mujkic, M.; Lentz, D. *Dalton Transactions* **2012**, *41*, 839-849.

(21) a) Harris, S. A.; Ciszewski, J. T.; Odom, A. L. *Inorganic Chemistry* **2001**, *40*, 1987-1988. b) Littler, B. J.; Miller, M. A.; Hung, C.-H.; Wagner, R. W.; O'Shea, D. F.; Boyle, P. D.; Lindsey, J. S. *The Journal of Organic Chemistry* **1999**, *64*, 1391-1396.

(22) Novak, A.; Blake, A. J.; Wilson, C.; Love, J. B. *Chemical Communications* **2002**, 2796-2797.

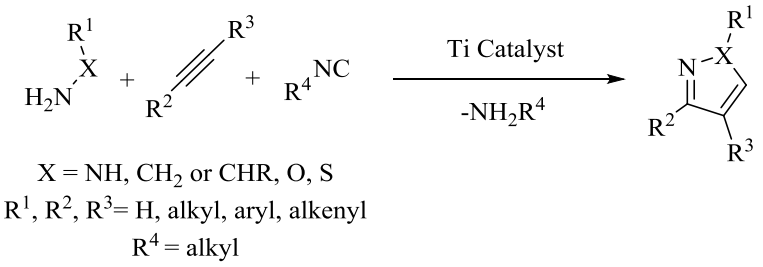
(23) a) Aksın-Artok, Ö.; Krause, N. *Advanced Synthesis & Catalysis* **2011**, *353*, 385-391. b) Marshall, J. A.; Cleary, D. G. *The Journal of Organic Chemistry* **1986**, *51*, 858-863. c) Mio, M. J.; Kopel, L. C.; Braun, J. B.; Gadzikwa, T. L.; Hull, K. L.; Brisbois, R. G.; Markworth, C. J.; Grieco, P. A. *Organic Letters* **2002**, *4*, 3199-3202.

(24) Gupton, J. T.; Krolikowski, D. A.; Yu, R. H.; Riesinger, S. W.; Sikorski, J. A. *The Journal of Organic Chemistry* **1990**, *55*, 4735-4740.

CHAPTER 4. SINGLE-STEP SYNTHESIS OF PYRROLE-2-AMIDATES

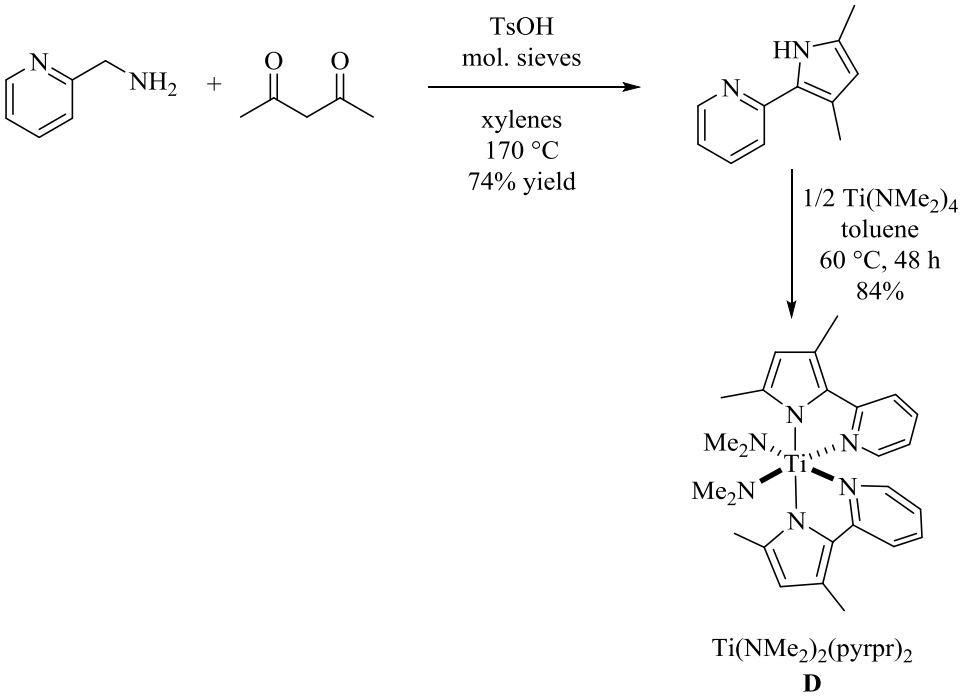
4.1 Introduction

An extension of the titanium MCR previously described (see Chapter 1) is the replacement of amine sources with bifunctional amine containing molecules, producing 1,3-diiamines that self-condensate to heterocyclic compounds in a single step (**Scheme 4.1**). A bifunctional amine, such as hydrazine (X = NH), contains a second atom of suitable nucleophilicity to react with the aldimine carbon. Typically speaking, this is non-trivial as molecules with multiple nucleophilic atoms can compete with ligands for metal complexation, therefore, robust catalyst are required.



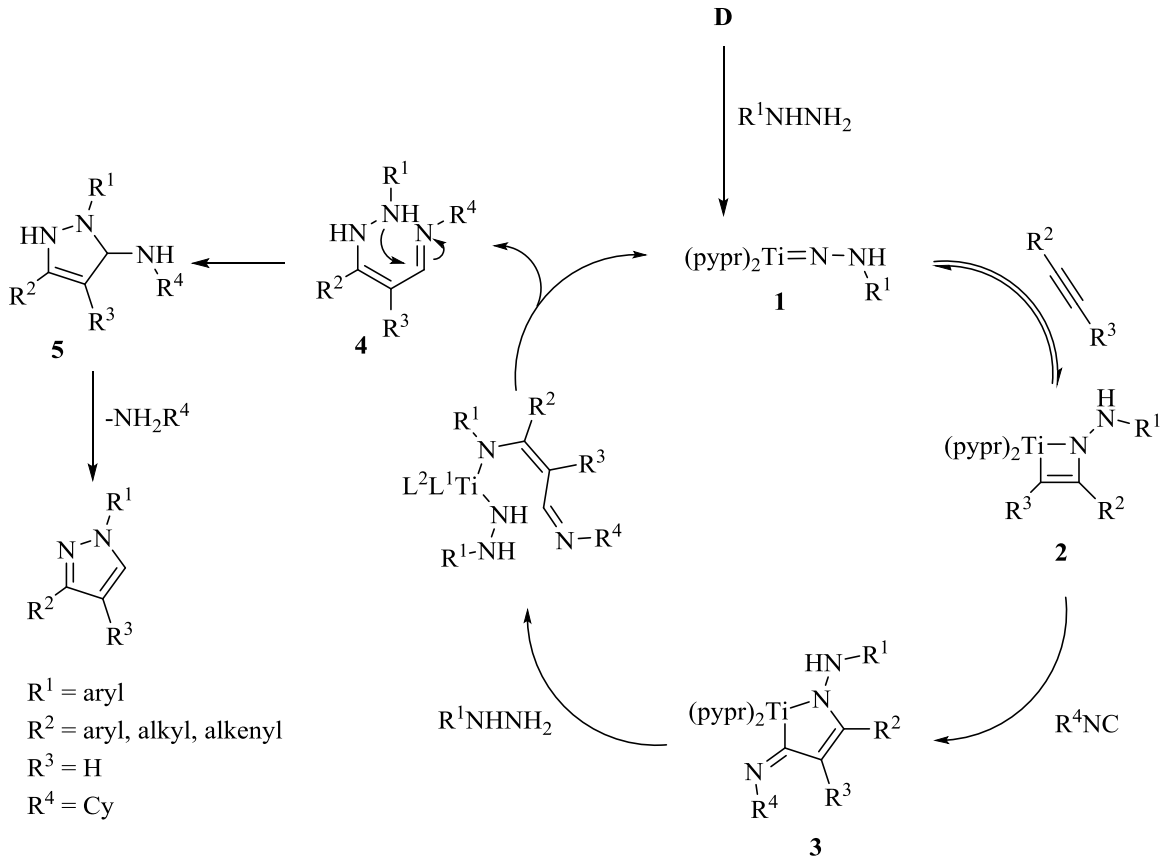
Scheme 4.1 Envisaged single-step heterocycle synthesis

A reaction developed by Odom et al, is a single-step synthesis of pyrazoles through the titanium catalyzed MCR of mono-substituted hydrazines, terminal alkynes, and cyclohexylisonitrile.[1] According to Amila A. Dissanayake, several titanium catalyst were unsuitable for this reaction. The cause of inactivity in most cases was proteolytic removal of ancillary ligands by aggressive mono-substituted hydrazines, forming inactive bridged hydrazido complexes. A catalyst that was efficient in providing pyrazoles in a single step is the pyrrole-pyridyl-based titanium catalyst **D** (see Chapter 2 for short description). The ancillary ligand[2] is synthesized in one step from commercially available materials, and is introduced to titanium in good yield by reaction with $Ti(NMe_2)_4$ (**Scheme 4.2**).[1]



Scheme 4.2 Synthesis of catalyst **D**

The proposed catalytic cycle is an extension of the Bergman hydroamination reaction[3] and similar to iminoamination mechanism (**Scheme 4.3**).[4] Introduction of mono-substituted hydrazine to catalyst **D** provides hydrazido complex **1**. Alkyne addition occurs via a [2+2] cycloaddition to **1** and forms four-membered metallacycle **2**. Insertion of isonitrile between Ti-C bond provides expanded metallacycle **3**. Protonolysis with second addition of hydrazine provides intermediate **4** and regenerates active catalyst **1**. This intermediate cyclizes through nitrogen attack of aldimine carbon to heterocycle **5** and elimination of amine provides aromatic heterocycle, pyrazole.



Scheme 4.3 Proposed catalytic cycle for pyrazole formation

This MCR affords pyrazoles as a single isomer (1,3-pyrazoles) in modest to good yields.[1] The regioselectivity is, as such, the alkynyl-substituent is position away from the metal. This is an unusual result as aryl alkynes stabilize the carbon bound to titanium and the opposite isomer should be observed (see Chapter 1**).**[5] Investigations into the underlying causes of this unusual regioselectivity, as well as optimization of yields, is currently underway.

Are there other coupling partners that could be successfully employed using this catalysis? If yes, then many of the two-step one-pot syntheses previously described (see Chapter 2) may be converted to single-step synthesis.[6] In comparison, higher levels of atom economy are achieved in the single step synthesis; one equivalent of amine waste is removed (**Figure 4.1**). Here in,

preliminary results for a single-step synthesis of pyrrole-2-amidates is discussed. Protecting group chemistry is also shown as a means of extended substrate possibilities.

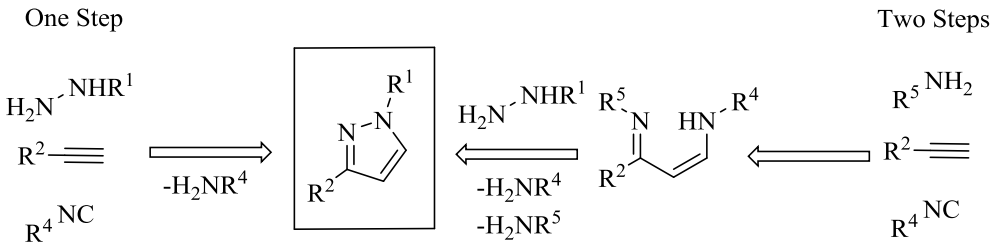


Figure 4.1 Atom economy of two-step process versus single-step process.

4.2 Results and Discussion

Initial investigations into a single-step pyrrole synthesis utilized the free base (FB) of glycine ethyl ester (extracted from basic water solution with CH_2Cl_2). Several titanium catalyst (**Figure 4.2**) were employed in this study and all were prepared by reaction of ancillary ligand with $Ti(NMe_2)_4$ according to literature procedures.[1,7] Substrate 1-hexyne was used as the source of alkyne for all reactions. Cyclohexylisonitrile was applied as source of isocyanide.[8]

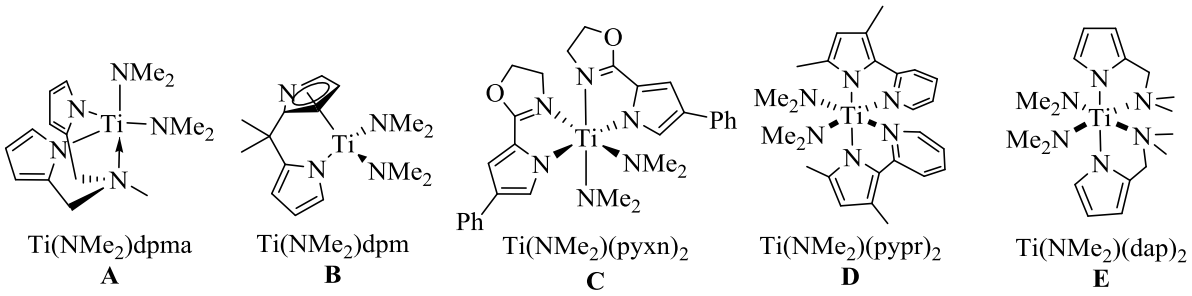
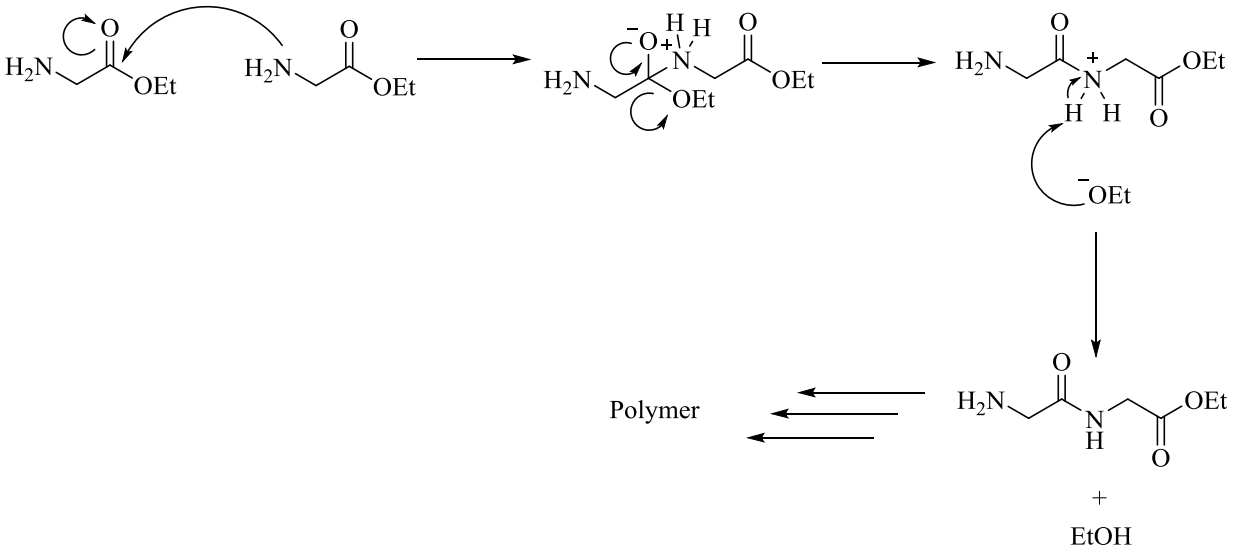


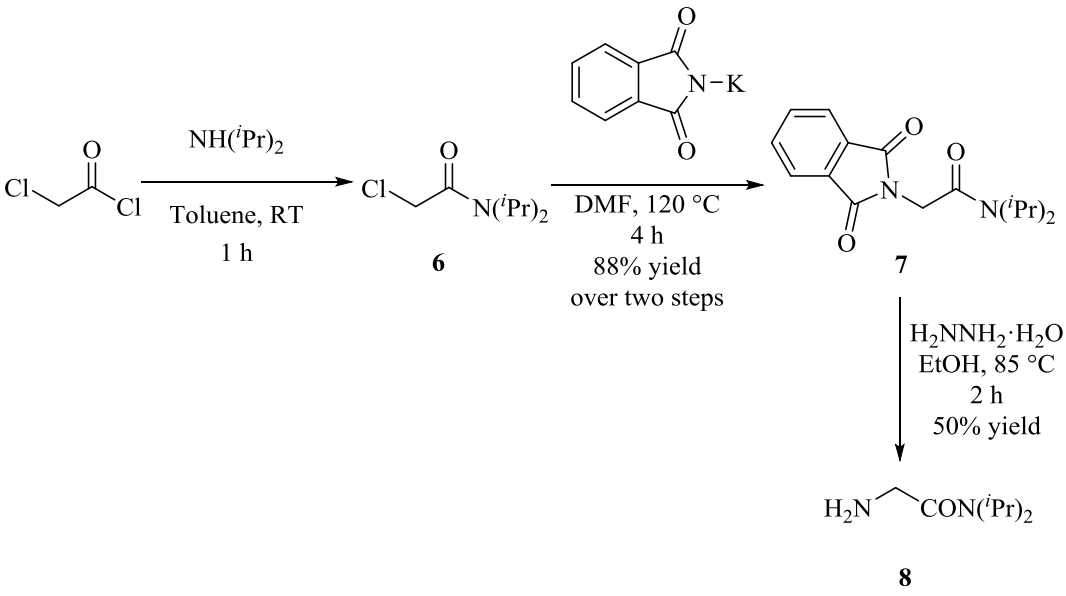
Figure 4.2 Titanium catalyst screened for single-step pyrrole synthesis

All experiments where the FB of glycine ethyl ester was introduced to a titanium catalyst, free ligand visible by NMR was observed. At first, it was believed that the ester was completely incompatible with these titanium metal complexes. However, a NMR spectrum of glycine ethyl ester revealed ethanol contaminant. The source of ethanol is from hydrolysis or amidation of ethyl ester functional group (**Scheme 4.4**). The FB of glycine ethyl ester (oil) polymerizes readily in air to a white powder. Even freshly prepared and distilled FB glycine ethyl ester produced similar results.



Scheme 4.4 Production of ethanol upon self-amidation of glycine.

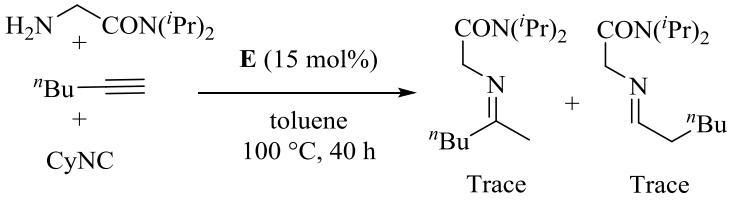
A more stable substrate was required for continuing this investigation. Amides are more stable to hydrolysis, with carbonyl carbon being markedly less reactive. Amide **8** was prepared through acid chloride substitution followed by Gabriel's synthesis (**Scheme 4.5**).[9] It was envisioned that the diisopropyl groups would restrict possible oxygen or amide nitrogen coordination, thus avoiding potential side reactions.



Scheme 4.5 Synthesis of amino amide substrate.

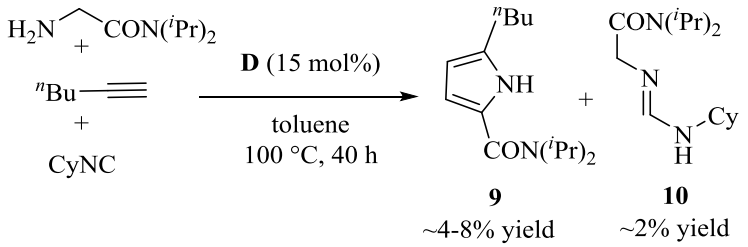
With a more stable substrate, investigation continued and provided some significant preliminary results. Mixtures of **8** with 10 mol% of both catalyst **A** and **B** remained relatively unreactive at room temperature (i.e. no color change or precipitate). To these two solutions was added 1-hexyne and cyclohexylisonitrile followed by heating at 100 °C for 18 h. Free ligand was observed by NMR in both cases with no formation of any expected products (GC-MS showed mostly unreacted amide **8**).

Catalyst **E**, which was found effective at forming 3CC of 1,1-disubstituted hydrazine, alkyne and isonitrile; was attempted next (**Scheme 4.6**).[10] Observable quantities of hydroamination isomers had formed according to mass spectra (m/z 240). However, amide **8** remains mostly unreacted even after 40 h and pyrrole formation was unobserved.



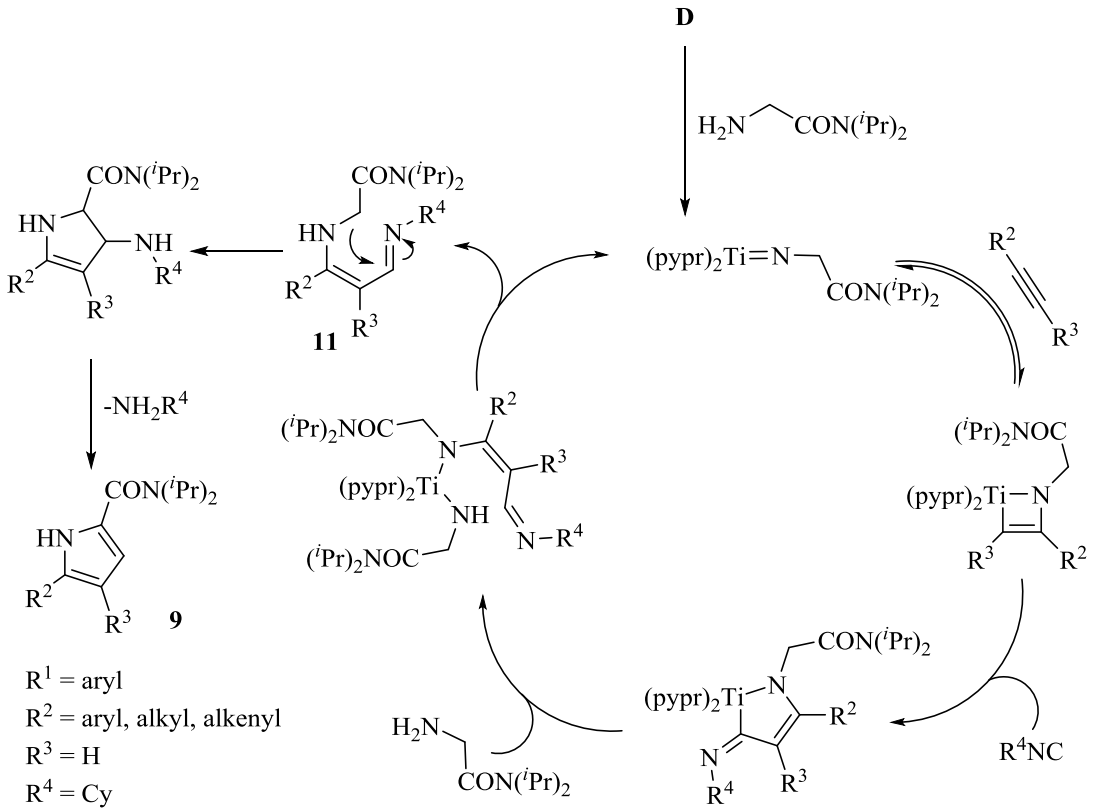
Scheme 4.6 Catalyst E transforms amine, 1-hexyne, and cyclohexylisonitrile.

Ecstatically, catalyst **D** provided approximately 4-8% yield of pyrrole-2-amidate **9** (m/z 250**)** according to un-calibrated GC-FID (**Scheme 4.7**). Also observed was formamide **10** (m/z 267) in 2% yield which may indicate formation of titanium imido species. Conversion was incomplete at 40 h, and multiple unidentified peaks in the GC-MS indicate the reaction is not occurring cleanly. It must also be stated that 15 mol% catalyst **D** was applied, which means the reaction is possibly not occurring catalytically (unless one molecule is working incredibly hard). Additionally, similar results were observed when using phenylacetylene in place of 1-hexyne.



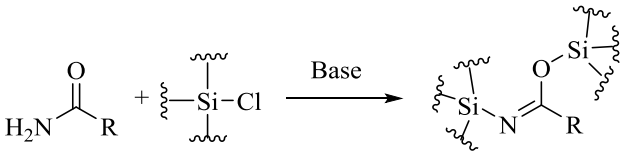
Scheme 4.7 MCR to form pyrrole-2-amidate

If the reaction were to be catalytic, the mechanism could be similar to that of pyrazole (**Scheme 4.8**).[1] However, there are two main concerns for the low yield over lengthy reaction times. Increased electronic donation to the metal center decreases Lewis acidity and could be slowing down the catalysis.[11] Diisopropyl groups may not be sterically encumbering enough to prevent oxygen coordination to titanium. Another potential issue is that the acidity of methylene CH on amide **8** becomes more acidic upon formation of intermediate 3CC **11**. Protonolysis of pypr ancillary ligand would lead to catalyst deactivation.



Scheme 4.8 Proposed mechanism for pyrrole-2-amidate formation.

To obviate the first concern, investigation into protection groups (PG) of amides was initiated. Surprisingly, this area of study is severely limited for PGs suitable with titanium catalysis. Many traditional amide PG contain oxygen atoms (i.e. Boc, Fmoc, Ts, Ms) that react with sensitive titanium catalyst.[12] Successful PG used in previous reports included silyl groups (i.e. TMS, TBS, TBDPS) and reductively cleaved benzyl PG group.[13] Silyl group incorporation to amides have been successful at creating *N*,*O*-bis(silyl)amidinates (**Scheme 4.9**).[14]



Scheme 4.9 General procedure for *N*,*O*-bis(silyl)amidinates.

Application of silylated amidinates have been primarily used as mild silylating reagents or 1,3-dipolarophiles. To the best of this researchers knowledge there haven't been any reports enlisting this type of molecule as a protected amide against transition metal catalysis. The potential benefits of an *N*,*O*-PG would be removal of atom donation by sterically encumbering both atoms, whereas before oxygen remained completely unblocked on one side (**Figure 4.3**).

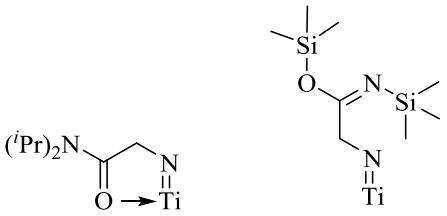
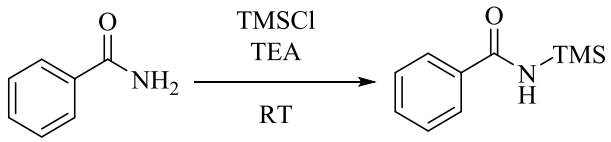


Figure 4.3 Oxygen coordination removed by silylation (ligands omitted for clarity).

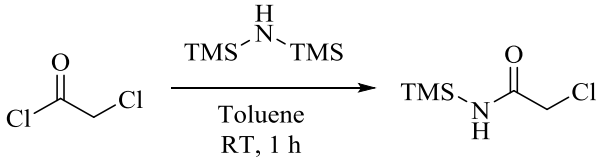
Model compound, benzamide, was applied as starting material to generate *N*,*O*-bis(silyl)amidinates. Reaction of benzamide with two equivalents of trimethylsilylchloride in TEA was performed at room temperature (**Scheme 4.10**). A white slurry forms instantly and this mixture was stirred for several hours. Isolation through extraction with CH_2Cl_2 provided only mono-silylated product. Repeating experiment with 1:1 mixture of CH_2Cl_2:TEA and four equivalents of trimethylsilylchloride, reacting overnight at room temperature, provided reaction mixture that fumed heavily in air. Expected product was not isolated, however, starting benzamide was recovered. The *N*,*O*-bis(silyl)amidinates maybe extremely water sensitive due to the lability of trimethylsilyl groups and so a more stable silyl group is required.



Scheme 4.10 Attempted synthesis of *N*,*O*-bis(silyl)benzamidinate.

A second route to *N*,*O*-bis(silyl)amidinates was attempted, which involved silyl migration to

oxygen. Reaction of HMDS with α-chloroacetlychloride, similar to the synthesis of amide **8**, should provide *N*,*O*-bis(silyl)amidinate according to the literature (**Scheme 4.11**). However, isolation revealed only mono-silylated-α-chloroamide had formed.



Scheme 4.11 Second Attempt

4.3 Conclusion

These results are only preliminary and a more thorough investigation is required. The MCR between amide **6**, 1-hexyne, and isonitrile is successfully mediated by titanium complex **D**. The exact cause for the reaction terminating before all substrates are consumed is unclear at this time. Catalyst **D** is limited to terminal alkynes and reaction times of 36 h are required for pyrazole formation. Optimization of this similar reaction could lead to an amenable procedure for pyrrole-2-amidates.

Protecting groups for certain substrates are required in order to be compatible with Odom group chemistry. Amides are a useful synthetic handle for post-modification, which makes them a desirable functional group. Expanding the potential types of protecting groups for both the amide nitrogen and oxygen creates new compatibilities that will expand transition metal catalysis.

4.4 Experimental

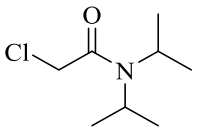
General Considerations: All manipulations of air-sensitive compounds were carried out in an MBraun drybox under a purified nitrogen atmosphere. All glassware was heated at 150 °C for 4 h and stored in a drybox under nitrogen. Toluene was purified by first sparging with dry nitrogen to remove oxygen and then ran through activated alumina to remove water. ^{1}H and ^{13}C NMR spectra were recorded on a VXR-500 spectrometer in $CDCl_3$ or CD_3OD. Melting points were measured on a Mel-Temp II apparatus (Laboratory Devices Inc, USA) with a mercury thermometer in an open capillary tube.

Catalyst shown in **Figure 4.2** and the corresponding ancillary ligands were prepared according to literature procedures.[1,7] Phenylacetylene and 1-hexyne were purchased from GFS chemical and dried with CaO, followed by distillation. Phthalimide, diisopropylamine, HMDS, benzamide Trimethylsilylchloride were all purchased from Sigma Aldrich and used as received. The α-chloroacetlychloride was purchased from Alpha Aesar and used as received. Cyclohexylisonitrile was prepared according to the literature procedure.

Potassium phthalimide was prepare by reacting phthalimide with excess potassium carbonate in ethanol. The product was crashed out with addition of water and collected by vacuum filtration.

Preparative Details

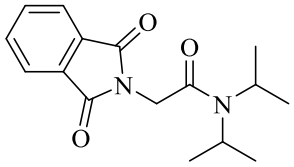
Synthesis of 2-chloro-N,N-diisopropylacetamide (6)



An oven dried round-bottom flask containing magnetic stir bar was cooled under nitrogen and charged with diisopropylamine (285 mmol, 40 mL) and toluene (40 mL). A solution of α-

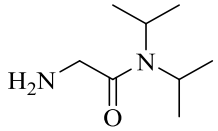
chloroacetylchloride (104.3 mmol, 8.3 mL) in toluene (20 mL) was added dropwise via a syringe. A precipitate began to form immediately and the solution turned brown. After complete addition the reaction was stirred for 1 h and then quenched with saturated $NaHCO_3$ solution. The product was extracted with ethyl acetate twice (40 mL portions) and the organic layers were combined. The organic layer was rinsed with water and dried with magnesium sulfate. The solution was filtered and volatiles removed yielding a brown oil that was reasonably pure by NMR and used without further purification. ^{1}H NMR ($CDCl_3$): δ 4.02 (2H, s, CH_2), 3.92 (1H, septet, J_{HH} = 6 Hz, CH), 3.45 (1H, broad, CH), 1.40 (6H, d, J_{HH} = 6 Hz, CH_3), 1.25 (6H, d, J_{HH} = 6 Hz, CH_3).

Synthesis of 2-(1,3-dioxoisoindolin-2-yl)-N,N-diisopropylacetamide (7)



An oven dried two-neck round-bottom flask containing magnetic stir bar was cooled under nitrogen and charged with compound **6** (9.5 g, 53.5 mmol), potassium phthalimide (14.8 g, 80.0 mmol) and DMF (20 mL). The flask was fitted with condenser and flushed with nitrogen. The reaction was heated at 120 °C for 4 h. The brownish solution with small amounts of precipitate was cooled briefly before pouring into a beaker containing crushed ice (100 g). The off brown precipitate was collected by vacuum filtration. After drying the compound, product **7** (13.6 g, 88% over two steps) was reasonably pure by NMR and used without further purification. ^{1}H NMR ($CDCl_3$): δ 7.87 (2H, dd, J_{HH} = 3 Hz, 5 Hz, Ar-H), 7.72 (2H, dd, J_{HH} = 3 Hz, 5 Hz, Ar-H), 4.45 (2H, s, CH_2), 3.98 (1H, septet, J_{HH} = 7.0 Hz, CH), 3.54 (1H, broad, CH), 1.37 (6H, d, J_{HH} = 7.0 Hz, CH_3), 1.33 (6H, d, J_{HH} = 7.0 Hz, CH_3).

Synthesis of 2-amino-N,N-diisopropylacetamide (8)



A round-bottom flask containing magnetic stir bar was charged with compound **7** (13.6 g, 47.2 mmols), EtOH (60 mL), and hydrazine monohydrate (3.57 g, 71.4 mmols). The flask was fitted with a condenser and the solution was refluxed for 2 h. After 30 minutes a large amount of white precipitate had formed. After 2 h, the solution was cooled to room temperature. The solution was filtered and the solid precipitate rinsed with EtOH several times (30 mL portions). The volatiles were removed and the product (3.73 g, 50% yield) appears as an amber oil. ^{1}H NMR ($CDCl_3$): δ 3.80 (1H, septet, J_{HH} = 6.4 Hz, CH), 3.45 (1H, broad, CH), 3.37 (2H, s, CH_2), 1.68 (2H, broad s, NH_2), 1.37 (6H, d, J_{HH} = 6.4 Hz, CH_3), 1.16 (6H, d, J_{HH} = 6.4 Hz, CH_3).

General Procedure for pyrrole-2-amidate

The reaction mixture was prepared under inert atmosphere in an Mbraun drybox. A pressure-tube was charged with magnetic stir bar, $Ti(NMe_2)_2(pypr)_2$ (**D**) (71.7 mg, 15 mol%) in toluene (2 mL), amide **6** (158 mg, 1 mmol), 1-hexyne (114 μL, 1 mmol), and cyclohexylisonitrile (187 μL, 1.5 mmol). The pressure tube was sealed and placed in oilbath at 100 °C for 40 h. The reaction was removed from heat and allowed to cool to room temperature. Pyrrole-2-amidate **9** was observed by GC-MS (m/z 250) and quantification was estimated by GC-FID to be approximately 4-8% yield relative to catalyst loading.

REFERENCES

REFERENCES

(1) Dissanayake, A. A.; Odom, A. L. *Chemical Communications* **2012**, *48*, 440-442.

(2) Klappa, J. J.; Rich, A. E.; McNeill, K. *Organic Letters* **2002**, *4*, 435-437.

(3) a) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *Journal of the American Chemical Society* **1992**, *114*, 1708-1719. b) Pohlki, F.; Doye, S. *Angewandte Chemie International Edition* **2001**, *40*, 2305-2308.

(4) Cao, C.; Shi, Y.; Odom, A. L. *Journal of the American Chemical Society* **2003**, *125*, 2880-2881.

(5) a) Straub, B. F.; Bergman, R. G. *Angewandte Chemie* **2001**, *113*, 4768-4771. b) Bytschkov, I.; Doye, S. *European Journal of Organic Chemistry* **2003**, *2003*, 935-946. c) Zhang, Z.; Leitch, D. C.; Lu, M.; Patrick, B. O.; Schafer, L. L. *Chemistry – A European Journal* **2007**, *13*, 2012-2022. d) Cao, C.; Ciszewski, J. T.; Odom, A. L. *Organometallics* **2001**, *20*, 5011-5013.

(6) Odom, A. L.; McDaniel, T. J. *Accounts of Chemical Research* **2015**, *48*, 2822-2833.

(7) a) Harris, S. A.; Ciszewski, J. T.; Odom, A. L. *Inorganic Chemistry* **2001**, *40*, 1987-1988. b) Huang, J.-H.; Chi, L.-S.; Huang, F.-M.; Kuo, P.-C.; Zhou, C.-C.; Lee, G.-H.; Peng, S.-M. *Journal of the Chinese Chemical Society* **2000**, *47*, 895-900. c) Novak, A.; Blake, A. J.; Wilson, C.; Love, J. B. *Chemical Communications* **2002**, 2796-2797. d) Shi, Y.; Hall, C.; Ciszewski, J. T.; Cao, C.; Odom, A. L. *Chemical Communications* **2003**, 586-587.

(8) a) Sharma, S.; Maurya, R. A.; Min, K.-I.; Jeong, G.-Y.; Kim, D.-P. *Angewandte Chemie International Edition* **2013**, *52*, 7564-7568. b) Polisar, J. G.; Li, L.; Norton, J. R. *Tetrahedron Letters* **2011**, *52*, 2933-2934.

(9) a) Röhnert, H. *Archiv der Pharmazie* **1960**, *293*, 573-576. b) Sivey, J. D.; Roberts, A. L. *Environmental Science & Technology* **2012**, *46*, 2187-2195. c) Salach, O. A.; Hadad, S.; Haj-Yehia, A.; Sussan, S.; Bialer, M. *Pharmaceutical Research*, *11*, 1429-1434. d) Bell, K. J.; Westra, A. N.; Warr, R. J.; Chartres, J.; Ellis, R.; Tong, C. C.; Blake, A. J.; Tasker, P. A.; Schröder, M. *Angewandte Chemie International Edition* **2008**, *47*, 1745-1748.

(10) a) Cao, C.; Shi, Y.; Odom, A. L. *Organic Letters* **2002**, *4*, 2853-2856. b) Banerjee, S.; Shi, Y.; Cao, C.; Odom, A. L. *Journal of Organometallic Chemistry* **2005**, *690*, 5066-5077.

(11) a) DiFranco, S. A.; Maciulis, N. A.; Staples, R. J.; Batrice, R. J.; Odom, A. L. *Inorganic Chemistry* **2012**, *51*, 1187-1200. b) Bemowski, R. D.; Singh, A. K.; Bajorek, B. J.; DePorre, Y.; Odom, A. L. *Dalton Transactions* **2014**, *43*, 12299-12305.

(12) Isidro-Llobet, A.; Álvarez, M.; Albericio, F. *Chemical Reviews* **2009**, *109*, 2455-2504.

(13) a) Pasko, C. M.; Dissanayake, A. A.; Billow, B. S.; Odom, A. L. *Tetrahedron* **2016**, *72*, 1168-1176. b) Dissanayake, A. A.; Staples, R. J.; Odom, A. L. *Advanced Synthesis & Catalysis* **2014**, *356*, 1811-1822. c) Dissanayake, A. A.; Odom, A. L. *Tetrahedron* **2012**, *68*, 807-812. d) Majumder, S.; Odom, A. L. *Tetrahedron* **2010**, *66*, 3152-3158. e) Barnea, E.; Majumder, S.; Staples, R. J.; Odom, A. L. *Organometallics* **2009**, *28*, 3876-3881. f) Majumder, S.; Gipson, K. R.; Odom, A. L. *Organic Letters* **2009**, *11*, 4720-4723. g) Majumder, S.; Gipson, K. R.; Staples, R. J.; Odom, A. L. *Advanced Synthesis & Catalysis* **2009**, *351*, 2013-2023.

(14) a) Becker, W.; Benthin, U.; Eschenhof, E.; Pfeil, E. *Angewandte Chemie* **1963**, *75*, 93-93. b) Rigaudy, J.; Lytwyn, E.; Wallach, P.; Kim Cuong, N. *Tetrahedron Letters* **1980**, *21*, 3367-3370. c) Fleming, I. In *Category 1, Organometallics*; 1st Edition ed.; Fleming, I., Ley, S. V., Eds.; Georg Thieme Verlag: Stuttgart, 2002; Vol. 4. d) Samples, M. S.; Yoder, C. H. *Journal of Organometallic Chemistry* **1987**, *332*, 69-73.