DEVELOPMENT OF TRANSITION METAL - CATALYZED REACTIONS FOR ORGANIC SYNTHESIS

by

Matthew P. Rainka

B.S.
University of Rochester, 2000

SUBMITTED TO THE DEPARTMENT OF CHEMISTRY IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY IN ORGANIC CHEMISTRY
AT THE
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

June 2005

Signature of Author:.....
Department of Chemistry
May 16, 2005

Certified by:.....
Stephen L. Buchwald
Camille Dreyfus Professor of Chemistry
Thesis Supervisor

Accepted by:.....
Robert W. Field
Chairman, Department Committee on Graduate Students

This doctoral thesis has been examined by a committee of the Department of Chemistry as follows:

Professor Rick L. Danheiser.....
Chairman

Professor Stephen L. Buchwald.....
Thesis Supervisor

Professor Gregory C. Fu.....

DEVELOPMENT OF TRANSITION METAL - CATALYZED REACTIONS FOR ORGANIC SYNTHESIS

by

Matthew P. Rainka

Submitted to the Department of Chemistry May, 2005
in Partial Fulfillment of the Requirements for the Degree of
Doctor of Philosophy in Organic Chemistry

ABSTRACT

Chapter 1.
A general catalyst system for the synthesis of tetra-*ortho*-substituted biaryls via the Suzuki-Miyaura cross-coupling reaction is described. It was found that the most efficient catalyst system is based on a phenanthrene-substituted biaryl phosphine ligand. Utilizing this ligand, a number of tetra-*ortho*-substituted biaryls were synthesized in good to excellent yields.

Chapter 2.
A procedure for the arylation of methyl and cyclic ketone enolates with *o*-halonitroarenes was developed. An unusual additive effect of phenols on the outcome of the reaction was observed and explored. This process has provided for the regioselective synthesis of a wide variety of substituted indoles from commercially available materials.

Chapter 3.
The first method for the asymmetric copper-catalyzed conjugate reduction of α,β-unsaturated esters containing β-heteroatoms was developed. We found that this system tolerated the presence of both lactams as well as azaheterocycles in the β-position of various enoates. This has led to the asymmetric synthesis of a number of interesting β-amino acid derivatives.

Chapter 4.
A copper-catalyzed conjugate reduction reaction that allows for a variety of γ-aryl containing α,β-unsaturated butenolides to be reduced in both high enantiomeric and diastereomeric excess was developed. While a number of catalysts based on chiral bisphosphines were found to successfully perform this transformation, optimal enantioselectivity was obtained when employing the commercially SYNPHOS ligand.

Thesis Supervisor: Stephen L. Buchwald
Title: Camille Dreyfus Professor of Chemistry

Acknowledgments

I would first like to thank my research advisor, Professor Stephen L. Buchwald. Steve has allowed me to work at my own pace on projects of interest to me, for which I am very grateful. I am indebted to him for the lessons I have learned both on science and on life while in his lab. I would also like to thank Professor Rick Danheiser for his helpful and insightful discussions as my thesis committee chair. I have had the pleasure of working with wonderful coworkers during my time at MIT including: Dr. Jingjun Yin, Dr. Xiao-Xiang Zhang, Dr. Jennifer Rutherford, Ms. Yimon Aye, and Dr. Jacqueline Milne. I am especially grateful to Jingjun, who mentored me in the ways of the lab when I first joined the Buchwald group. I would also like to thank the many other wonderful chemists who I have had the pleasure of working alongside during the past five years. In particular, I thank Joe Martinelli for bearing the brunt of my griping, for stepping up beyond the call of duty, and for always making me laugh. My experience here would certainly not have been what it was without the wonderful friendship and support of my classmates, Edward Hennessy and Eric Strieter. We have been through a lot together, and I am truly grateful for everything they have done for me over the past several years.

None of this would be possible without the support and guidance of my undergraduate research advisor, Professor Robert K. Boeckman Jr., who truly inspired my interest in organic chemistry. I would also like to thank his former group members for their support and guidance during my time in the lab with them. They made my experience truly memorable.

I would like to thank my lifelong friends Dave Schmitter and Kevin Louis whose support and friendship throughout the years have been tremendous.

I would be remiss to not thank Dave Smith, Dave Williams, and Julie Shepelavy for instilling a love of science in me at an early age.

Thank you cannot adequately express my feelings to my family. I thank my grandparents for showing me where I come from and what hard work really is. I thank my sister Kate for always keeping me on my toes. Her love, support, and friendship have made it a privilege to be her big brother. I thank my parents for their continued love and support throughout my life. I also would like to thank them for showing me how to be a good person and for making me believe that any goal is attainable when you set your mind to it.

Finally, and most importantly, I need to thank the love of my life, my wife Sharon. Her love and support for me have far exceeded my expectations. She believes in me and forces me to believe in myself and my abilities. For that and many other wonderful reasons, I love her and thank her.

PREFACE

This thesis has been adapted, in part, from the following articles co-written by the author:

"A Highly Active Suzuki Catalyst for the Synthesis of Sterically Hindered Biaryls: Novel Ligand Coordination" Yin, J.; Rainka, M. P.; Zhang, X. –X. Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162.

"An Annulative Approach to Highly Substituted Indoles: Unusual Effect of Phenolic Addititves on the Success of the Arylation of Ketone Enolates" Rutherford, J. L.; Rainka, M. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 15168.

"Copper-Catalyzed Asymmetric Conjugate Reduction as a Route to Novel Beta-Azaheterocyclic Acid Derivatives" Rainka, M. P.; Aye, Y.; Buchwald, S. L. *Proc. Natl. Acad. Sci., USA* **2004**, *101*, 5821.

TABLE OF CONTENTS

Introduction

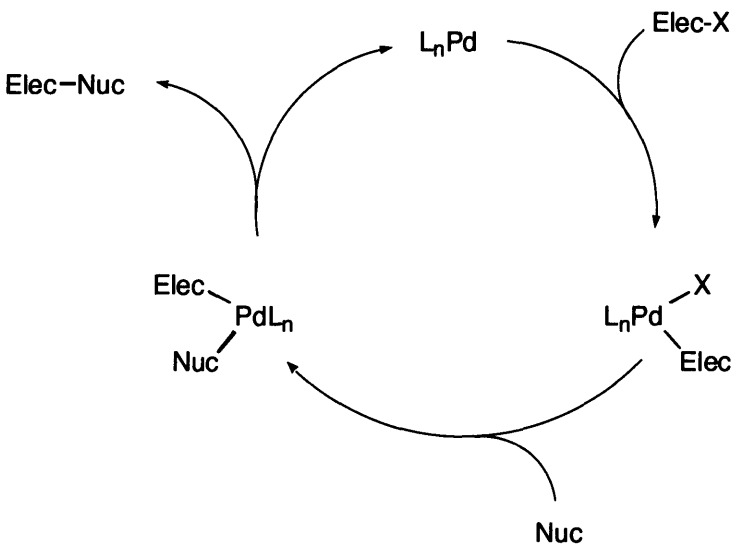
The use of transition metal-mediated reactions in organic synthesis has become of increasing importance over the past several decades.[1,2] In particular, a variety of methods have been developed to allow for the formation of a number of types of bonds, including C-C, C-H, C-N, C-O, C-S, and C-P. These developments have allowed for the synthesis of myriad complex molecules in a manner never before possible.[1b]

While a number of transition metals have been employed for these classes of reactions, catalysts based on palladium and copper have recently emerged as capable of performing a number of transformations in high yield, while maintaing low loadings, high functional group tolerance, and mild reaction conditions. Many of these features have been obtained through the proper choice of supporting ligands for the metal catalyst. A great deal of research has been undertaken in the development of new ligands and their use in various transition metal-catalyzed processes.

One area in which palladium catalysis has had a major impact in chemistry has been in the formation of carbon-carbon bonds. Of the several methods that have been developed, cross-coupling reactions (in particular the Suzuki-Miyaura reaction) have emerged as some of the most powerful and widely utilized transformations. In these reactions, the palladium catalyst typically undergoes oxidative addition with an electrophile (such as an aryl halide). The palladium(II) species can then react with a nucleophilic organometallic species to form a new palladium species that can then

undergo reductive elimination to generate the cross-coupled product and regenerate the catalyst (Figure 1).[1a]

Figure 1.



In addition to palladium catalysts, copper catalysts have also emerged as powerful tools in organic synthesis. In addition to oxidative couplings and cross-couplings,[2] copper catalysts have also proven to be quite efficient for conjugate addition and reduction chemistry.[3] In particular, significant progress has been made in utilizing copper catalysts for the selective 1,4-reduction of unsaturated carbonyl,[4] nitro,[5] and nitrile[6] compounds, including enantioselectively. An example of this type of transformation in shown in Figure 2.

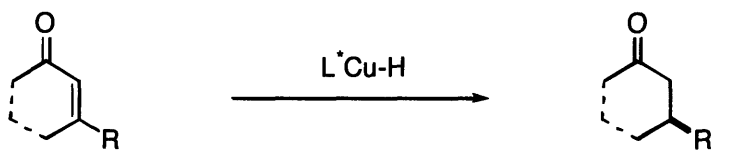


Figure 2.

The research presented in this thesis addresses the development of new or improved reactions or reaction conditions of importance to the synthetic organic

community through the use of transition metal catalysis. The work is presented in two sections. In the first section, progress made in the area of carbon-carbon bond formation through the use of palladium-catalyzed cross-coupling reactions will be discussed. Additionally, the significance of the cross-coupling reaction will be demonstrated through the synthesis of highly substituted indoles. The second portion of this thesis will be dedicated to research in the area of asymmetric copper-catalyzed conjugate reductions of α,β-unsaturated carbonyl compounds. The utility of this reduction chemistry will be demonstrated in the total synthesis of the natural product, eupomatilone-3.

References

(1) For general reviews see: (a) *Metal-Catalyzed Cross-coupling Reactions*, 2; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004. (b) Hegedus, L. S. *Transition Metals In the Synthesis of Complex Organic Molecules*; University Science Book: Mill Valley, CA, 1994. (c) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*; Permagon, 2000. (d) Miyaura, N. *Topics in Current Chemistry: Cross-coupling Reactions-/-A Practical Guide*, **2002**, *219*, 1-241. (e) Fairlamb, I. J. S. *Ann. Rep. Prog. Chem., Sect. B*, **2004**, *100*, 113.

(2) (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (b) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(3) (a) Riant, O.; Mostefaï, N.; Courmarcel, J. *Synthesis*, **2004**, 2943. (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, *19*, 3221.

(4) (a) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253. (b) Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *14*, 2417. (c) Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 2892. (d) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797. (e) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473. (f) Yun, J.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1129. (g) Lipshutz, B. H.; Servesko, J. M.; Peterson, T. B.; Papa, P.; Lover, A. A. *Org. Lett.* **2004**, *6*, 1273. (h) Lipshutz, B. H.; Servesko, J. M. *Angew. Chem., Int. Ed. Eng.* **2003**, *42*, 4789. (i) Lipshutz, B. H.; Lower, A.; Noson, K. *Org. Lett.* **2002**, *4*, 4045.

(5) (a) Czekelius, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 4575. (b) Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed. Eng.* **2003**, *115*, 4941. (c) Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed. Eng.* **2003**, *42*, 4793.

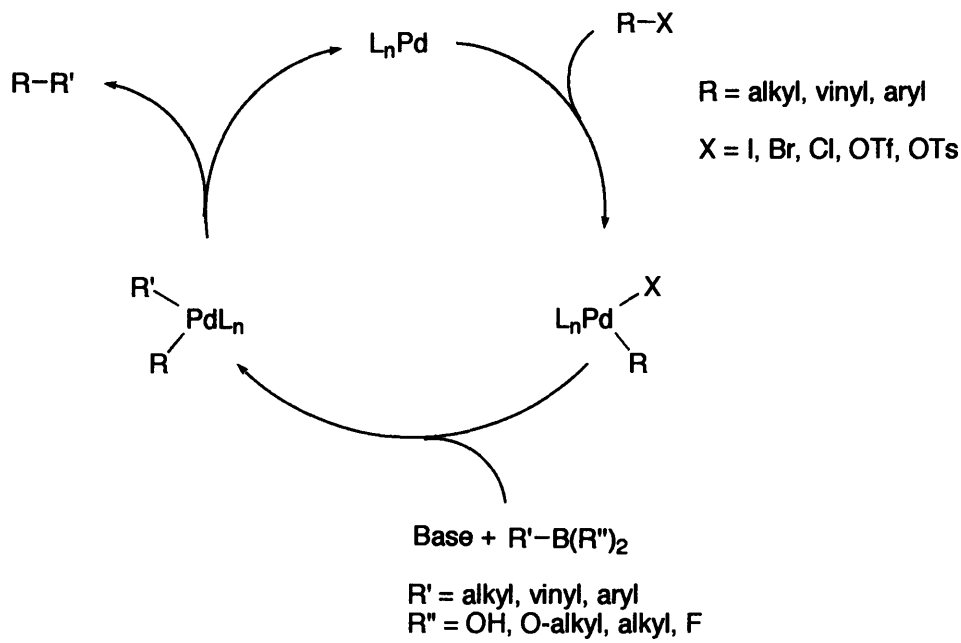
(6) Kim, D.; Park, B. –M.; Yun, J. *Chem. Commun.* **2005**, *13*, 1755.

Section 1.
Palladium-Catalyzed Carbon-Carbon Bond Formation

Chapter 1.
A Highly Active Suzuki-Miyaura Catalyst for the Synthesis of Sterically Hindered Biaryls

Introduction

The Suzuki-Miyaura cross-coupling reaction is among the most powerful C-C bond forming transformations available to synthetic organic chemists.[1] Owing to a great deal of research on this transformation, it now enjoys a broad scope and wide functional group tolerance. A possible catalytic cycle for this reaction is shown below.[1b] Oxidative addition of the electrophilic component (R-X) to a ligated palladium (0) species generates a new palladium (II) species. This species can undergo transmetalation with the boronic acid to generate a new palladium (II) species. Reductive elimination of this complex provides the desired product and regenerates the active catalyst.



While this reaction has been widely studied and utilized, at the time of this work, reactions involving sterically hindered coupling partners (where R and R' are both 2,6-disubstituted arenes) had realized only limited success[2,3] (subsequent to this work, there have been reports of various palladium-catalyzed cross-couplings involving sterically encumbered substrates).[4] The ability to perform these hindered cross-couplings is of

interest due to the presence of hindered biaryls in numerous natural products and polymeric materials.[1] Additionally, overcoming this limitation would aid in the development of more general asymmetric syntheses of axially chiral biaryl compounds.[1,6b] However, a general method for the coupling of two hindered arenes, particularly where each reactant possesses two *ortho* substituents, had yet to be realized.[1c,3,5] Foglesong has reported a Suzuki-Miyaura coupling to prepare an unsymmetrical biaryl with tetra-*ortho*-substitution in 12% yield.[3a] As part of his elegant work, Fu reported a single example of the preparation of a tetra-*ortho*-substituted biaryl in 76% yield (Negishi coupling), however, two *ortho* substituents were smaller than a methyl group.[5e] As part of our ongoing studies of the Suzuki-Miyaura coupling reaction[6], we have found general catalysts to prepare tetra-*ortho*-substituted unsymmetrical biaryls in modest to excellent yields.

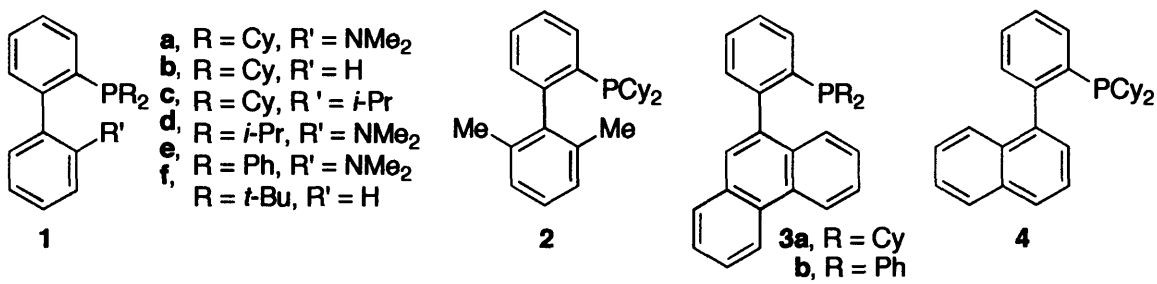


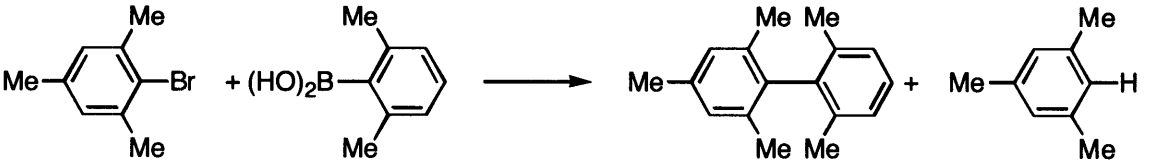
Figure 1. Hindered biarylphosphine ligands

Results and Discussion

In initial studies with biphenyl-based ligands **1a-c**, significant amounts of arene resulting from the reduction of aryl bromide were observed (Table 1, entries 1-3).[7] The use of ligands bearing either di-*iso*-propyl- or diphenylphosphino- groups yielded

increased amounts of mesitylene byproduct (entries 4 & 5). Increasing the size of the phosphine alkyl groups to *tert*-butyl resulted in the production of less than 1% of the desired biaryl. Doubly *ortho*- substituted ligand **2** furnished a slightly improved catalyst. Phenanthrene-based ligand **3a** gave superior results both in terms of reaction rate and biaryl:arene ratio (entry 8). The reaction proceeded to completion in less than 24 h with 4 mol% Pd and 8 mol% **3a**, affording the biaryl in 91% yield (GC) along with 9%

Table 1. Ligand Effects in the Coupling of Hindered Reacting Partners [a]



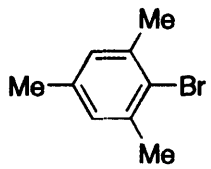
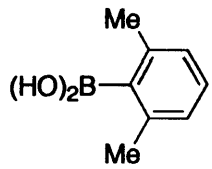
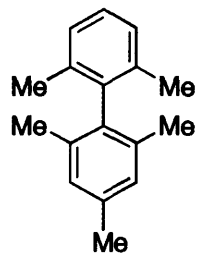
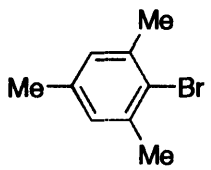
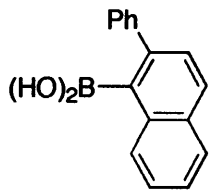
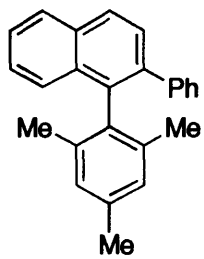
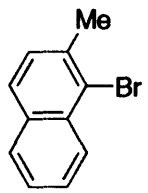
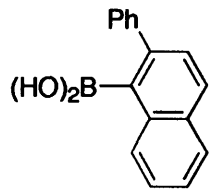
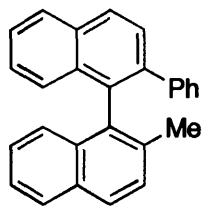
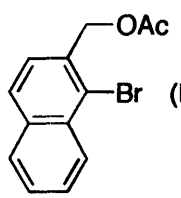
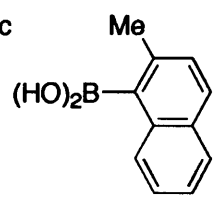
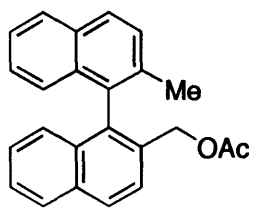
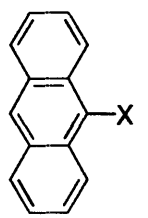
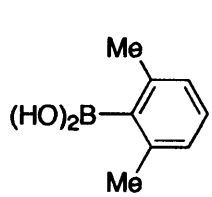
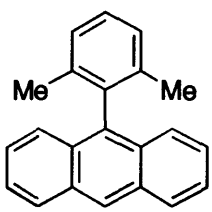
Entry	Ligand	Conv (%)	Biaryl (%)[b]	Biaryl / Aryl-H
1	**1a**	47	33	2.3
2	**1b**	20	10	0.9
3	**1c**	74	40	1.9
4	**1d**	68	34	1.6
5	**1e**	49	25	1.3
6	**1f**	21	<1	<0.3
7	**2**	56	48	5
8	**3a**	100	91	10
9	**3a**[c]	57	50	7.4
10	**4**	20	16	4.1

[a] Reaction conditions: 1.0 equiv ArBr, 1.4 equiv Ar'B(OH)$_2$, 3.0 equiv K_3PO_4, toluene, 2 mol% $Pd_2(dba)_3$, 8 mol% ligand, 110 °C, 17-24 h. [b] GC yield. [c] 0.5 mol% $Pd_2(dba)_3$, 1.2 mol% ligand used.

mesitylene. The phenanthrene ring of **3a** appears critical as lower conversion and biaryl:arene ratios were observed with naphthyl-based ligand **4** (entry 9). In all cases, <4% homocoupling of either reactant was detected. While detailed studies on the origin of the reduction of the aryl halide have not been undertaken, it is evident from the ligand screen that phenanthrene based ligands are particularly successful in preventing this side reaction. One hypothesis on the origin of the reduction product is that unligated palladium initiates a radical reaction that generates an aryl radical. This radical can then abstract a hydrogen atom from a number of potential sources, including the boronic acid, boric acid, or the ligand. This would give rise to the reduced aryl bromide and likely precipitate palladium black (which is observed in all cases, but to a lesser extent in the case where phenanthrene based ligands are employed). Therefore, the lower amount of reduction could be evidence that there is a unique binding of the phenanthrene portion of ligand **3a** (which has been observed in the solid state) that is unique relative to the other biaryl phosphine ligands examined, and allows for more of the palladium to remain ligated.[8]

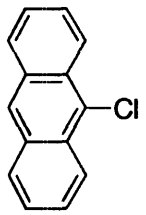
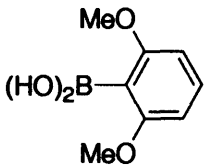
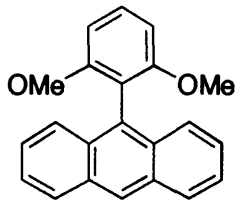
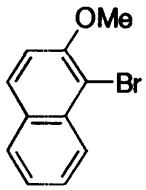
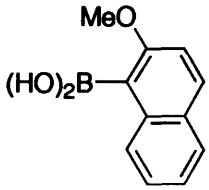
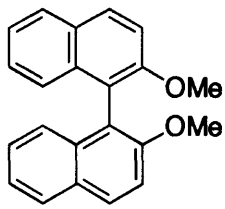
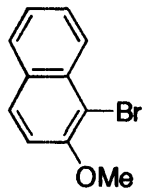
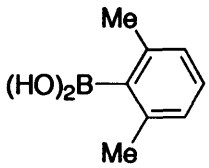
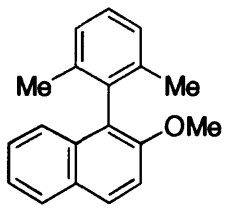
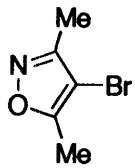
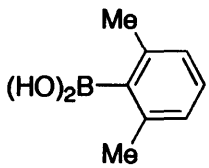
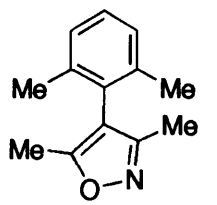
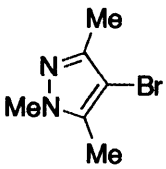
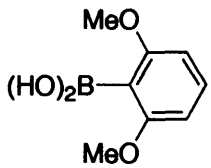
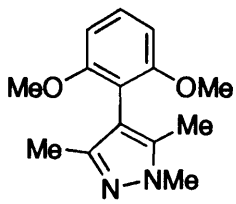
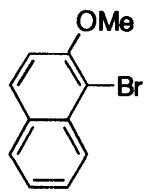
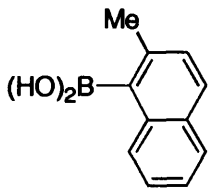
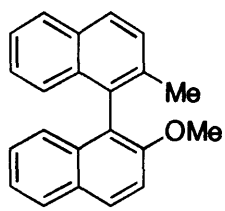
Phosphine **3a** and diphenyl analog **3b** proved in general to be excellent ligands for Suzuki-Miyaura cross-coupling reactions to form sterically hindered tetra-*ortho*-substituted biaryls in good yields (Table 2). *Ortho* substituents such as methyl, 1° alkyl, phenyl and alkoxy groups are accommodated by these catalyst systems. It proved necessary to use 2.0 equiv of the boronic acid to effect complete consumption of the aryl bromide in some cases, presumably due to competitive protodeboronation (entries 2, 3, 5-7, 11)[2] of the boronic acid. While **1a** was not suitable as a ligand for the synthesis of biaryls with four methyl groups, it could be used to prepare products in which one or two

Table 2. Electron-neutral cross-couplings employing **3a/b**

Entry	ArBr	$Ar'B(OH)_2$	Product	L	mol% Pd/ L	Yld,[a] %
1				3a	4/8	82
2				3b	4/8	70[b,c,d,e]
3				3b	2/4	90 [b,c,e]
4				3a	4/8	98
5 (Br) 6 (Cl)				3a 3a	1/1.2 1/1.2	80[b,c] 82[b,c]

[a] Reaction conditions: 1.0 equiv ArX, 1.5 equiv $Ar'B(OH)_2$, 3.0 equiv K_3PO_4, $Pd_2(dba)_3$, ligand, toluene, 110 °C. Isolated yields (average of 2 runs) of compounds estimated to be >95% pure as determined by ^1H NMR and GC or combustion analysis. [b] 2.0 equiv $Ar'B(OH)_2$ used. [c] *o*-Xylene as solvent. [d] 120 °C. [e] Experiments performed by Dr. Jingjun Yin.

Table 3. Electron-neutral or –rich cross-couplings employing **3a/b**

Entry	ArBr	$Ar'B(OH)_2$	Product	L	mol% Pd/ L	Yld,[a] %
1				3b	2/2.4	93[b,c,f]
2				1a	5/10	78[f]
3				1a	5/10	89
4				3b	10/12	60
5				3a	5/6	58[b,d,e]
6				3a	4/4.8	82

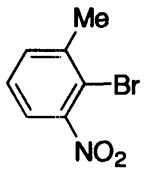
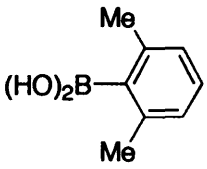
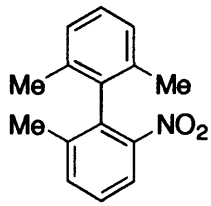
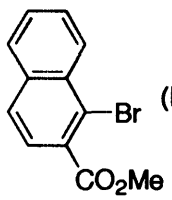
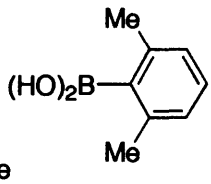
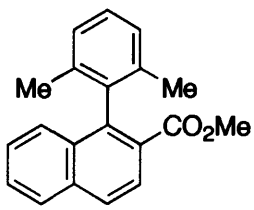
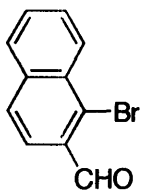
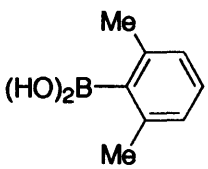
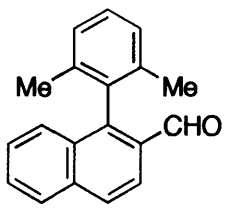
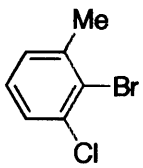
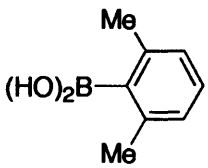
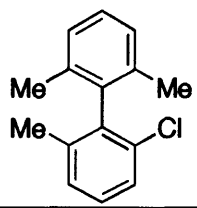
[a] Reaction conditions: 1.0 equiv ArX, 1.5 equiv $Ar'B(OH)_2$, 3.0 equiv K_3PO_4, $Pd_2(dba)_3$, ligand, toluene, 110 °C. Isolated yields (average of 2 runs) of compounds estimated to be >95% pure as determined by ^1H NMR and GC or combustion analysis. [b] 2.0 equiv $Ar'B(OH)_2$ used. [c] *o*-Xylene as solvent. [d] 120 °C. [e] 1.0 equiv 2,6-dimethylphenol as additive. [f] Experiments performed by Dr. Jingjun Yin.

of the four *ortho* substituents were methoxy groups (entries 8, 9). In several examples, *o*-xylene was found to be a superior solvent to toluene (entries 2, 3, 5-8). In addition to hindered aryl bromides, we were interested in employing aryl chlorides as coupling partners in this reaction. Pd-catalyzed cross-coupling reactions with unactivated aryl chlorides have received considerable attention recently.[2f,4,9] In cases where phosphine ligands that have been used for this purpose, the ligands employed are usually electron-rich di- or trialkylphosphines. Thus, it was surprising that during our investigation of this reaction, it was found that employing **3b** as the supporting ligand, 9-chloroanthracene was coupled in good yield (entry 7). Additionally, we became interested in expanding the scope of this reaction to include heteroaryl halides. It was observed that several heteroaryl halides could be employed in this reaction (Table 2, entries 10 and 11), although they did require the use of high catalyst loadings and elevated temperatures. Additionally, it was found that the reaction of the pyrrazole benefited from the addition of 1 equivalent of a phenol additive.

Unfortunately, the reaction conditions described above were not suitable when the aryl halide possessed an *ortho* electron-withdrawing group. In these cases, significant amounts of the corresponding phenol, presumably due to water present in the K_3PO_4 and/or boronic acid, were isolated. The use of DPEphos as ligand resulted in decreased phenol formation, and further inhibition of this side reaction was realized by the inclusion of freshly activated 4Å molecular sieves. Utilizing this modified system, a number of hindered aryl bromides with *ortho* electron-withdrawing groups were efficiently coupled with 2,6-dimethylphenyl boronic acid (Table 3). The DPEphos-based system could also

be used with unactivated aryl bromides (entry 4). Unfortunately, the **3b**/Pd catalyst system failed to chemoselectively activate the bromide. In other cases where **3b**- and DPEphos- based systems were compared (where the aryl halide did not contain an *ortho*-electron withdrawing group), the **3b**/Pd-catalyst afforded higher conversions of the aryl halide and higher biaryl:arene ratios.

Table 4. Cross-couplings of electron-deficient aryl bromides employing **DPEphos**

Entry	ArBr	$Ar'B(OH)_2$	Product	mol% Pd	T (°C)/ t (h)	Yld,[a] %
1				10	130/ 48	69
2				5	110/ 21	87
3				5	110/ 19	89[b]
4				6	120/ 24	96[b]

[a] Reaction conditions: 1.0 equiv ArBr, 2.0 equiv $Ar'B(OH)_2$, 3.0 equiv K_3PO_4, $Pd_2(dba)_3$, DPEphos (L:Pd=1.2:1), toluene, activated 4 Å mol. sieves. Isolated yields (average of 2 runs) of compounds estimated to be >95% pure as determined by ^1H NMR, and GC or combustion analysis. [b] Experiments performed by Dr. Jingjun Yin.

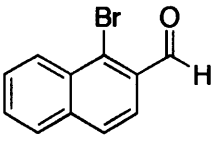
Conclusions

In summary, we have described a general catalyst system for the synthesis of tetra-*ortho*-substituted biaryls via the Suzuki-Miyaura cross-coupling reaction. The most efficient catalyst described is based on the phenanthrene-substituted ligand **3a**. Additionally, it was found that aryl halides containing electron-withdrawing substituents in the *ortho*-position performed best in hindered cross-coupling reactions when DPEphos was employed as the supporting ligand.

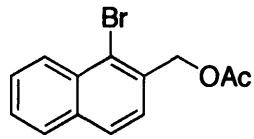
Experimental Section:

General Considerations. All reactions were carried out under an argon atmosphere in flame-dried glassware. Toluene was purchased from J. T. Baker in CYCLE-TAINER® solvent delivery kegs, which were vigorously purged with argon for 2 h. The toluene was purified by passing through two packed columns of neutral alumina and copper (II) oxide under argon pressure.[10] Anhydrous 1,2-dimethoxyethane (DME) and *o*-xylene were purchased from Aldrich Chemical Co. in a SureSeal® bottle and was used without further purification. Flash chromatography purifications with silica gel were performed using Silicycle ultra pure silica gel (230-400 mesh) packed columns. DPEphos and tris(dibenzylideneacetone)-dipalladium were purchased from Strem Chemical Company and used without further purification. K_3PO_4 was purchased from Fluka. 2-Phenyl-1-naphthylboronic acid[11], 2-methyl-1-naphthylboronic acid[12], and 2-methoxy-1-naphthylboronic acid[13] were prepared from the corresponding aryl bromides and *n*-BuLi and $B(OMe)_3$ following the procedures previously described. 1-Bromo-2-carbomethoxynaphthalene[14] was prepared according to literature procedures. 1-Bromo-2-

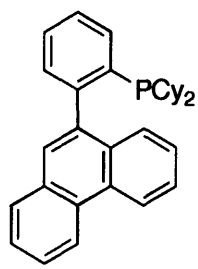
naphthylmethanol was prepared as described previously.[15] Ligands **1a-f**, **2**, and **4** were prepared according to literature procedures.[16] ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 MHz NMR spectrometer. IR spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. Elemental analyses were performed by Atlantic Microlabs Inc, Norcross, GA. Yields in Tables 2 and 3 refer to isolated yields (average of two runs) of compounds estimated to be ≥95% pure as determined by ^{1}H NMR, and GC analysis or combustion analysis. The procedures described in this section are representative, thus the yields may slightly differ from those given in Tables 2 and 3.



1-Bromo-2-formylnaphthalene. Pyridinium chlorochromate (323 mg, 1.5 mmol) was added in one portion to a stirring solution of 1-bromo-2-naphthylmethanol (237 mg, 1.0 mmol) in dichloromethane (4.0 mL) at room temperature. Diethyl ether (10 mL) was added to the reaction after 1.5 hours. The reaction mixture was then filtered through a plug of silica gel eluting first with diethyl ether, followed by dichloromethane and finally ethyl acetate. The filtrate was then concentrated and the resulting brown solid was purified by flash chromatography on silica gel eluting first with hexane, then with 3:1 hexane : ethyl acetate, to yield 209 mg (89%) of the title compound as a white solid whose spectra were in agreement with those reported in the literature.[17]



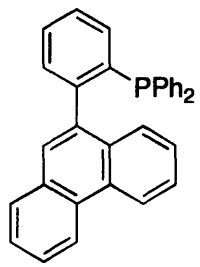
1-Bromo-2-acetoxymethylnaphthalene. An oven dried Schlenk flask with magnetic stir bar was charged with 1-bromo-2-naphthylmethanol (474 mg, 2.0 mmol) and dimethylaminopyridine (12 mg, 0.1 mmol). The flask was then evacuated, backfilled with argon, and this process was then repeated. Triethylamine (0.42 mL, 3.0 mmol) and dichloromethane (4 mL) were added and stirring was initiated. Acetic anhydride (0.21 mL, 2.2 mmol) was then slowly added to the reaction mixture. When addition was complete, the reaction mixture was allowed to stir at room temperature for 90 minutes. The reaction mixture was then filtered through a plug of silica gel eluting first with hexane, then with 3:1 hexane : ethyl acetate. The remaining eluent was then concentrated *in vacuo* to give 549 mg (98%) of the title compound as a white solid whose spectra were in agreement with those reported in the literature.[18]



2-(9-phenanthryl)phenyl-dicyclohexylphosphine. (3a) A round bottomed flask with a magnetic stirbar was charged with 9-bromophenanthrene (7.71 g, 30.0 mmol) and magnesium turnings (1.40 g, 57.5 mmol). The flask was then evacuated and refilled with argon. THF (50 mL) was added via syringe, and the mixture heated in an oil bath at 60 °C until the bromophenanthrene was consumed (as judged by GC analysis of an aliquot

that had been quenched with MeOH). 2-Bromochlorobenzene (4.78 g, 2.92 mL, 25 mmol) was then added dropwise via syringe over the course of approximately 20 min. The mixture was allowed to stir at 60 °C for 2 h, at which point the flask was removed from the oil bath and the mixture was permitted to cool to room temperature. Copper (I) chloride (3.22 g, 32.5 mmol) was then added, and stirring was continued for 5 min. At this point, dicyclohexylchlorophosphine (7.54 g, 7.25 mL, 32.5 mmol) was added dropwise via syringe. The resulting mixture was stirred at room temperature for 2 days, and hexane (90 mL) was added to the flask. The mixture was then filtered on a Büchner funnel. The filtered solid was then transferred to a beaker and stirred for approximately 15 min with ethyl acetate (250 mL) and conc. NH_4OH (250 mL). The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. A mixture of ethyl acetate and hexane (1:1, 125 mL) was added to the residue. The white solid that did not dissolve was filtered and dried *in vacuo*, and was identified as the pure title compound (2.43 g). The filtrate was concentrated and redissolved in a minimal amount of CH_2Cl_2. Hexane was added to the cloud point, and the mixture was concentrated *in vacuo* until white crystalline material became visible. After standing, the white solid was filtered to provide an additional 1.68 g of the title compound. The combined yield was 4.11 g (37%): mp 141-142 °C; ^{1}H NMR (300 MHz, C_6D_6) δ 8.51 (m, 1 H), 7.75 (m, 1 H), 7.63 (m, 3 H), 7.43-7.20 (m, 7 H), 1.90 (m, 1 H), 1.70-1.52 (m, 11 H), 1.22-0.98 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 148.5, 139.5, 139.4, 136.3, 136.1, 133.0, 132.5, 131.4, 131.2, 130.3, 130.1, 128.7, 128.6, 128.0, 127.1, 126.8, 126.5, 126.3, 122.9, 35.6, 33.5, 31.0, 30.2, 30.0, 29.8, 28.9, 27.8, 27.7, 27.3, 27.1, 26.6; ^{31}P NMR (121 MHz, $CDCl_3$) d -11.9; IR ($CHCl_3$, cm^{-1}) 3074, 3054, 2925, 2850, 252,

2163, 2009, 1493, 1447, 1428, 1001, 905, 851, 724; Anal. Calcd. For $C_{32}H_{35}P$: C, 85.30; H, 7.83. Found; C, 85.43; H, 7.96.

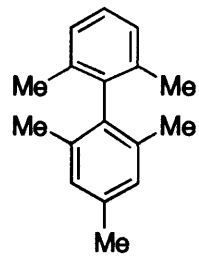


2-(9-phenanthryl)phenyl-diphenylphosphine. (3b) A round bottomed flask with a magnetic stirbar was charged with magnesium turnings (0.260 g, 10.7 mmol). The flask was then evacuated and refilled with argon. This evacuation/refill procedure was then repeated. A solution of 9-bromophenanthrene (1.50 g, 5.83 mmol) and THF (8 mL) was added via syringe to the magnesium, and the mixture heated in an oil bath at 60 °C until the bromophenanthrene was consumed (as judged by GC analysis of an aliquot that had been quenched with MeOH). The reaction mixture was allowed to cool to room temperature, and 2-bromochlorobenzene (568 μL, 4.86 mmol) was then added dropwise via syringe. The mixture was allowed to stir at 60 °C for 2 h, at which point the flask was removed from the bath and the mixture allowed to cool to room temperature. A solution of diphenylchlorophosphine (1.05 mL, 5.83 mmol) in THF (2 mL) was added dropwise via cannula. The resulting mixture was stirred at 60 °C for 17 h. The reaction mixture was allowed to cool to room temperature, and the solvent was removed *in vacuo* to yield a viscous brown oil. Water (15mL) was added and the product was extracted into ether (3 x 25 mL). The combined organic layers were filtered through silica gel, and the solvent was removed *in vacuo*. The mixure was purified by flash chromatography

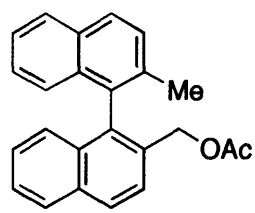
eluting with 20% toluene/80% hexanes. The resulting impure product was dissolved in a minimal amount of CH_2Cl_2, filtered through Celite, and triturated by the addition of EtOH. The solid was collected and dried *in vacuo* to yield 538 mg of the desired ligand as a white solid (21%): mp 136-138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76-8.70 (m, 2H), 7.66-7.14 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2, 136.1, 134.7, 134.4, 134.0, 133.6, 131.6, 131.5, 130.9, 130.4, 130.3, 129.2, 129.1, 128.9, 128.8, 127.5, 126.8, 123.1, 122.7; ^{31}P NMR (121 MHz,$CDCl_3$) δ -13.6; IR ($CHCl_3$, cm^{-1}) 3072, 3056, 2925, 2856, 1602, 1584, 1493, 1478, 1466, 1451, 1436, 1380, 1358, 1181, 1164, 1140, 1129,1119, 1090, 1069, 1044, 1027, 1000, 780, 768, 751, 697; Anal. Calcd. For $C_{32}H_{23}P$: C, 87.65; H, 5.29. Found; C, 87.62; H, 5.3.

General Procedure for Pd-Catalyzed Suzuki-Miyaura Couplings of Aryl Halides and Aryl Boronic Acids. (Tables 2 and 3) A flame-dried resealable Schlenk tube was charged with the indicated amounts of $Pd_2(dba)_3$ (0.5 mol% refers to 1 mol% of Pd), ligand, the solid reactant(s) (1.0 equiv of the aryl halide, 1.5 or 2.0 equiv of the aryl boronic acid, and, if indicated in the Tables, 4 Å molecular sieves (freshly activated by flame-drying under vacuum), and K_3PO_4 (3.0 equiv). The Schlenk tube was capped with a rubber septum, evacuated and backfilled with argon. The liquid reactant (if the aryl halide is a liquid) and toluene (or *o*-xylene as indicated in the Tables) (2-6 mL/ mmol aryl halide) were added through the septum. The septum was replaced with a teflon screwcap. The Schlenk tube was sealed, and the mixture was stirred at the indicated temperature (100-130 °C) for the indicated time (18-48 h) until the starting aryl halide had been completely consumed as judged by GC analysis. The reaction mixture was then cooled

to room temperature, diluted with dichloromethane or ether (10 mL), filtered through a pad of silica gel with ether, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel.

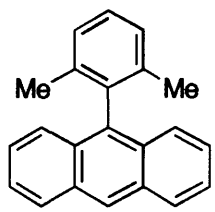


2,2',4,6,6'-Pentamethylbiphenyl. (Table 2, entry 1): The general procedure on a 0.5 mmol scale with toluene (1.0 mL) gave 92 mg of the title compound (82%) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.08 (m, 3 H), 6.94 (s, 2 H), 2.32 (s, 3 H), 1.90 (s, 6 H), 1.86 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 140.2, 137.2, 136.3, 135.9, 135.4, 128.5, 127.7, 127.6, 126.9, 21.3, 20.1, 20.0, 19.9; IR ($CHCl_3$, cm^{-1}) 2943, 2917, 2856, 1464, 850, 768, 753; Anal. Calcd. For $C_{17}H_{20}$: C, 91.01; H, 8.99. Found; C, 90.92; H, 9.12.[19]

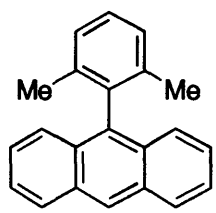


2-Acetoxymethyl-2'-methyl-1,1'-binaphthyl. (Table 2, entry 4) The general procedure on a 0.2 mmol scale with toluene (1.0 mL) gave 66 mg (97%) of the title compound as a white solid: mp 104-105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 8.7 Hz, 1 H), 7.90 (m, 2 H), 7.68 (d, J = 8.4 Hz, 1 H), 7.48 (m, 2 H), 7.38 (m, 1 H), 7.22 (m, 3 H), 7.10

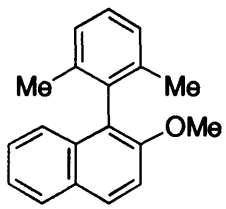
(d, J = 8.4 Hz, 1 H), 6.99 (d, J = 8.7 Hz, 1 H), 4.84 (ab pattern, 2 H), 2.05 (s, 3 H), 1.85 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 136.7, 134.9, 133.6, 133.3, 133.2, 132.7, 132.3, 132.1, 128.8, 128.3, 128.3, 128.2, 126.8, 126.5, 126.4, 126.3, 125.9, 125.2, 65.0, 20.9, 20.8; IR ($CHCl_3$, cm^{-1}) 3054, 3012, 2952, 2919, 2858, 1739, 1509, 1362, 1233, 1027, 814; Anal. Calcd. For $C_{24}H_{20}O_2$: C, 84.68; H, 5.92. Found; C, 84.56; H, 6.02.



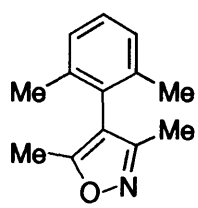
9-(2',6'-Dimethylphenyl)-anthracene. (Table 2, entry 5) The general procedure using 9-bromoantharacene on a 0.5 mmol scale with *o*-xylene (1.0 mL) gave 120 mg (85%) of the title compound as a white solid: mp 145-146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54, (s, 1 H), 8.12-8.10 (m, 2 H), 7.53-7.48 (m, 4 H), 7.44-7.31 (m, 5 H), 1.80 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 137.7, 135.8, 131.8, 129.7, 128.8, 127.9, 127.7, 126.4, 126.0, 125.9, 125.4, 20.1; IR ($CHCl_3$, cm^{-1}) 3047, 2916, 1440, 884, 845, 738; Anal. Calcd. For $C_{22}H_{18}$: C, 93.58; H, 6.42. Found; C, 93.29; H, 6.48.



9-(2',6'-Dimethylphenyl)-anthracene. (Table 2, entry 6) The general procedure using 9-chloroantharacene on a 0.5 mmol scale with *o*-xylene (1.5 mL) gave 121 mg (86%) of the title compound as a white solid. See above for the spectral data.

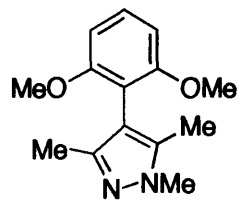


1-(2',6'-Dimethylphenyl)-2-methoxynaphthalene (Table 3, entry 3) The general procedure on a 0.4 mmol scale with toluene (1.0 mL) gave 90 mg (86%) of the title compound as a white solid: mp 96-98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J = 9.0 Hz, 1 H), 7.86 (m, 1 H), 7.40 (d, J = 8.7 Hz, 1 H), 7.37-7.26 (m, 3 H), 7.20 (m, 3 H), 3.85 (s, 3 H), 1.93 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 137.5, 135.9, 133.0, 129.3, 129.1, 128.2, 127.5, 127.4, 126.7, 124.5, 123.7, 123.4, 113.6, 56.5, 20.3; IR ($CHCl_3$, cm^{-1}) 3062, 3014,2939, 2919, 1621, 1594, 1507, 1465, 1331, 1272, 1256, 1246, 1148, 1094, 1067, 1021, 808, 772; Anal. Calcd. For $C_{19}H_{18}O$: C, 86.99; H, 6.92. Found; C, 86.69; H, 6.87.

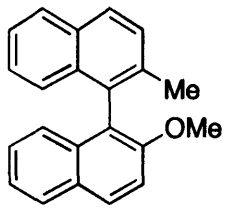


4-(2',6'-Dimethylphenyl)-3,5-dimethylisoxazole. (Table 3, entry 4) The general procedure on a 0.5 mmol scale with toluene (1.5 mL) gave 58 mg (58%) of the title

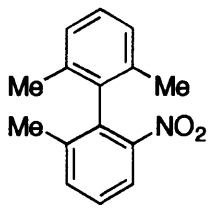
compound as a yellow solid: mp 105-107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 1 H), 7.13 (m, 2 H), 2.18 (s, 3 H), 2.04 (s, 6 H), 2.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 159.6, 138.2, 128.7, 128.4, 127.6, 114.8, 20.4, 16.5, 11.3, 10.5; IR ($CHCl_3$, cm^{-1}) 3068, 3024, 2964, 2954, 2927, 2861, 2246, 2159, 2030, 1638, 1465, 1445, 1410, 1233, 998, 920,778, 727; Anal. Calcd. For $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found; C, 77.74; H, 7.57; N, 6.48.



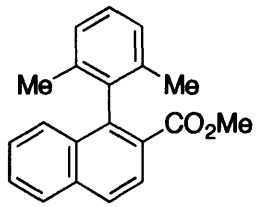
4-(2',6'-Dimethoxyphenyl)-1,3,5-trimethylpyrazole. (Table 3, entry 5) The general procedure on a 0.3 mmol scale at 120 °C with toluene (0.8 mL) gave 40 mg (55%) of the title compound as a light yellow solid: mp 98-99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (t, J = 8.4 Hz, 1 H), 6.63 (d, J = 8.4 Hz, 2 H), 3.77 (s, 9 H), 2.07 (s, 3 H), 2.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 1158.5, 146.9, 138.2, 111.1, 103.9, 55.8, 41.8, 36.2, 16.6, 12.8, 10.8; IR ($CHCl_3$, cm^{-1}) 3066, 3010, 2941, 2923, 2840, 1623, 1594, 1507, 1466, 1443, 1434, 1376, 1331, 1272, 1248, 1113, 1067, 1021, 808, 778, 731, 679; Anal. Calcd. For $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37. Found; C, 68.16; H, 7.37.



2-methoxy-2'-methyl-1,1'-binaphthyl. (Table 3, entry 6) The general procedure on a 0.25 mmol scale with toluene (0.8 mL) gave 61 mg (82%) of the title compound as a white solid. Spectroscopic data for this compound were in agreement with those reported in the literature.[20]



2,2'6-Trimethyl-6'-nitrobiphenyl. (Table 4, entry 1) The general procedure on a 0.25 mmol scale at 130 °C with activated 4Å molecular sieves and toluene (1.5 mL) gave 41 mg (68%) of the title compound as a yellow solid: mp 123-124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 8.3 Hz, 1 H), 7.54 (d, J = 7.7 Hz, 1 H), 7.41 (t, J = 7.7 Hz, 1 H), 7.25-7.11 (m, 3 H), 1.98 (s, 3 H), 1.94 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ139.1, 135.7, 135.4, 134.5, 134.4, 128.1, 128.0, 127.7, 121.6, 20.1, 19.9; IR ($CHCl_3$, cm^{-1}) 3060, 2968, 2912, 1520, 1362, 798, 747; Anal. Calcd. For $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27. Found; C, 74.67; H, 6.25.



1-(2',6'-dimethylphenyl)-2-carbomethoxynaphthalene. (Table 4, entry 2) The general procedure on a 0.20 mmol scale with activated 4Å molecular sieves and toluene (1.2 mL) gave 52 mg (90%) of the title compound as a white solid: mp 71-73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 8.5 Hz, 1 H), 7.94-7.91 (m, 2 H), 7.60-7.54 (m, 1 H), 7.43-7.33 (m, 2 H), 7.29-7.22 (m, 1 H), 7.18-7.15 (m, 2 H), 3.67 (s, 3 H), 1.83 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 141.2, 138.2, 136.4, 135.3, 131.9, 128.3, 127.9, 127.7, 127.54, 127.53, 127.2, 127.1, 126.9, 126.0, 52.2, 20.4; IR ($CHCl_3$, cm^{-1}) 3060, 2948, 2918, 1729, 1240, 1132, 768; Anal. Calcd. For $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found; C, 82.79; H, 6.35.

References:

(1) Reviews: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (c) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263. (d) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (e) Miura, M. *Angew. Chem., Int. Ed. Eng.* **2004**, *43*, 2201. (f) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419. (g) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (h) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.

(2) (a) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207. (b) Hoye, T. R.; Chen, M. *J. Org. Chem.* **1996**, *61*, 7940. (c) Kamikawa, K.; Watanabe, T.; Uemura, M. *J. Org.*

Chem. **1996**, *61*, 1375. (d) Anderson, J. C.; Namli, H.; Roberts, C. A. *Tetrahedron*, **1997**, *53*, 15123. (e) Zhang, H.; Kwong, F. Y.; Tian, Y.; Chan, Chan, K. S. *J. Org.Chem.* **1998**, *63*, 6886. (f) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (g) Chaumeil, H.; Signorella, S.; Le Drian, C. *Tetrahedron* **2000**, *56*, 9655.

(3) (a) Johnson, M. G.; Foglesong, R. J. *Tetrahedron Lett.* **1997**, *38*, 7001. Two groups have each reported a single example of the preparation of a hindered symmetrical binaphthyl: (b) Anderson, N. G.; Maddaford, S. P.; Keay, B. A *J. Org. Chem.* **1996**, *61*, 9556. (c) Cammidge, A. N.; Crépy, K. V. *Chem. Commun.* **2000**, 1723.

(4) (a) Barder, T.E.; Walker, S.D.; Martinelli, J.R.; Buchwald, S.L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. (b) Milne, J.E.; Buchwald, S.L. *J. Am. Chem. Soc.* **2004**, *126*, 13028. (c) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed. Eng.* **2004**, *43*, 1871. (d) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195. (e) Su, W.; Urgaonkar, S.; McLaughlin, P. A.; Verkade, J. G. *J. Am. Chem. Soc.* **2004**, *126*, 16433.

(5) Other Pd or Ni-based methods: (a) Miyano, S.; Okada, S.; Suzuki, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2044. (b) Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153. (c) Saa, J. M.; Martorell, G. *J. Org. Chem.* **1993**, *58*, 1963. (d) Terfort, A.; Brunner, H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1477. (e) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719 and references therein.

(6) (a) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem Soc.* **1999**, *121*, 9550. (b) Yin, J.; Buchwald, S. L. *J. Am. Chem Soc.* **2000**, *122*, 12051 and references therein.

(7) Synthesis of ligands **1a-f**, **2**, **4**: Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334.

(8) Yin, J.; Rainka, M. P.; Zhang, X. –X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162.

(9) (a) Bei, X. H.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Petersen, J. L. *J. Org. Chem.* **1999**, *64*, 6797-6803. (b) Zapf, A.l Ehrentraut, A.; Beller, M. *Angew. Chem. Int. Ed.* **2000**, *39*, 4153. (c) Bedford, R. B.; Welch, S. L. *Chem. Commun.* **2001**, 129.

(10) (a) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520. (b) Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Ed.* **2001**, *78*, 64.

(11) Yin, J. J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101-1104.

(12)Chelucci, G.; Bacchi, A.; Fabbri, D.; Seba, A.; Ulgheri, F. *Tetrahedron Lett.* **1999**, *40*, 553-556.

(13) Clews, J.; Curtis, A. D. M.; Malkin, H.; *Tetrahedron* **2000**, *44*, 8735-8746.

(14) Rosini, C.; Tanturli, R.; Pertici, P.; Salvadori, P. *Tetrahedron: Asymmetry* **1996**, *7*, 2971-2982.

(15) Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2001**, *123*, 7925.

(16) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334-5341.

(17) Smith, J. G.; Dibble, P. W.; Sandborn, R. E. *J. Org. Chem.* **1986**, *51*, 3762-3768.

(18) Cornejo, J. J.; Ghodsi, S.; Johnson, R. D.; Woodling, R.; Rickborn, B. *J. Org. Chem.* **1983**, *48*, 3869-3875.

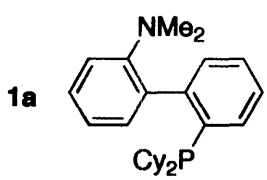
(19) Brotzeller, U.; Nyitrai, J.; Musso, H. *Chem. Ber.* **1980**, *113*, 3610-3620.

(20) Tami, Y.; Nakano, T.; Miyano, S. *J. Chem. Soc., Perkins Trans. 1* **1994**, 439-445.

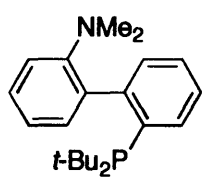
Chapter 2.
An Annulative Approach to Highly Substituted Indoles: Unusual Effect of Phenolic Additives on the Success of the Arylation of Ketone Enolates

Introduction

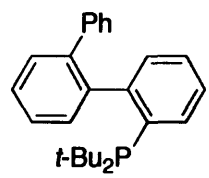
The synthesis of indoles has occupied organic chemists for well over a century.[1] The combination of traditional and modern methods has provided accessibility to a wide variety of structural variations of this important class of heterocycles.[2-9] Still, a general, mild, and efficient method to access 4-, 5-, 6- as well as 5,6- and other polysubstituted indoles from simple and readily accessible (non aryl iodide) precursors has proved elusive. Herein we disclose a method, based on the Pd-catalyzed arylation of ketone enolates, that concatenates simple ketones with widely available chloro- and bromoaromatics,[10] to provide a wide range of polysubstituted indole derivatives. The success of the method is due to an unexpected additive effect in the ketone arylation process: the inclusion of a catalytic quantity of a phenol in the enolate arylation of *o*-halonitroarenes effects a remarkable increase in the efficiency of the transformation. Despite the emergence of the palladium-catalyzed ketone arylation reaction,[11] to our knowledge, *o*-halonitroarenes have never previously appeared as coupling partners in this reaction.



1a



1b



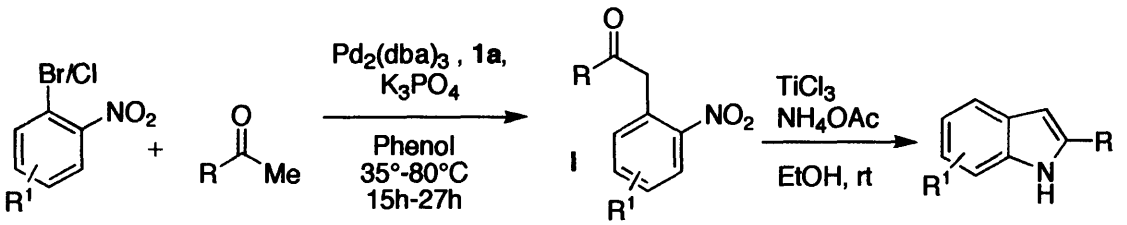
1c

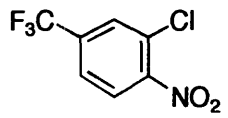
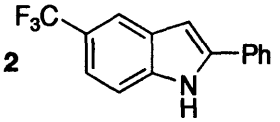
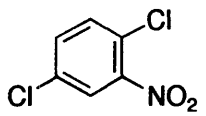
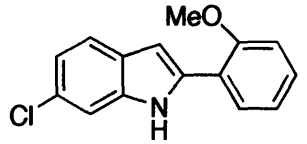
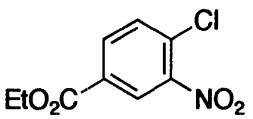
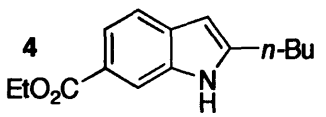
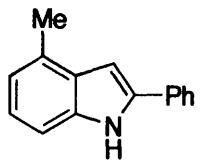
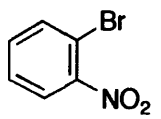
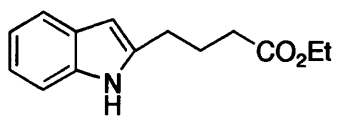
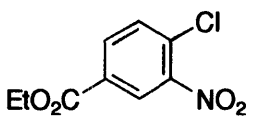
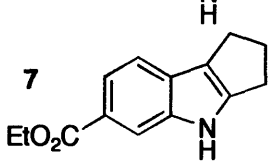
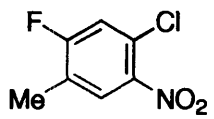
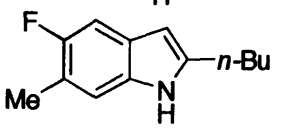
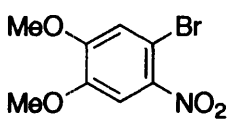
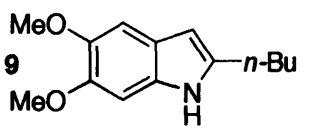
Results and Discussion

Our first attempts to couple ketone enolates with *o*-halonitroarenes furnished trace product along with the persistent formation of 2-nitrophenol. Any attempt to lessen the quantity of this phenolic impurity also resulted in suppression of product formation, indicating that the phenol might be performing a beneficial role. In fact, we found that addition of 20 mol% phenol, in combination with phosphine **1a**, led to the development of a highly efficient process for coupling *o*-halonitroarenes with ketones. Moreover, the products of the arylation reaction of ketones with *o*-halonitroarenes allowed for the synthesis of substituted indoles in a straightforward manner following previously described reductive cyclization procedures.[9,12]

The substrate scope of this reaction was found to be quite broad, as is depicted in Table 1. Both electron-rich and -deficient *o*-bromo or *o*-chloro nitroarenes were effective coupling partners using mild reaction conditions. The reactions were carried out at 35-50 °C (save entry 9) in toluene using K_3PO_4 as the base in the presence of 20 mol % of a phenol additive (4-methoxyphenol was found to be optimum in most cases).

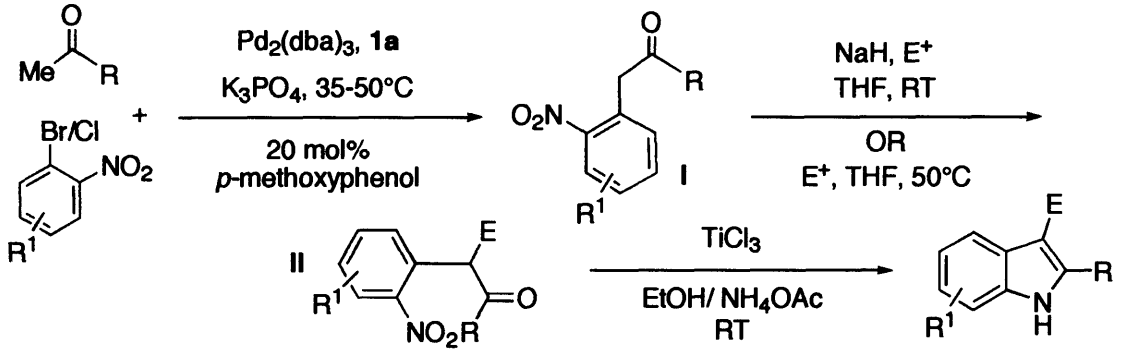
Table 1. Synthesis of 2,n-substituted indoles

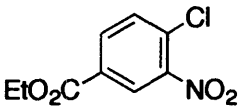
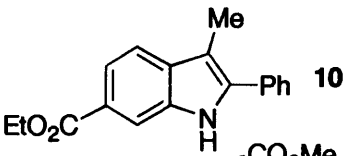
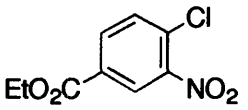
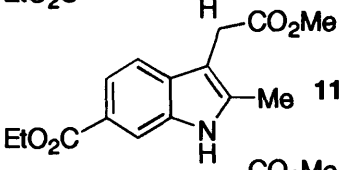
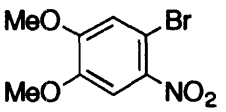
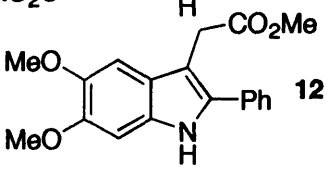
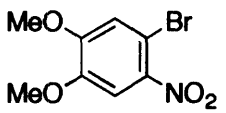
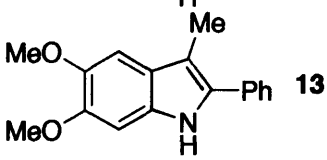
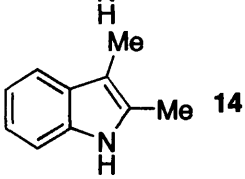
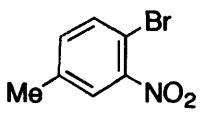
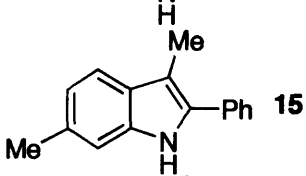
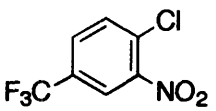
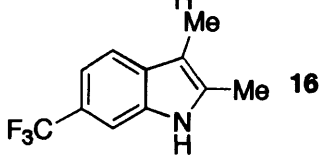


Entry	Aryl Halide	Indole	T (°C) / t (h)	Yield (%)[a]
1		**2** 	50/25	79[f]
2		**3** 	50/24	64[b,f]
3		**4** 	35/27	65[f]
4		**5** 	80/25	71[c,e,f]
5		**6** 	50/23	65[f]
6		**7** 	35/26	55[d,f]
7		**8** 	50/23	71
8		**9** 	50/23	75

[a] 20 mol% of phenol, 2 mol% Pd, 4 mol% **1a** with 2.2 equiv ketone on a 1 mmol scale. Isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ^{1}H NMR and GC or combustion analysis. [b] 4 mol% Pd, 8 mol% Ligand. [c] 2.0 equiv ketone used. [d] 6 equiv ketone used. [e] **1c** used as ligand. [f] Experiments performed by Dr. J. Rutherford.

Table 2. Synthesis of 2,3,n-substituted indoles

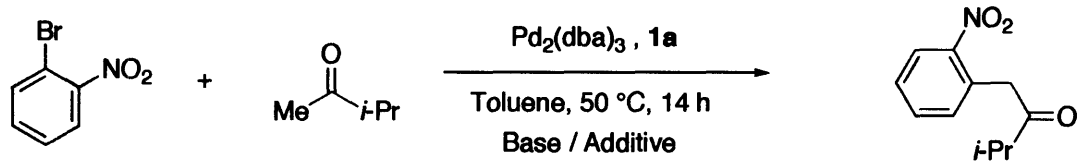


Entry	Aryl Halide	Electrophile	Indole		Yield (%)
1		MeI		**10**	61
2				**11**	71[c]
3				**12**	65
4		MeI		**13**	84[d]
5		MeI		**14**	76[c]
6		MeI		**15**	90[b]
7		MeI		**16**	54[c,d]

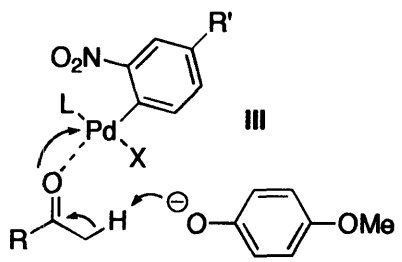
[a] Reaction conditions: 1.0 equiv ArX, 2.0 equiv ketone, 2.5 equiv K_3PO_4, 0.2 equiv 4-methoxyphenol, 1 mol% $Pd_2(dba)_3$, 4 mol% **1a**, 1 mL toluene, 22 hours. Isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ^1H NMR and GC or combustion analysis. [b] 1.1 equiv ketone, 2.0 equiv K_3PO_4. [c] 6.0 equiv ketone. [d] 1.5 equiv iodomethane, 1 mL THF added upon completion of ketone arylation.

Acetophenone derivatives, as well as alkyl methyl ketones, including acetone, were viable substrates in this process. However, the current reaction conditions are successful only when arylating either methyl or cyclic ketones. Mitigating this limitation was that the arylated ketones **I** could be deprotonated and efficiently alkylated with several electrophiles, and subsequently submitted to the reductive cyclization conditions to give 2,3,n-substituted indoles in moderate to excellent yields (Table 2). In our first alkylation protocol, the ketone arylation process was carried out followed by aqueous workup and isolation of the crude product. Without purification, this material was alkylated with the electrophile (1.1 equiv) using NaH (1.2 equiv) as the base in THF at room temperature to give **II**. Alternatively, we found that upon completion of the ketone arylation reaction, addition of iodomethane and THF (as a co-solvent) to the crude reaction mixture, and then heating at 50°C provided the same intermediate **II** as obtained above. In both cases, the alkylated material was carried on crude to the reductive cyclization step. This method allows for the independent variation of the three substrate components, providing a route to numerous indoles not previously readily available.
To date, we have only observed such a remarkable phenol additive effect in the case of electron-deficient aryl halide substrates. Moreover, its magnitude is significantly larger for *o*-halonitrobenzene derivatives than for other substrates containing electron withdrawing groups. In order to delineate the reason for the effect of the added phenol, a series of experiments were performed as outlined in Figure 1. From these, we found that no desired product was formed in the presence of an excess of the phenolic addititive, or in its absence. However, good results were obtained when the reaction was performed in the presence of a catalytic quantity of a phenol. There are several plausible explanations

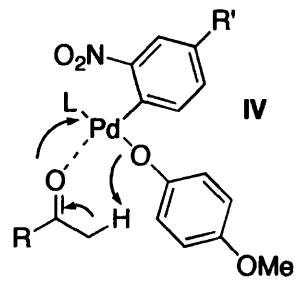
Figure 1.



Entry	Base	Additive	Result
1	2.2 equiv K_3PO_4	none	Low Conversion No Desired Product
2	2.2 equiv K_3PO_4	0.2 equiv phenol	50% Conversion Desired Product
3	2.2 equiv K_3PO_4	0.2 equiv KOPh	50% Conversion Desired Product
4	2.2 equiv K_3PO_4	1.2 equiv KOPh	Low Conversion No Desired Product
5	none	1.2 equiv KOPh	Low Conversion No Desired Product
6	none	0.2 equiv KOPh	10-20% Conversion Desired Product



III



IV

to account for these observations. The simplest of these is that the formation of an intermediate palladium phenoxide (e.g., **IV**) stabilizes an otherwise unstable intermediate preventing catalyst decomposition.[13] A second explanation is that intermediate **III** serves as a Lewis acid while the phenoxide serves as a base to deprotonate the coordinated ketone.[14] A third explanation is that **IV** can coordinate to the ketone, facilitating deprotonation with concomitant formation of a Pd-O bond. At present we have been unable to differentiate between the possibilities discussed above. However, we favor the third, intermediacy of a complex of type **IV**, as a dramatic decrease in efficiency is seen as more hindered phenols are used with the same substrate combination.

Conclusions

In summary, we have described a procedure for the arylation of methyl and cyclic ketone enolates with *o*-halonitroarenes. The success of this reaction was found to be dramatically impacted by the presence of catalytic quantities of phenolic additives. This process has provided for the regioselective synthesis of a wide variety of substituted indoles from commercially available materials.

Experimental Section:

General Considerations. All palladium-catalyzed reactions were carried out under an argon atmosphere in oven-dried glassware. Toluene was purchased from J. T. Baker in CYCLE-TAINER[15] solvent delivery kegs, which were purged with argon for 2 hours and purified by passing the toluene through two packed columns of neutral alumina and copper(II) oxide under argon pressure. All other reagents were used as purchased without further purification. 2-Bromo-5-fluoronitrobenzene and 3-chloro-4-nitrobenzotrifluoride were purchased from Marshallton Research Laboratories. All other halides and ketones were purchased from Aldrich or Alfa-Aesar. 4-Methoxyphenol was purchased from Acros and phenol was purchased from Aldrich. An aqueous titanium(III) chloride solution, 20% in 3% hydrochloric acid, was purchased from Alfa Aesar and each bottle was titrated with potassium bromate prior to use. The solutions were routinely 1.3

- 1.5M $TiCl_3$. Potassium phosphate was obtained from Fluka as a granular solid. Other sources of potassium phosphate are powders or hard solid pieces and often resulted in reduced rates when utilized in the reactions. More consistent results could be obtained when the potassium phosphate pieces were ground into a powder, but the current preferred source for potassium phosphate is Fluka. Pd_2dba_3 was purchased from Strem Chemical Company. 2-Dicyclohexylphosphino-2'-dimethylaminobiphenyl[16], 2-di-*t*-butylphosphino-2'-dimethylaminobiphenyl[16] and1-(di-*t*-butylphosphino)-*o*-terphenyl[17] were synthesized according to literature procedures. 2-Dicyclohexylphosphino-2'-dimethylaminobiphenyl and 2-di-*t*-butylphosphino-2'-dimethylaminobiphenyl are also commercially available from Strem Chemical Company.

Reported yields are the isolated yields of compounds determined to be greater than 95% pure as determined by proton NMR spectroscopy and gas chromatographic analysis. New compounds were characterized by elemental analysis or high resolution mass spectrometry combined with proton and carbon NMR spectroscopic analysis. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. IR spectra were obtained on a Perkin Elmer 1600 series FT-IR spectrometer. NMR spectra were recorded on a Varian XL 300 instrument with chemical shifts reported in ppm relative to trimethylsilane or residual deuterated solvent. Gas chromatographic analyses were carred out on a Hewlett Packard 6890 instrument with a FID detector and a HP-1 10m x 0.1 mm i.d. column.

General Procedure for the One-Pot Synthesis of Indoles: Arylation of Ketones with *Ortho*-nitro Aryl Halides Followed by Reductive Cyclization.

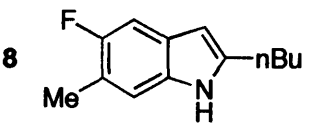
The synthesis of all compounds followed this general procedure. Details such as temperature and time are included in Table 1.

To an oven-dried resealable Schlenk tube containing a stir bar, Pd_2dba_3 (0.01 mmol), the ligand (0.04 mmol), K_3PO_4 (2.3 mmol), and the phenol (0.2 mmol) were added. If a solid, the *ortho*-nitro aryl halide (1.0 mmol) was also placed into the tube. The tube was fitted with a rubber septum and was evacuated and backfilled with argon twice. Toluene (2 mL) and the ketone (2.2 mmol) were syringed into the tube. If a liquid, the *ortho*-nitro aryl halide (1.0 mmol) was added via syringe to the reaction vessel as well. The tube was sealed with a teflon screw cap and was stirred at the indicated temperature (35 - 80 °C) for the indicated time when the starting halide was judged to be completely consumed by GC analysis (15-26.5h). After allowing the reaction to cool to room temperature, the reaction mixture was extracted with a total of 10 mL ethyl acetate and 10 mL water. The separated organic layer was concentrated *in vacuo*. The material was used, without purification, for the next step.

To a 100 mL round-bottom flask, aqueous $TiCl_3$ (16.5 mmol), aqueous ammonium acetate (15 mL; 6.6M), and ethanol (5 mL) were added. The flask was fitted with a rubber septum and a needle, connected via tubing to an argon tank, was inserted to provide a constant argon purge. Ethanol (15 mL) was added to dissolve the crude ketone.

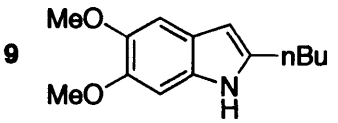
If the crude mixture was not completely soluble in ethanol, ethyl acetate (2-3 mL) was also added. The crude ketone solution was slowly added by syringe to the titanium trichloride solution and the resulting mixture was stirred at room temperature for 15 min (except for the cyclization of 2-isopropylindole, which was stirred at room temperature for 2.5 h).

The reaction mixture was extracted with diethyl ether (3 X 25 mL). The combined organic extracts were washed with saturated sodium bicarbonate, followed by brine, dried over sodium sulfate, and concentrated *in vacuo*. Purification of the crude product was carried out by column chromatography on silica gel.



2-Butyl-5-fluoro-6-methyl-1*H*-indole (Table 1, entry 13).

The general procedure was followed using 4-methoxyphenol. Column chromatography over silica gel eluting with 5:95 ethyl acetate:hexanes gave 144 mg (70%) of the title compound as a yellow solid: mp = 109-111 °C; ^{1}H NMR($CDCl_3$, 300MHz) δ7.71 (bs, 1H), 7.13 (m, 1H), 7.04 (m, 1H), 6.17 (m, 1H), 2.75 (t, J = 7.4 Hz, 2H), 2.38 (s, 3H), 1.68 (quint, J = 7.4 Hz, 2H), 1.44 (hext, J = 7.4 Hz, 2H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ155.3, 140.9, 132.4, 127.3, 118.5 (m), 111.67 (m), 104.3 (m), 99.5, 31.5, 28.3, 22.7, 15.6, 14.2; IR ($CDCl_3$, cm^{-1}) 3473, 2960, 2931, 1466, 1175, 1092, 859; Anal. Calcd for $C_{13}H_{16}FN$: C, 76.06; H, 7.86; Found: C, 76.08; H, 7.86.



2-Butyl-5,6-dimethoxy-1*H*-indole (Table 1, entry 14).

The general procedure was followed using 4-methoxyphenol. Column chromatography over silica gel eluting with 1:5 ethyl acetate:hexanes gave 175 mg (75%) of the title compound as a bright yellow oil: ^{1}H NMR($CDCl_3$, 300MHz) δ7.96 (bs, 1H), 7.06 (s, 1H), 6.70 (s, 1H), 6.16 (s, 1H), 3.93 (s, 3H), 3.83 (s, 3H), 2.71 (t, J = 7.4 Hz, 2H), 1.71 (quint, J = 7.4 Hz, 2H), 1.44 (hext, J = 7.4 Hz, 2H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ145.8, 144.5, 138.7. 130.0, 121.4, 101.9, 98.7, 94.5, 56.4, 56.2, 31.6, 28.1, 22.6, 14.1; IR ($CDCl_3$, cm^{-1}) 3736, 3477, 2960, 2937, 1486, 1314, 1200, 1123, 1009, 841, 725; Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; Found: C, 71.94; H, 8.25.

General Procedure for the Synthesis of 2,3-Substituted Indoles : Arylation of Ketones with *Ortho*-nitro Aryl Halides Followed by Alkylation, then Reductive Cyclization.

Procedure A. Details such as temperature and time are included in Table 2.

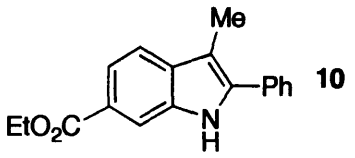
To an oven-dried resealable Schlenk tube containing a stir bar was added Pd_2dba_3 (0.01 mmol), the ligand (0.04 mmol), K_3PO_4 (2.3 mmol), and 4-methoxyphenol (0.2 mmol). If a solid, the *ortho*-nitro aryl halide (1.0 mmol) was also placed into the tube. The tube was fitted with a rubber septum and was evacuated and backfilled with argon twice.

Toluene (2 mL) and the ketone (2.0 mmol) were added via syringe to the tube. If a liquid, the *ortho*-nitro aryl halide (1.0 mmol) was added by syringe to the reaction vessel as well. The tube was sealed with a teflon screw cap and was stirred at the indicated temperature (35 – 50 °C) for the indicated time when the starting halide was judged to be completely consumed by GC analysis. (24 h) The reaction mixture was allowed to cool to room temperature, then diluted with 1 : 1 ethyl acetate : 2N NaOH. The layers were separated and the aqueous layer was extracted two times with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. The residue was then dissolved in THF (2 mL) and the electrophile (1.1 mmol) was added. This solution was then added to a stirring suspension of sodium hydride (52 mg, 1.3 mmol, 65% as a dispersion in mineral oil) in THF (2 mL). The reaction was allowed to stir at room temperature for two h, and then concentrated to dryness. The residue was then ***carefully*** dissolved in ethanol (4 mL) (this will also quench any residual NaH) and slowly added to a stirring solution of $TiCl_3$ (13 mL, 16 mmol) and ammonium acetate (16 mL, 6M) in ethanol (16 mL). When the addition was complete, the reaction mixture was allowed to stir at room temperature for an additional fifteen min, and was then diluted with diethyl ether. The layers were separated and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were then carefully washed with saturated aqueous sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated. The residue was then purified by flash chromatography over silica gel to give the desired indole product.

General Procedure for the Synthesis of 2,3-Substituted Indoles : Arylation of Ketones with *Ortho*-nitro Aryl Halides Followed by Alkylation, then Reductive Cyclization.

Procedure B. Details such as temperature and time are included in the Table 2.

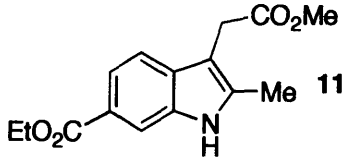
The method of procedure A was followed to prepare the arylated ketone. At this point, under a positive pressure of argon, the screw cap was removed and THF (1 mL) and methyl iodide (94 μL, 1.5 mmol) were added. The screw cap was replaced and the reaction flask was placed back in a 50 °C oil bath and left for 18 h. The reaction mixture was allowed to cool to room temperature, then diluted with a 1 : 1 mixture of ethyl acetate : water. The layers were separated and the aqueous layer was extracted two times with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated. This residue was then dissolved in ethanol (5 mL) and slowly added to a stirring solution of $TiCl_3$ (10 mL, 14 mmol) and ammonium acetate (11 mL, 6M) in ethanol (10 mL). When addition was complete, the reaction mixture was allowed to stir at room temperature for an additional fifteen min, then the reaction mixture was diluted with diethyl ether. The layers were separated and the aqueous layer was extracted two times with diethyl ether. The combined organic layers were then carefully washed with saturated aqueous sodium bicarbonate, brine, dried over magnesium sulfate, filtered and concentrated. The residue was then purified by flash chromatography over silica gel to give the desired indole product.



10

3-Methyl-2-phenyl-1*H*-indole-6-carboxylic acid ethyl ester (Table 2, entry 1).

General procedure A was followed at 50°C. Column chromatography over silica gel eluting with 1:1:8 ethyl acetate:dichloromethane:hexanes gave 167 mg (60%) of the title compound as a light yellow solid: mp = 133-135 °C; ^{1}H NMR ($CDCl_3$, 300MHz) δ8.43 (bs, 1H), 8.17 (m, 1H), 7.85 (m, 1H), 7.62 (m, 3H), 7.51 (m, 2H), 7.41 (m, 1H), 4.42 (q, *J* = 7.2 Hz, 2H), 2.50 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ167.8, 137.5, 135.1, 133.5, 132.7, 129.0, 128.0, 124.0, 120.7, 118.5, 113.1, 109.2, 99.9, 61.0, 14.8, 10.0; IR ($CDCl_3$, cm^{-1}) 3465, 2981, 1698, 1320, 1285, 1216, 1096, 770; Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; Found: C, 77.09; H, 6.04.

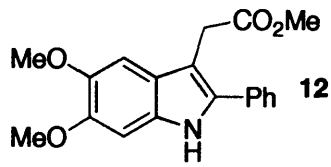


11

3-Methoxycarbonylmethyl-2-methyl-1*H*-indole-6-carboxylic acid ethyl ester (Table 2, entry 2).

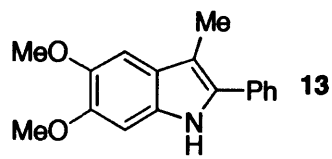
General procedure A was followed at 35°C with 6.0 equiv of ketone. Column chromatography over silica gel eluting with 1:4 ethyl acetate:hexanes gave 188 mg (68%) of the title compound as a yellow solid: mp = 107-110 °C; ^{1}H NMR ($CDCl_3$, 300MHz) δ8.34 (bs, 1H), 8.03 (m, 1H), 7.80 (m, 1H), 7.51 (m, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 3.72 (s, 2H), 3.70 (s, 3H), 2.45 (s, 3H), 1.44 (t, *J* = 7.2 HZ, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ172.3, 167.9, 136.7, 134.4, 132.1, 123.2, 120.9, 117.5, 112.7, 105.3, 60.9, 52.3, 30.3,

14.8, 12.3; IR ($CDCl_3$, cm^{-1}) 3751, 3651, 1735, 1698, 1314, 1301, 1270, 1208, 1021; Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; Found: C, 65.49; H, 6.29.



12

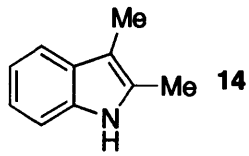
(5,6-Dimethoxy-2-phenyl-1*H*-indol-3-yl)-acetic acid methyl ester (Table 2, entry 3). General procedure A was followed at 50°C. Column chromatography over silica gel eluting with 1:3 ethyl acetate:hexanes gave 230 mg (70%) of the title compound as a yellow solid: mp = 43-45 °C; ^1H NMR ($CDCl_3$, 300MHz) δ8.1 (bs, 1H), 7.61 (m, 2H), 7.46 (m, 2H), 7.39 (m, 1H), 7.11 (s, 1H), 6.89 (s, 1H), 3.97 (s, 3H), 3.92 (s, 3H), 3.84 (s, 2H), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ172.7, 147.5, 145.3, 134.8, 132.7, 130.2, 129.0, 127.9, 127.7, 121.9. 105.4, 101.0, 94.5, 56.6, 56.4, 52.3, 31.4; IR ($CDCl_3$, cm^{-1}) 3724, 3465, 2956, 1733, 1484, 1341, 1245, 1216, 1160, 1003, 700; HRMS calc : 325.1314; found : 325.1295.



13

5,6-Dimethoxy-3-methyl-2-phenyl-1*H*-indole (Table 2, entry4). General procedure B was followed at 50°C. Column chromatography over silica gel eluting with 1:9 ethyl acetate:hexanes gave 212 mg (79%) of the title compound as a yellow solid: mp = 157-158 °C; ^1H NMR ($CDCl_3$, 300MHz) δ7.87 (bs, 1H), 7.53 (m, 2H), 7.43 (m, 2H), 7.32 (m, 1H), 7.01 (s, 1H), 6.89 (s, 1H), 3.97 (s, 3H), 3.93 (s, 3H),

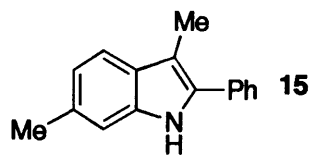
2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ147.3, 145.0, 133.6, 132.8, 130.2, 128.9, 127.4, 126.9, 122.9, 108.6, 100.8, 94.4, 56.6, 56.4, 10.3; IR ($CDCl_3$, cm^{-1}) 3749, 3691, 1482, 1243, 1216, 1000, 722; HRMS calc : 267.1259; found : 267.1245.



14

2,3-Dimethyl-1*H*-indole (Table 2, entry 5).[18]

General procedure A was followed at 50°C with 6.0 equiv of ketone. Column chromatography over silica gel eluting with 1:3 ethyl acetate:hexanes gave 103 mg (71%) of the title compound as a off white solid. Melting point and spectral data are identical to those previously described.

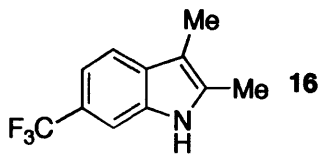


15

3,6-Dimethyl-2-phenyl-1*H*-indole (Table 2, entry 6).

General procedure A was followed at 50°C with 1.1 equiv of ketone and 2.0 equiv of K_3PO_4. Column chromatography over silica gel eluting with 5:95 ethyl acetate:hexanes gave 198 mg (90%) of the title compound as an off white solid: mp = 122-124 °C; ^1H NMR ($CDCl_3$, 300MHz) δ7.88 (bs, 1H), 7.58 (m, 2H), 7.51 (m, 3H), 7.37 (m, 1H), 7.17 (bs, 1H), 7.02 (m, 1H), 2.53 (s, 3H), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ136.3, 133.6, 133.4, 132.3, 128.9, 128.0, 127.7, 127.2, 121.4. 188.8, 110.8, 108.7, 22.1, 10.1; IR

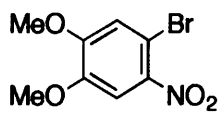
($CDCl_3$, cm^{-1}) 3464, 2923, 1461, 1034, 1007, 733, 698; HRMS calc : 221.1204; found : 221.1207.



16

2,3-Dimethyl-6-trifluoromethyl-1*H*-indole (Table 2, entry 7).

General procedure B was followed at 50°C with 6.0 equiv of ketone. Column chromatography over silica gel eluting with 5:95 ethyl acetate:hexanes gave 108 mg (51%) of the title compound as a yellow solid: mp = 156-157 °C; ^1H NMR ($CDCl_3$, 300MHz) δ7.85 (bs, 1H), 7.53 (m, 2H), 7.33 (m, 1H), 2.42 (s, 3H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ134.0, 131.7, 127.4, 123.8, 123.0, 122.6, 118.2, 115.8 (m), 107.5 (m), 11.9, 8.7; IR ($CDCl_3$, cm^{-1}) 3409, 2925, 2865, 1426, 1331, 1275, 1160, 1150, 1108, 874, 820; Anal. Calcd for $C_{11}H_{10}F_3N$: C, 61.97; H, 4.73; Found: C, 61.99; H, 4.78.



2-Bromo-4,5-dimethoxy-nitrobenzene.[18]

The procedure used is adjusted from that reported in the literature. A 250 mL round bottom flask equipped with a magnetic stir bar was charged with bromoveratrole (3 mL, 20.86 mmol) and glacial acetic acid (5 mL). This stirring mixture was cooled to between -4° and -8°C, then fuming nitric acid (1.77 mL, 41.71 mmol) was added dropwise. When addition was complete, the reaction mixture was allowed to warm to room temperature, then stirred at this temperature for an additional 30 min. Water (50 mL) was then added

to the reaction and the resulting precipitate was collected by filtration and recrystalized from ethanol to give 4.16 g (76%) of the title compound as light yellow needles. Melting point and spectral data are identical to those previously described.

References:

(1) For a recent review on indoles: Saxton, J.E. *Nat. Prod. Rep.* **1997**, 559.

(2) For reviews on indole syntheses: (a) Sundberg, R. J. *Indoles*; Academic Press: San Diego, 1996. (b) Gribble, G.W. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1045. (c) Gilchrist, T.L. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 2491.

(3) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111 and references therein.

(4) Chen, C.; Lieberman, D.R.; Larsen, R.D.; Verhoeven, T.R.; Reider, P.J. *J. Org. Chem.* **1997**, *62*, 2676.

(5) Tokuyama, H.; Fukuyama, T. *Chem. Rec.* **2002**, *2*, 37 and references therein.

(6)Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671 and references therein.

(7) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 2488.

(8) Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662.

(9) (a) Iwama, T.; Birman, V.B.; Kozmin, S.A.; Rawal, V.H. *Org. Lett.* **1999**, *1*, 673. (b) Kozmin, S.A.; Iwama, T.; Huang, Y.; Rawal, V.H. *J. Am. Chem. Soc.* **2002**, *124*, 4628.

(10) For other syntheses of α-aryl ketones see reference 9 and: (a) Kuehne, M.E. *J. Am. Chem. Soc.* **1962**, *84*, 837. (b) Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831. (c) RajanBabu, T.V.; Chenard, B.L.; Petti, M.A. *J. Org. Chem.* **1986**, *51*, 1704.

(d) Gassman, P.G.; Van Bergen, T.J. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. 6, 601. (e) Banwell, M. G.; Kelly, B. D.; Kokas, O. J.; Lupton, D. W. *Org. Lett.* **2003**, *5*, 2497.

(11) (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (b) Fox, J.M.; Huang, X.; Chieffi, A.; Buchwald, S.L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.

(12) (a) Ho, T.L.; Wong, C.M. *Synthesis* **1974**, 45. (b) Moody, C.J.; Rahimtoola, K.F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 673.

(13) A similar concept has been proposed in the Pd-catalyzed amination of aryl halides: Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996,** *118,* 13109.

(14) For another example where KOPh was used as a base in a Pd-catalyzed vinylation reaction see: Solé, D.; Urbaneja, X.; Bonjoch, J. *Adv. Synth. Catal.* **2004**, *346*, 1646.

(15) (a) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520. (b) Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Ed.* **2001**, *78*, 64.

(16) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334.

(17) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121,* 4369.

(18) Raucher, S.; Koolpe, G. A. *J. Org. Chem.* **1983**, *48*, 2066.

(19) Dillard, R. D.; Yen, T. T.; Stark, P.; Pavey, D. E. *J. Med. Chem.* **1980,** *23(7),* 717.

Section 2.
Copper-Catalyzed Asymmetric Conjugate Reduction Chemistry

Chapter 3.
Copper-Catalyzed Asymmetric Conjugate Reduction As a Route to Novel β-Azaheterocyclic Acid Derivatives

Introduction

β-Amino acids and their derivatives are of interest as structural components and due to their biological activity.[1] The asymmetric synthesis of these compounds has been realized through a variety of methods,[2] most notably asymmetric Mannich reactions,[3] diastereoselective or enantioselective conjugate additions,[4,5] and the reduction of β-amido α,β-unsaturated esters or nitriles.[6,7] While the reduction of α,β-unsaturated esters has proven to be a particularly powerful tool for this transformation, the various methods employed are generally limited to substrates that contain a primary amido group in the β-position.[8]

We recently described a versatile system for the asymmetric conjugate reduction of a wide variety of α,β-unsaturated carbonyl compounds.[9,10] Appropriately substituted acyclic α,β-unsaturated esters, cyclopentenones, lactones, and lactams could all be reduced in high yield and with excellent levels of enantioselectivity. However, to our knowledge there have been no successful conjugate reductions of substrates containing β-heteroatoms. One possible explanation for the absence of this class of substrates is that deactivation of the enoate can occur by the interaction of a lone pair of electrons on the heteroatom with the conjugated π-system of the enoate. We therefore reasoned that suitable substrates for this reaction that contained β-heteroatoms would possess functional groups in which this interaction is minimized. We report here the first method for the asymmetric conjugate reduction of α,β-unsaturated carbonyl compounds substituted with a nitrogen atom in the β-position. This method allows for the preparation of a variety of azaheterocycles and derivatives not available by other methods of asymmetric reduction.

Results and Discussion

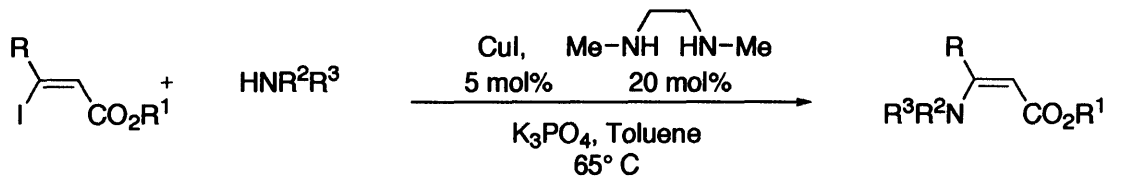
At the onset of this study, it was desirable to have a protocol for the synthesis of substrates that would allow for the introduction of a variety of nitrogen substituents in the β-position of α,β-unsaturated carbonyl compounds. In particular, we were interested in synthesizing compounds with a carbonyl adjacent to the nitrogen atom. The recently reported copper-catalyzed vinylation of amides and carbamates provided access to these types of compounds, and appeared to be a general system for the incorporation of a variety of nitrogen nucleophiles.[11] However, our initial attempts to couple β-iodo enoates[12] with 2-azetidinone using a copper (I) iodide / diamine catalyst with cesium carbonate as base in THF were unsuccessful. Only a trace amount of the desired product was observed employing these conditions previously successful for similar substrate combinations. Instead, a large amount of the corresponding alkynoate (originating from elimination of HI from the iodo-enoate) was formed. These results prompted examination of the effect of a variety of bases and solvents on the outcome of the reaction. While a variety of solvents and inorganic bases did promote the desired reaction, it was observed that the combination of potassium phosphate (weak base) in toluene (non-polar solvent) gave superior results and allowed for a number of vinyl iodides to be employed in the vinylation of 2-azetidinone, as shown in Table 1. Moreover, as shown in entry 11, a highly substituted enamide derived from 2-pyrrolidinone was also successfully synthesized using these conditions.

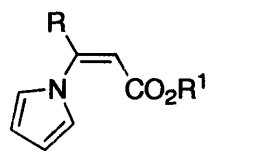
Extension of this protocol to aromatic nitrogen heterocycles provided access to another class of β-amino substituted α,β-unsaturated esters. While there are published

systems describing the arylation of nitrogen heterocycles,[13] copper-catalyzed vinylation of these heterocycles had remained previously unexplored.[14] Using the mild conditions described above, several vinyl iodides were successfully coupled with both pyrrole and indole. Sterically demanding systems (Table 1, entries 3,4,5) were also effective with this protocol, albeit in modest yields.

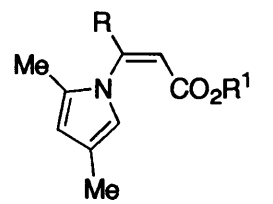
With a means to access a variety of β-amino substituted α,β-unsaturated esters, we attempted to carry out their conjugate reduction employing our previously reported reaction protocol. This entailed the use of copper (I) chloride, (S)-*p*-tol-BINAP, sodium *tert*-butoxide (1 eq relative to CuCl), and PMHS (polymethylhydrosiloxane), a mild and

Table 1. Synthesis of β-Nitrogen-Containing Enoates

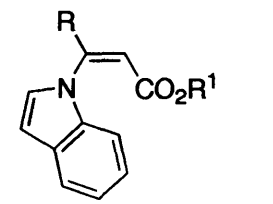




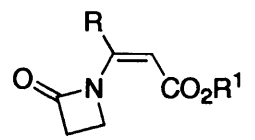
	R	R^1	Yield[a]
1)[b]	Me	Et	70
2)	Pent	Me	67
3)	Ph	Et	54
4)[b]	*t*-Bu	Et	59



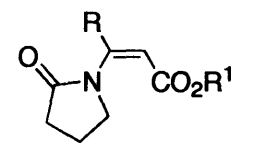
	R	R^1	Yield[a]
5)[c]	Me	Et	41



	R	R^1	Yield[a]
6)	Me	Et	83
7)	Pent	Me	62



	R	R^1	Yield[a]
8)[c]	Me	Et	70
9)	Pent	Me	75
10)	Ph	Et	67

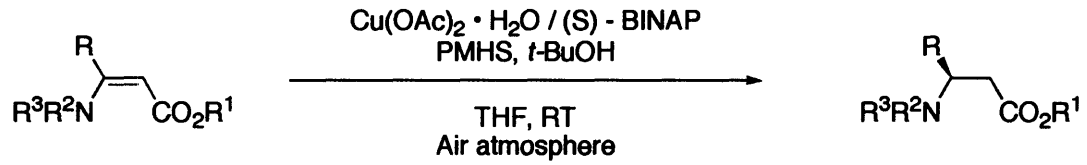


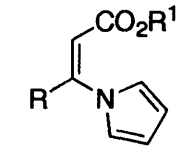
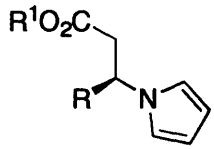
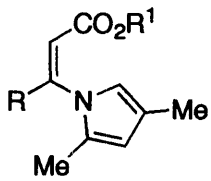
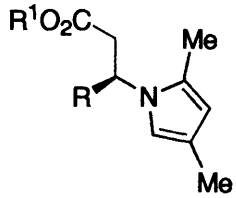
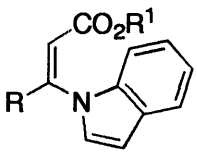
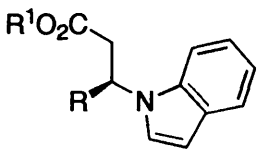
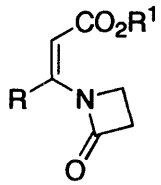
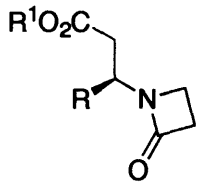
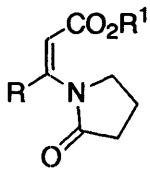
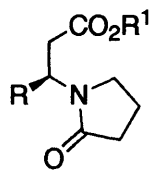
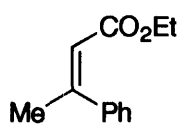
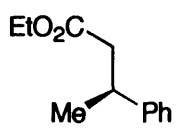
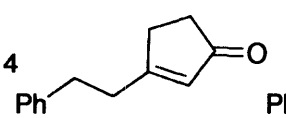
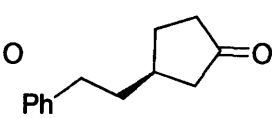
	R	R^1	Yield[a]
11)[d]	Me	Et	70

[a] Isolated yield average of two runs determined to be >95% purity by ^{1}H NMR or GC. [b] 10 mol% Cu, 20 mol% diamine. [c] 20 mol% Cu, 40 mol% diamine. [d] 10 mol% Cu, 40 mol% diamine.

inexpensive hydride source, in toluene.[9] While our initial results with this system did show conversion to the desired product, further optimization was required. Examination of various copper (I) and copper (II) salts indicated that a number of different copper sources were effective precatalysts. Interestingly, we found that $Cu(OAc)_2 \cdot H_2O$ was effective as a precatalyst for the reaction even in the absence of added sodium *tert*-butoxide. Several solvents or solvent mixtures could be employed, however, the use of THF provided faster reaction rates than that observed with other solvents. This rate enhancement is likely due to greater solubility of the copper precatalyst in THF. An additional increase in rate was observed, as in previous systems,[9a,15] when sterically hindered alcohols were added to the reaction mixture. Further, when reactions were performed under an atmosphere of air, the reaction rates were faster than those carried out under inert atmosphere. This phenomenon has been observed previously in reactions containing copper-hydride catalysts.[9a, 16] While detailed mechanistic studies on this effect have not been carried out, there are several plausible explanations. One hypothesis on the origin of this rate enhancement is that oxygen accelerates the formation of either the precatalyst or active catalyst.[16] A second rationalization could be that trace water in the atmosphere may facilitate protonation of the copper enolate, helping turn over the catalyst. It should be noted that in all of these studies the enantiomeric excess of the product remained unchanged. The combination of these findings led to the protocol for the reduction of 3-aza-2-enoates, the scope of which was examined and the results are summarized in Table 2.

Table 2. Asymmetric Conjugate Reduction



Entry[c]	Substrate	Product	R	R^1	Time (h)	Yield[a]	%ee[b]
1			**12** Me	Et	1	88	81
2			**13** Pent	Me	1	90	87
3[d]			**14** Ph	Et	20	87	86
4[d,e]			**15** *t*-Bu	Et	24	83	86
5[d]			**16** Me	Et	24	83	86
6			**17** Me	Et	1.25	96	90
7[f]			**18** Pent	Me	2	96	86
8[e]			**19** Pent	Me	24	94	86
9[e,g]			**20** Me	Et	24	86	80
10[d,e]			**21** Pent	Me	24	98	94
11[d]			**22** Ph	Et	24	96	99
12[d,e]			**23** Me	Et	9	90	82
13			**24**		3	84	92
14			**25**		1	85	89

[a] Isolated yield (average of two runs) determined to be >95% purity by ^{1}H NMR or GC. [b] Determined by HPLC. [c] 5 mol% Cu, 5 mol% BINAP, 4 equiv PMHS, 4 equiv *t*-BuOH. [d] 10 equiv PMHS. [e] 10 mol% Cu, 10 mol% BINAP. [f] 5 mol% Cu, 5 mol% BINAP, 6 equiv PMHS, 45 °C. [g] 8 equiv PMHS.

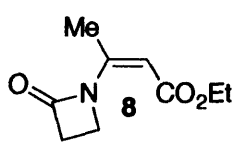
Various *N*-vinyl pyrroles (Table 2, entries 1-4) were reduced in excellent yield with high levels of enantioselectivity, including the hindered substrate 4,4-dimethyl-3-pyrrol-1-yl-pent-2-enoic acid ethyl ester (Table 2, entry 4).[17] α,β-Unsaturated esters containing an indole moiety (Table 2, entries 6-8) in the β-position were also effectively transformed. In addition, substrates that possessed lactams in the β-position were also efficiently reduced. Both β-lactam- (Table 2, entries 9-11) and pyrrolidinone-containing substrates (Table 2, entry 12) gave excellent yields and enantioselectivities under the reduction conditions employed.

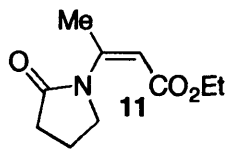
Hindered substrates (containing one or two large substituents at the β-position (Table 2, entries 3,4,5,8)) required long reaction times, likely a result of unfavorable steric interactions. The lower reaction rates necessitated the use 6-10 equivalents of PMHS, as the reaction of the silane with trace moisture in the atmosphere was competitive. Interestingly, when attempting to reduce the indole containing substrate **7**, it was found that the reaction could be performed either under the standard reaction conditions (room temperature) using a slightly higher catalyst loading and longer reaction time, (Table 1, entry 8) or could be run with a shorter reaction time and with less catalyst by performing the reaction in a sealed tube under nitrogen at 45 °C (Table 2, entry 7). These results suggest the enantioselectivity of the system appears to be independent of temperature over this range.

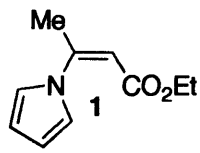
While substrates with either a heterocycle or a lactam in the β-position were viable under the reaction conditions, their reaction rates varied. Typically, substrates containing a lactam in the β-position required longer reaction times than those with a β-pyrrole or -indole substituent. A more detailed examination of the reaction rates of

several substrates was performed and the results are summarized in Table 3. Interestingly, when an equimolar amount of substrates **8** and **1** were mixed and subjected to the usual reaction conditions, a decrease in the rate of reduction of **1** was observed. Similar results were obtained when a mixture of **11** and **1** were submitted to the reaction conditions as well. Therefore, we propose that the carbonyl group of the lactam moiety likely coordinates to the copper in a non-productive manner, giving rise to lower reaction rates of **8** and **11** compared to substrate **1**. Additionally, when equal molar amounts

Table 3. Relative Rates in Conjugate Reduction Reaction[a]







	11+8	8+11	8+1	11+1
krel	1	2.6	95	1	2.6	32	32

[a] k_{rel} of mixed experiments are for the reduction of substrates indicated in bold.

of substrates **8** and **11** were mixed and subjected to the reaction conditions, their rates were identical to those run in the absence of the second substrate. This result suggests that although the coordination of the lactam to copper does inhibit the reaction, the more significant effect on the rate is the interaction of the lone pair on nitrogen with the π-system. The observed higher relative rate for the δ-lactam relative to the β-lactam is presumably due to the greater N=C character in the former. The observation that substrate **1** was the most reactive substrate in the study is consistent with this notion, as the interaction between the nitrogen's lone pair of electrons and the π-system in this substrate should be minimal.

The reaction conditions described here are more convenient than those we reported earlier for asymmetric conjugate reductions, eliminating the use of air- and

moisture-sensitive CuCl and hygroscopic sodium *tert*-butoxide. In addition to being effective for the reduction of β-heteroatom-containing α,β-unsaturated esters, these new conditions are also successful in the reduction of simple α,β-unsaturated ketones and esters (Table 2, entries 13,14) affording yields and enantioselectivities comparable to those obtained using previous systems.[9] It is noteworthy that as in previous studies, there is a change in the absolute stereochemistry of the products originating from the acyclic ester and the cyclopentenone.[9d,e] This could suggest that the two different classes of substrate may bind to the catalyst in different orientations.

Conclusions

In conclusion, we have developed a copper-catalyzed vinylation of nitrogen heterocycles that couples highly substituted vinyl iodides with pyrroles and indole. Additionally, the first method for the asymmetric conjugate reduction of α,β-unsaturated esters containing β-heteroatoms. We found this system tolerated the presence of both lactams as well as azaheterocycles in the β-position of various enoates. Moreover, the development of this reaction has led to the asymmetric synthesis of a number of interesting β-amino acid derivatives.

Experimental Section

I. General Considerations.

Unless otherwise noted, THF and toluene were purchased from J.T. Baker in CYCLE-TAINER® solvent-delivery kegs and vigorously purged with argon for 2h. The solvents were further purified by passing them under argon pressure through two packed columns

of neutral alumina (for THF) or through neutral alumina and copper (II) oxide (for toluene)[16]. Starting materials for substrate synthesis were purchased from commercial sources and used as is. Ethyl *trans*-β-methylcinnamate, PMHS (polymethylhydrosiloxane), *t*-BuOH, and N,N'-dimethylethylene diamine were purchased from Aldrich and used as is.

Yields refer to isolated yields of compounds of greater than 95% purity as estimated by capillary GC and ^{1}H NMR. Yields reported in this section refer to a single experiment, while those reported in the tables are the average of two or more runs.

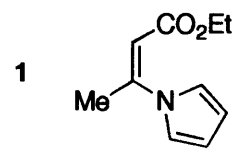
All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy, in addition to elemental analysis (Atlantic Microlabs, Inc) or HRMS. Nuclear Magnetic Resonance spectra were recorded on a Varian Mercury 300 or a Varian Unity 300 instrument. Infrared spectra were recorded on an ASI Applied Systems ReactIR 1000 (liquids and solids were measured neat on a DiComp probe). All ^{1}H NMR experiments are reported in δ units, parts per million (ppm) downfield from tetramethylsilane. All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.23 ppm), and all were obtained with ^{1}H decouling. Melting points (uncorrected) were obtained on a Mel-Temp capillary melting point apparatus. Optical rotations were taken on a Jasco Model-1010 Polarimeter at 23 °C. Gas Chromatographic analyses were performed on a Hewlett-Packard 6890 gas chromatography instrument with an FID detector using 25m x 0.20 mm capillary column with cross-linked methyl siloxane as a stationary phase. Chiral High Performance Liquid Chromatography analyses were performed on a Hewlett-Packard

1100 system with an HP 1100 Diode Array Detector, using the columns and wavelengths mentioned in section III. Separation conditions were determined from racemic material that was obtained via hydrogenation over Pd/C of the dehydro-β-amino acid derivatives.

II. Synthesis of Dehydro-β-Amino Acid Derivatives

General procedure A: An oven-dried Schlenk flask with Teflon-coated magnetic stir bar was allowed to cool to room temperature under nitrogen, and then charged with copper (I) iodide (0.10 mmol), potassium phosphate (1.5 mmol), and (if a solid) the nitrogen nucleophile (1.5 mmol). The flask was then capped with a rubber septum, evacuated, backfilled with nitrogen; this process was repeated one time. Toluene (0.50 mL) was added, followed by the diamine (0.20 mmol), (if a liquid) the nitrogen nucleophile (1.5 mmol), and the vinyl iodide (1.0 mmol) as a solution in toluene (0.50 mL). The septum was then replaced with a Teflon screw cap under a positive pressure of nitrogen and the flask was sealed and placed in a 65 °C oil bath with stirring for the time indicated. Upon complete conversion of the vinyl iodide (as judged by gas chromatography), the reaction mixture was allowed to cool to room temperature. The reaction solution was partitioned between water and ethyl acetate, the phases were separated, and the aqueous phase was extracted 3 additional times with ethyl acetate. The combined organic layers were then dried over magnesium sulfate, filtered, and the solvent removed with the aid of a rotory evaporator. The crude residue was then purified by flash chromatography on silica gel to give the desired compound.

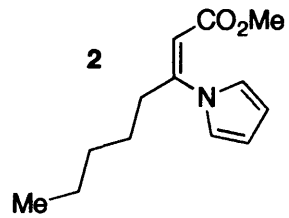
General Procedure B: A flame dried 25 mL round-bottom flask containing a Teflon-coated magnetic stir bar was allowed to cool to room temperature under nitrogen, then charged with copper (I) iodide (0.50 mmol), potassium phosphate (7.5 mmol), and (if a solid) the nitrogen nucleophile (7.5 mmol). The flask was then capped with a rubber septum, evacuated, backfilled with nitrogen; this process was repeated one time. Toluene (2.5 mL) was added, followed by the diamine (1.0 mmol), (if a liquid) the nitrogen nucleophile (7.5 mmol), and the vinyl iodide (5.0 mmol) as a solution in toluene (2.5 mL). The flask was then placed in a 65 °C oil bath with stirring for the time indicated. Upon complete conversion of the vinyl iodide (as judged by gas chromatography), the reaction mixture was allowed to cool to room temperature. The reaction solution was partitioned between water and ethyl acetate, the phases were separated, and the aqueous phase was extracted 3 additional times with ethyl acetate. The combined organic layers were then dried over magnesium sulfate, filtered, and the solvent removed with the aid of a rotory evaporator. The crude residue was then purified by flash chromatography on silica gel to give the desired compound.



3-Pyrrol-1-yl-but-2-enoic acid ethyl ester

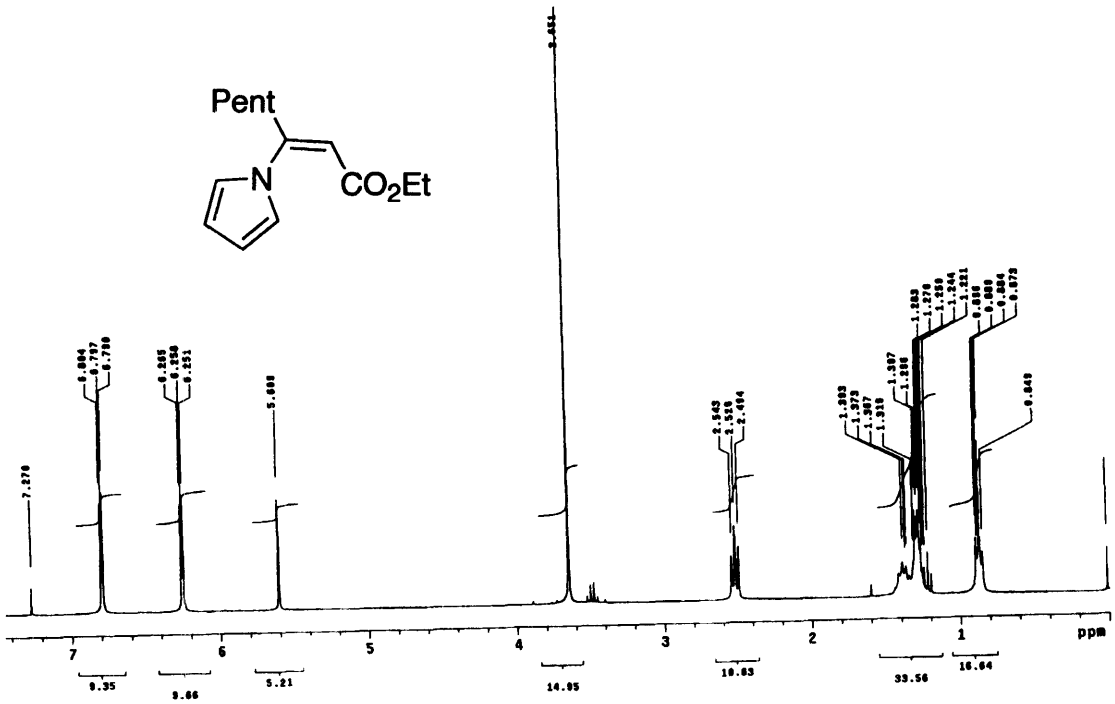
General procedure B was followed and the reaction mixture was allowed to stir for 15 h. Flash chromatography on silica gel eluting with 5 : 95 ethyl acetate : hexane gave 627 mg

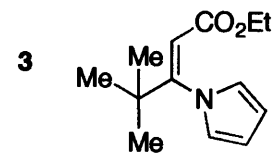
(70%) of the title compound as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.93 (t, J = 2 Hz, 2H), 6.25 (t, J = 2 Hz, 2H), 5.55 (q, J = 1 Hz, 1H), 4.13 (q, J = 7 Hz, 2H), 2.27 (d, J = 1 Hz, 3H), 1.22 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.1, 147.6, 121.3, 110.0, 107.5, 60.4, 24.4, 14.3; IR (cm^{-1}): 2358, 1715, 1644, 1482, 1273, 1187, 1082, 1050; Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31. Found: C, 66.83; H, 7.25.



3-Pyrrol-1-yl-oct-2-enoic acid methyl ester

General procedure B was followed using 0.05 equiv of copper (I) iodide and 0.20 equiv of N,N'-dimethylethylene diamine and the reaction mixture was allowed to stir for 15 h. Flash chromatography on silica gel eluting with 3 : 7 dichloromethane : hexane gave 690 mg (63%) of the title compound as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.80 (t, J = 2 Hz, 2H), 6.26 (t, J = 2 Hz, 2H), 5.61 (s, 1H), 3.65 (s, 3H), 2.52 (m, 2H), 1.29 (m, 6H), 0.87 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.5, 152.9, 121.1, 109.9, 108.3, 51.5, 37.7, 31.2, 26.8, 22.5, 14.1; IR (cm^{-1}): 2952, 2929, 1719, 1638, 1480, 1436, 1246, 1171, 1067, 723; HRMS calc: 221.1410; Found: 221.1406.

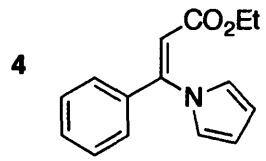




4,4-Dimethyl-3-pyrrol-1-yl-pent-2-enoic acid ethyl ester

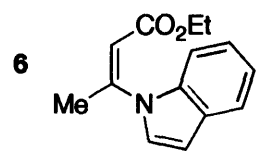
General procedure B was followed using 1.0 mmol (0.10 equiv) of copper (I) iodide and 2.0 mmol (0.20 equiv) of N,N'-dimethylethylene diamine, and the reaction mixture was allowed to stir for 48 h. Flash chromatogrpahy on silica gel eluting with 5 : 95 ethyl acetate : hexane gave 850 mg (77%) of the title compound as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.55 (t, J = 2 Hz, 2H), 6.23 (t, J = 2 Hz, 2H), 6.05 (s, 1H), 3.99 (q, J = 7 Hz, 2H), 1.18 (s, 9H), 1.10 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.9, 161.3, 122.4, 116.4, 108.2, 60.6, 38.3, 28.7, 14.2; IR (cm^{-1}): 2973, 1708, 1648, 1484,

1347, 1266, 1169, 1040; Anal. Calcd. for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65. Found: C, 70.45; H, 8.60.



3-Phenyl-3-pyrrol-1-yl-acrylic acid ethyl ester

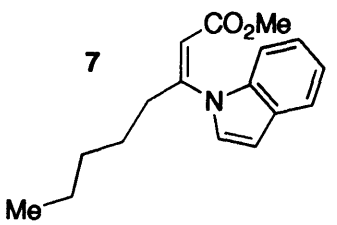
General procedure B was followed but on double the scale, with 0.50 mmol (0.05 equiv) of copper (I) iodide and 2.0 mmol (0.20 equiv) of N,N'-dimethylethylene diamine. The reaction mixture was allowed to stir for 36 h. Flash chromatography on silica gel eluting with 5 : 95 ethyl acetate : hexane gave 1.3 g (54%) of the title compound as an orange solid. MP: 44-46 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33 (m, 5H), 6.73 (t, J = 2 Hz, 2H), 6.30 (t, J = 2 Hz, 2H), 6.01 (s, 1H), 4.16 (q, J = 7 Hz, 2H), 1.24 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.9, 150.8, 137.3, 131.0, 128.8, 123.2, 109.9, 109.7, 99.9, 60.6, 14.4; IR (cm^{-1}): 1719, 1627, 1480, 1275, 1150, 1088, 1071, 773, 729, 692; Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27. Found: C, 74.80; H, 6.28.



3-Indol-1-yl-but-2-enoic acid ethyl ester

General procedure A was followed on a 1.5 mmol sclae using 0.075 mmol (0.05 equiv) of copper (I) iodide and 0.30 mmol (0.20 equiv) of N,N'-dimethylethylene diamine. The reaction mixture was allowed to stir for 14 h, and after flash chromatography on silica gel eluting with 3 : 7 dichloromethane : hexane gave 205 mg (60%) of the title compound as

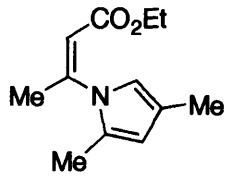
a light purple oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60 (m, 1H), 7.19 (m, 4H), 6.62 (m, 1H), 5.92 (q, J = 1 Hz, 1H), 3.89 (q, J = 7 Hz, 2H), 2.34 (d, J = 1 Hz, 3H), 0.87 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.6, 147.3, 135.9, 129.3, 127.0, 122.5, 121.2, 120.7, 113.5, 111.3, 104.4, 60.4, 24.1, 13.9; IR (cm^{-1}): 2983, 1719, 1648, 1459, 1358, 1229, 1181, 1131, 1046, 739; Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59. Found: C, 73.19; H, 6.54.



3-Indol-1-yl-oct-2-enoic acid methyl ester

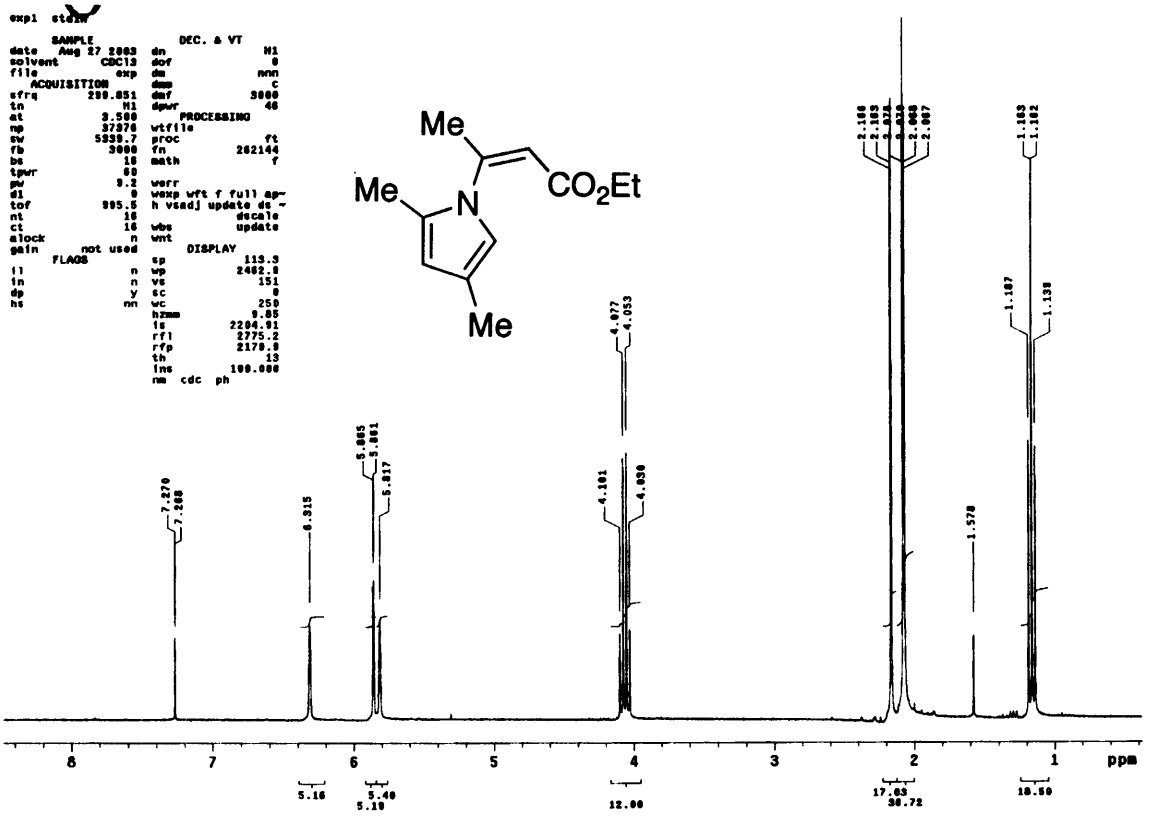
General procedure B was followed on a 8.0 mmol scale using 0.40 mmol (0.050 equiv) of copper (I) iodide and 1.6 mmol (0.20 equiv) of N,N'-dimethylethylene diamine. The reaction mixture was allowed to stir for 15 h, and after flash chromatography on silica gel eluting with 3 : 7 dichloromethane : hexane gave 1.5 g (69%) of the title compound as a light pink oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63 (m, 1H), 7.17 (m, 4H), 6.61 (m, 1H), 5.97 (s, 1H), 3.45 (s, 3H), 2.65 (m, 2H), 1.23 (m, 6H), 0.87 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.9, 152.2, 136.1, 127.2, 122.5, 121.3, 120.6, 113.2, 111.0, 104.2, 99.9, 51.6, 37.5, 31.3, 26.7, 22.4, 14.1; IR (cm^{-1}): 2952, 2931, 1719, 1708, 1648, 1455, 1436, 1281, 1223, 1210, 1173, 1133, 764, 739; Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80. Found: C, 75.24; H, 7.79.

5

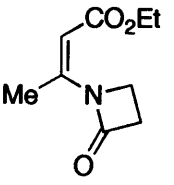


3-(2,4-Dimethyl-pyrrol-1-yl)-but-2-enoic acid ethyl ester

General procedure A was followed on a 2.0 mmol scale using 0.40 mmol (0.20 equiv) of copper (I) iodide and 0.80 mmol (0.40 equiv) of N,N'-dimethylethylene diamine. The reaction mixture was allowed to stir for 17 h, and after flash chromatography on silica gel eluting with 1 : 1 dichloromethane : hexane gave 170 mg (40%) of the title compound as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.32 (s, 1H), 5.86 (q, J = 1 Hz, 1H), 5.82 (s, 1H), 4.06 (q, J = 7 Hz, 2H), 2.16 (d, J = 1 Hz, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.16 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.4, 149.1, 128.9, 119.5, 116.5, 115.4, 110.1, 60.4, 25.3, 14.2, 12.3, 12.1; IR (cm^{-1}): 2979, 2929, 1719, 1708, 1656, 1414, 1221, 1140, 1044, 783; HRMS calc: 207.1254; Found: 207.1248.



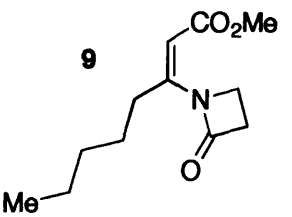
8



3-(2-Oxo-azetidin-1-yl)-but-2-enoic acid ethyl ester

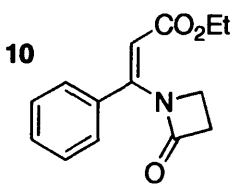
General procedure B was followed using 1.0 mmol (0.20 equiv) of copper (I) iodide and 2.0 mmol (0.40 equiv) of N,N'-dimethylethylene diamine. The reaction mixture was allowed to stir for 3 h, and after flash chromatography on silica gel eluting with 1 : 3 ethyl acetate : hexane gave 600 mg (66%) of the title compound as a white solid. MP: 48-50 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.93 (m, 1H), 4.11 (q, J = 7 Hz, 2H), 3.89 (t, J = 5 Hz, 2H), 3.01 (t, J = 5 Hz, 2H), 2.27 (d, J = 1 Hz, 3H), 1.27 (t, J = 7 Hz, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ: 167.2, 165.0, 146.9, 99.7, 59.9, 43.6, 37.1, 22.4, 14.5; IR (cm^{-1}): 1764, 1702, 1621, 1264, 1196, 1140, 725; Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15. Found: C, 59.17; H, 7.18.



3-(2-Oxo-azetidin-1-yl)-oct-2-enoic acid methyl ester

General procedure B was followed on a 7.0 mmol scale using 0.35 mmol (0.050 equiv) of copper (I) iodide and 1.4 mmol (0.20 equiv) of N,N'-dimethylethylene diamine. The reaction mixture was allowed to stir for 24 h, and after flash chromatography on silica get eluting with 1 : 3 ethyl acetate : hexane gave 1.25 g (79%) of the title compound as a light yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 5.00 (m, 1H), 3.85 (t, J = 5 Hz, 2H), 3.67 (s, 3H), 3.01 (t, J = 5 Hz, 2H), 2.56 (m, 2H), 1.54 (m, 2H), 1.29 (m, 4H), 0.89 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.6, 165.6, 151.4, 99.5, 51.3, 43.3, 36.9, 34.9, 31.4, 28.4, 22.6, 14.2; IR (cm^{-1}): 2952, 1764, 1708, 1611, 1407, 1254, 1183, 1123, 820; Anal. Calcd. for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50. Found: C, 63.61; H, 8.50.

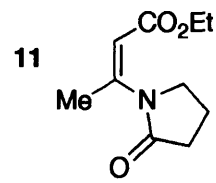


3-(2-Oxo-azetidin-1-yl)-3-phenyl-acrylic acid ethyl ester

General procedure B was followed on a 10 mmol scale using 0.50 mmol (0.050 equiv) of copper (I) iodide and 2.0 mmol (0.20 equiv) of N,N'-dimethylethylene diamine. The

reaction mixture was allowed to stir for 23 h, and after flash chromatography on silica gel eluting with 1 : 3 ethyl acetate : hexane gave 1.65 g (67%) of the title compound as a red oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 (m, 5H), 5.68 (s, 1H), 4.22 (q, J = 7 Hz, 2H), 3.72 (t, J = 5 Hz, 2H), 3.15 (t, J = 5 Hz, 2H), 1.31 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.0, 165.0, 146.1, 134.7, 130.6, 128.9, 128.3, 108.9, 60.5, 42.1, 37.2, 14.5; IR (cm^{-1}): 2977, 1764, 1702, 1609, 1383, 1275, 1152, 1109, 1027, 781, 696; Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16. Found: C, 68.51; H, 6.23

.



3-(2-Oxo-pyrrolidin-1-yl)-but-2-enoic acid ethyl ester

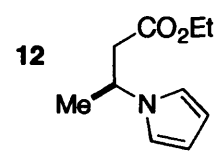
General procedure A was followed on a 2.0 mmol scale using 0.20 mmol (0.10 equiv) of copper (I) iodide and 0.40 mmol (0.2 equiv) of N,N'-dimethylethylene diamine. The reaction mixture was allowed to stir for 19 h, and after flash chromatography on silica gel eluting with 1 :3 ethyl acetate : hexane gave 250 mg (64%) of light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.69 (q, J = 1 Hz, 1H), 4.12 (q, J = 7 Hz, 2H), 3.64 (t, J = 7 Hz, 2H), 2.45 (t, J = 7 Hz, 2H), 2.11 (quint, J = 7 Hz, 2H), 2.03 (d, J = 1 Hz, 3H), 1.25 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.1, 164.7, 147.0, 114.4, 60.2, 48.4, 31.8, 21.7, 19.1, 14.4; IR (cm^{-1}): 2981, 1719, 1702, 1638, 1401, 1264, 1175, 1129, 1050, 845; Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67. Found: C, 59.7; H, 7.69.

III. Asymmetric Conjugate Reduction of Dehydro-β-Amino Acid Derivatives

General Procedure: A 1 dram vial equipped with a Teflon-coated magnetic stir bar was charged with copper (II) acetate monohydrate (0.05 equiv), and S-BINAP (0.05 equiv). The vial was capped with a screw-on top with a teflon center, through which a glass pipette filled with calcium sulfate was inserted. THF was then added to the vial via syringe and this was allowed to stir for approximately five min. Then PMHS (4.0 equiv) was added to the vial and this was again allowed to stir for five minutes. Finally, a solution of the substrate (0.33 molar in the total volume of THF) and t-BuOH (4.0 equiv) in THF was added to the vial and allowed to stir for the time indicated. Upon complete conversion of the starting material as judged by gas chromatography or thin layer chromatography, the reaction was worked up in one of two ways:

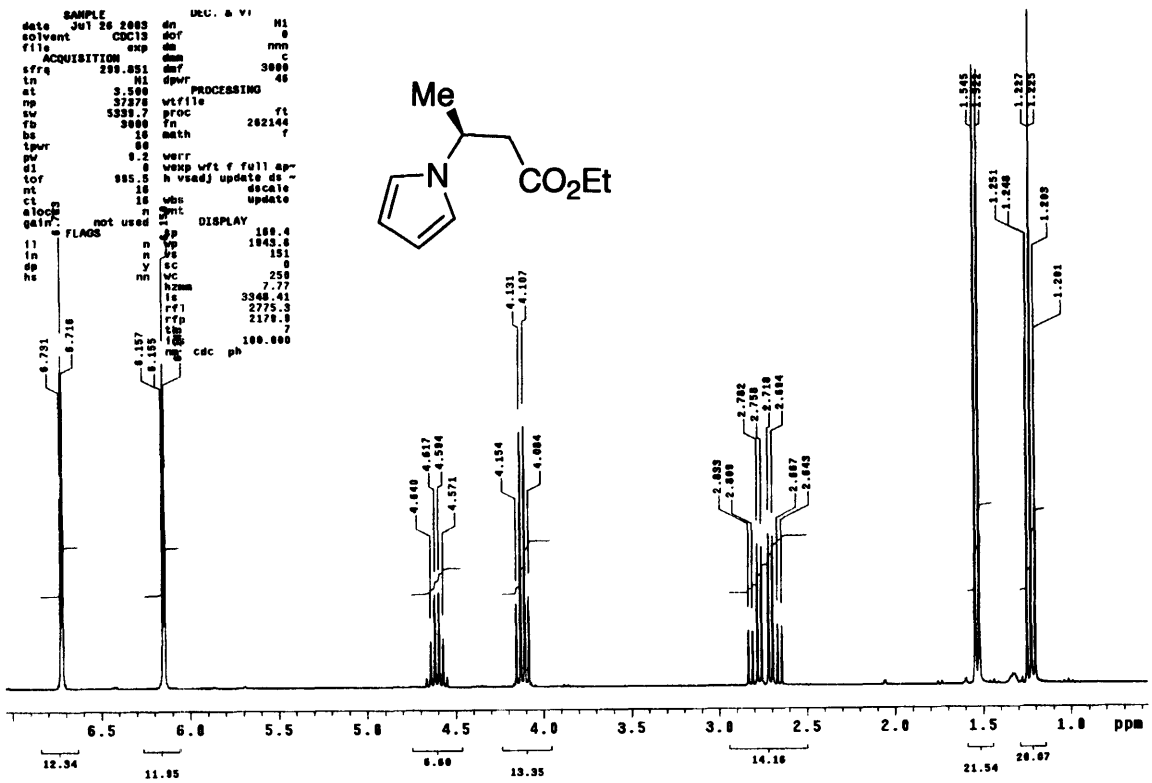
Workup A: The reaction mixture was diluted with ethyl acetate, and then partitioned between water and ethyl acetate. The phases were separated and the aqueous was extracted three times with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and the solvent removed with the aid of a rotory evaporator. The crude residue was then purified by flash chromatography over silica gel.

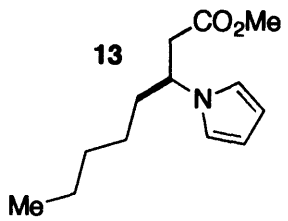
Workup B: The reaction mixture was loaded directly onto a silica gel column and purified by flash chromatography.



3-Pyrrol-1-yl-butyric acid ethyl ester

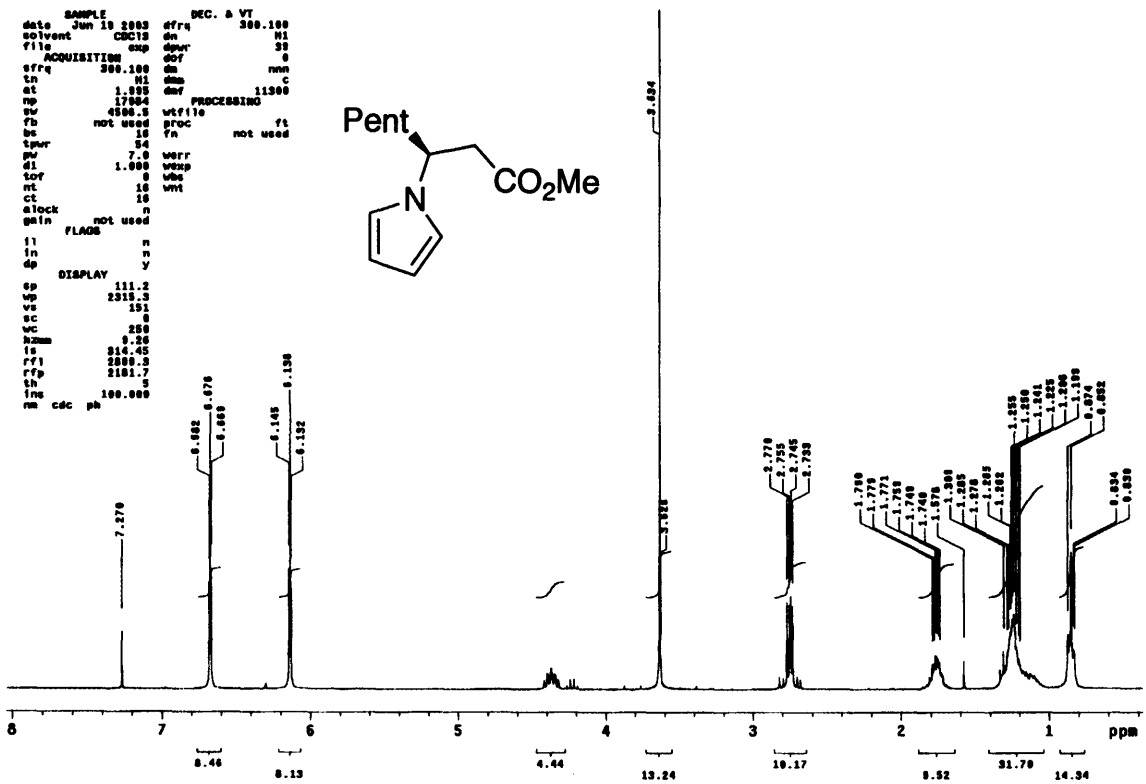
The general procedure was followed and the reaction was allowed to stir for 1 h. Workup A, eluting with 5 : 95 ethyl acetate : hexane gave 80 mg (88%) of the title compound as a colorless oil. Chiral HPLC analysis (Daicel Chiralpak® OD column (0.46cmØ x 25 cm), 0.7 mL/ min, 5% *i*-PrOH/ Hexane, 254 nm, 280 nm, retention times: 8.32 min (major), 9.81 min (minor)) showed 81% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.72 (t, J = 2 Hz, 2H), 6.15 (t, J = 2 Hz, 2H), 4.60 (sext, J = 7 Hz, 1H), 4.12 (q, J = 7 Hz, 2H), 2.74 (ABX, dd, J = 15 Hz, 7 Hz, 2H), 1.53 (d, J = 7 Hz, 3H), 1.22 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.9, 118.6, 108.2, 60.9, 52.0, 43.4, 21.9, 14.3; IR (cm^{-1}): 2979, 1735, 1181, 1167, 1088, 1034, 721; HRMS calc: 181.1097; Found: 181.1090. α_D (589 nm, 0.45 g/ 100 mL $CHCl_3$) = -17.5.

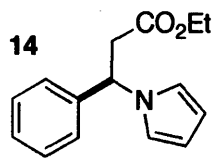




3-Pyrrol-1-yl-octanoic acid methyl ester

The general procedure was followed and the reaction was allowed to stir for 1 h. Workup A, eluting with 1 : 9 ethyl acetate : hexane gave 57 mg (85%) of the title compound as a colorless oil. Chiral HPLC analysis (Daicel Chiralpak® OD column (0.46cmØ x 25 cm), 0.7 mL/ min, 5% *i*-PrOH/ Hexane, 254 nm, 280 nm, retention times: 7.24 min (major), 9.66 min (minor)) showed 87% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.68 (t, J = 2 Hz, 2H), 6.14 (t, J = 2 Hz, 2H), 4.38 (m, 1H), 3.63 (s, 3H), 2.75 (m, 2H), 1.77 (m, 2H), 1.23 (m, 6H), 0.84 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.5, 119.0, 108.1, 56.8, 52.1, 41.9, 36.1, 31.5, 25.9, 22.6, 14.2; IR (cm^{-1}): 2956, 2931, 1737, 1490, 1262, 1246, 1165, 1090, 1069, 719; HRMS calc: 223.1561; Found: 223.1573. α_D (589 nm, 0.11 g/ 100 mL $CHCl_3$) = -12.0.

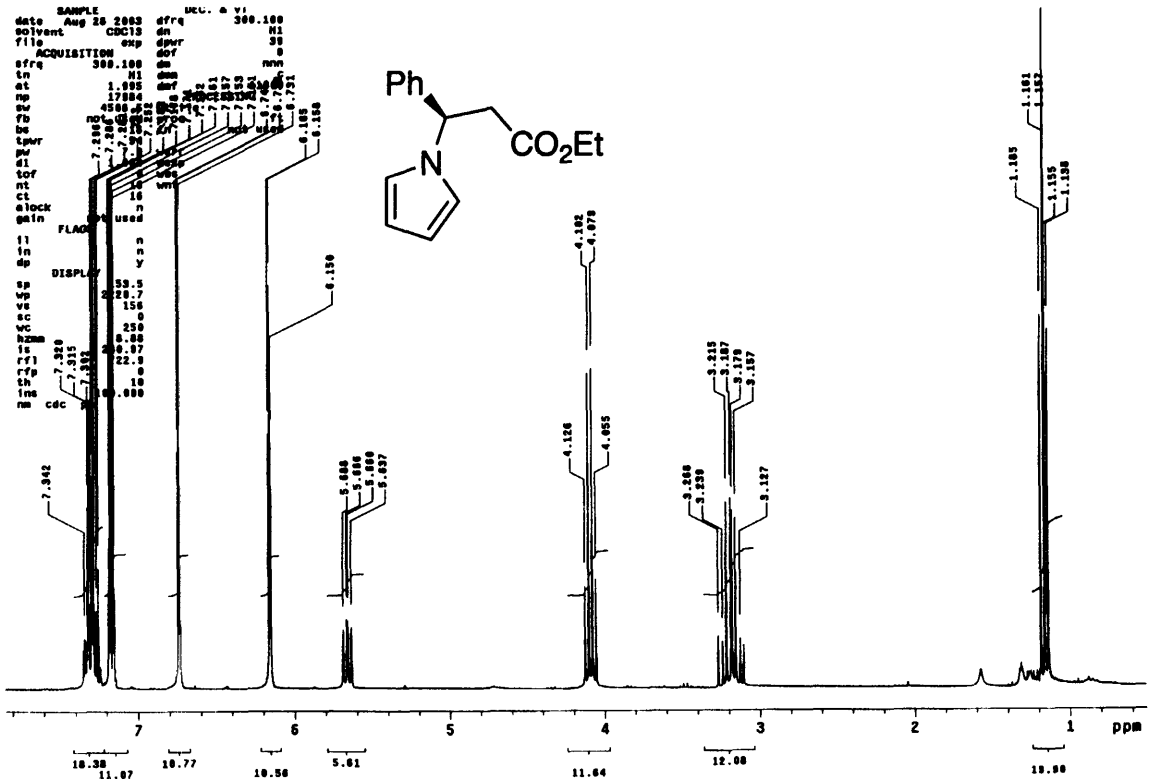




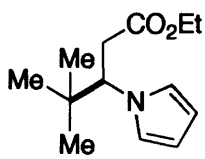
3-Phenyl-3-pyrrol-1-yl-propionic acid ethyl ester

The general procedure was followed using 10 equivalents of PMHS and the reaction was allowed to stir for 20 h. Workup B, eluting with 5 : 95 ethyl acetate : hexane gave 105 mg (87%) of the title compound as a yellow oil. Chiral HPLC analysis (Daicel Chiralpak® OJ column (0.46cmØ x 25 cm), 0.7 mL/ min, 3% *i*-PrOH/ Hexane, 254 nm, 280 nm, retention times: 31.84 min (major), 35.30 min (minor)) showed 83% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.25 (m, 3H), 7.16 (m, 2H), 6.74 (t, J = 2 Hz, 2H), 6.15 (t, J = 2 Hz, 2H), 5.66 (m, 1H), 4.09 (q, J = 7 Hz, 2H), 3.18 (ABX, dd, J = 15 Hz, 7 Hz, 2H)

1.16 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.4, 140.7, 128.9, 128.2, 126.5, 119.8, 108.6, 61.2, 59.5, 41.3, 14.2; IR (cm^{-1}): 2979, 1737, 1490, 1372, 1264, 1156, 1084, 1021, 721; HRMS calc: 243.1254; Found: 243.1252. α_D (589 nm, 0.10 g/ 100 mL $CHCl_3$) = -6.5.



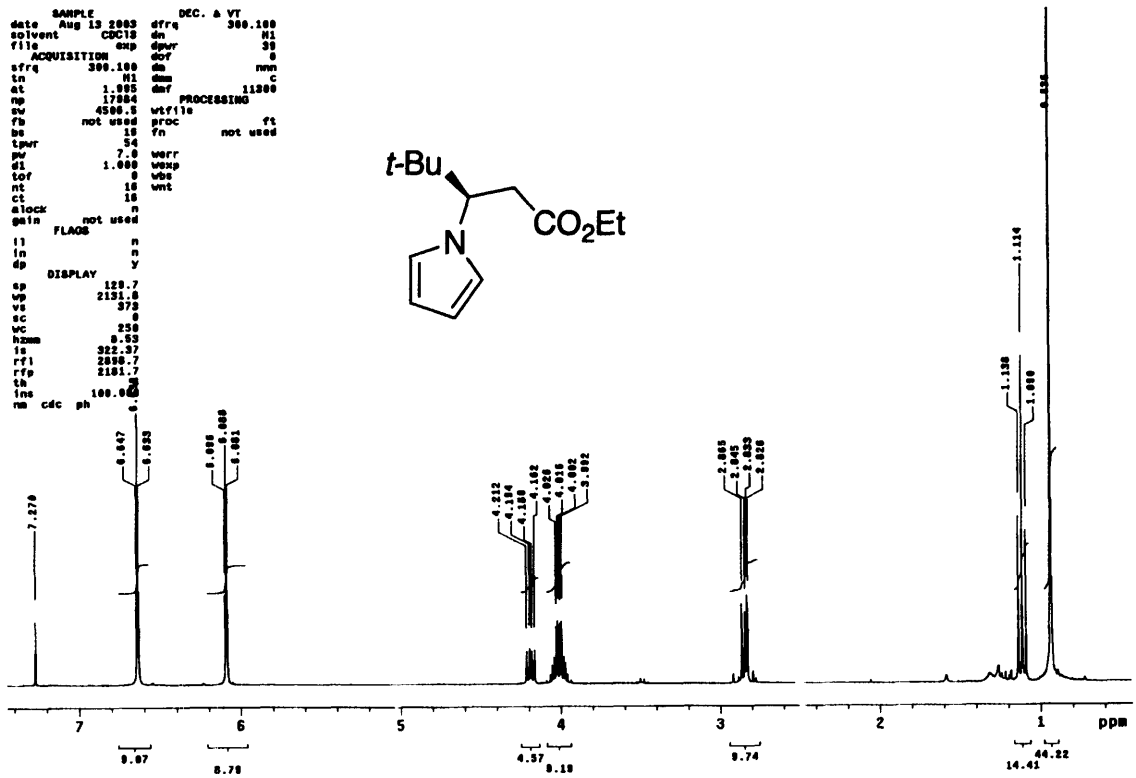
15

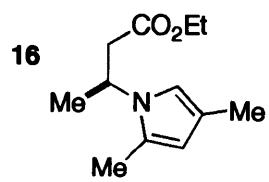


4,4-Dimethyl-3-pyrrol-1-yl-pentanoic acid ethyl ester

The general procedure was followed using 10 mol% catalyst and 10 equivalents of PMHS, and the reaction was allowed to stir for 22 h. Workup A, eluting with 5 : 95 ethyl acetate : hexane gave 92 mg (83%) of the title compound as a yellow oil. Chiral HPLC analysis (Daicel Chiralpak® AD-H column (0.46cmØ x 25 cm), 0.5 mL/ min, 1% *i*-

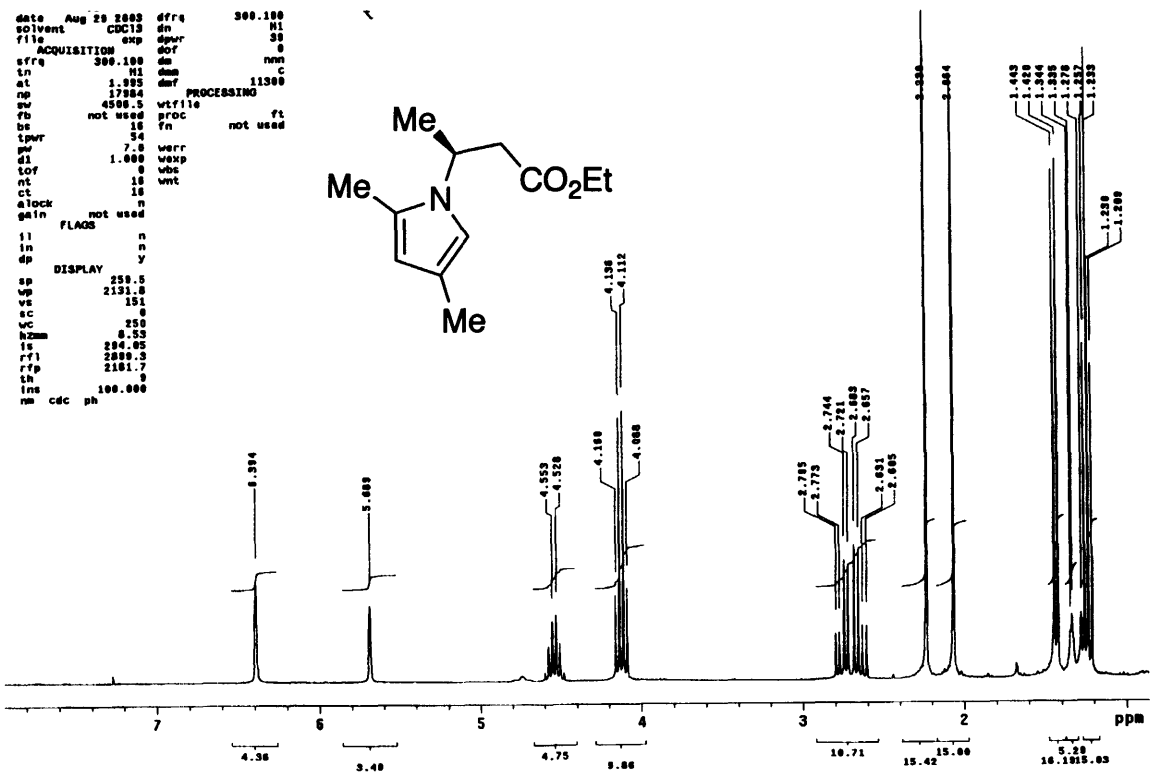
PrOH/ Hexane, 254 nm, 280 nm, retention times: 12.99 min (major), 13.98 min (minor)) showed 86% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.64 (t, J = 2 Hz, 2H), 6.09 (t, J = 2 Hz, 2H), 4.18 (m, 1H), 4.02 (m, 2H), 2.84 (m, 2H), 1.14 (m, 3H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.5, 120.9, 107.2, 65.8, 60.9, 36.1, 35.6, 27.2, 14.2; IR (cm^{-1}): 2966, 1737, 1370, 1299, 1248, 1152, 1094, 1030, 721; HRMS calc: 223.1567; Found: 223.1568. α_D (589 nm, 0.50 g/ 100 mL $CHCl_3$) = -9.4.

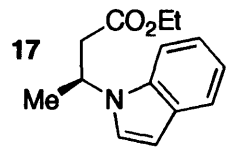




3-(2,4-Dimethyl-pyrrol-1-yl)-butyric acid ethyl ester

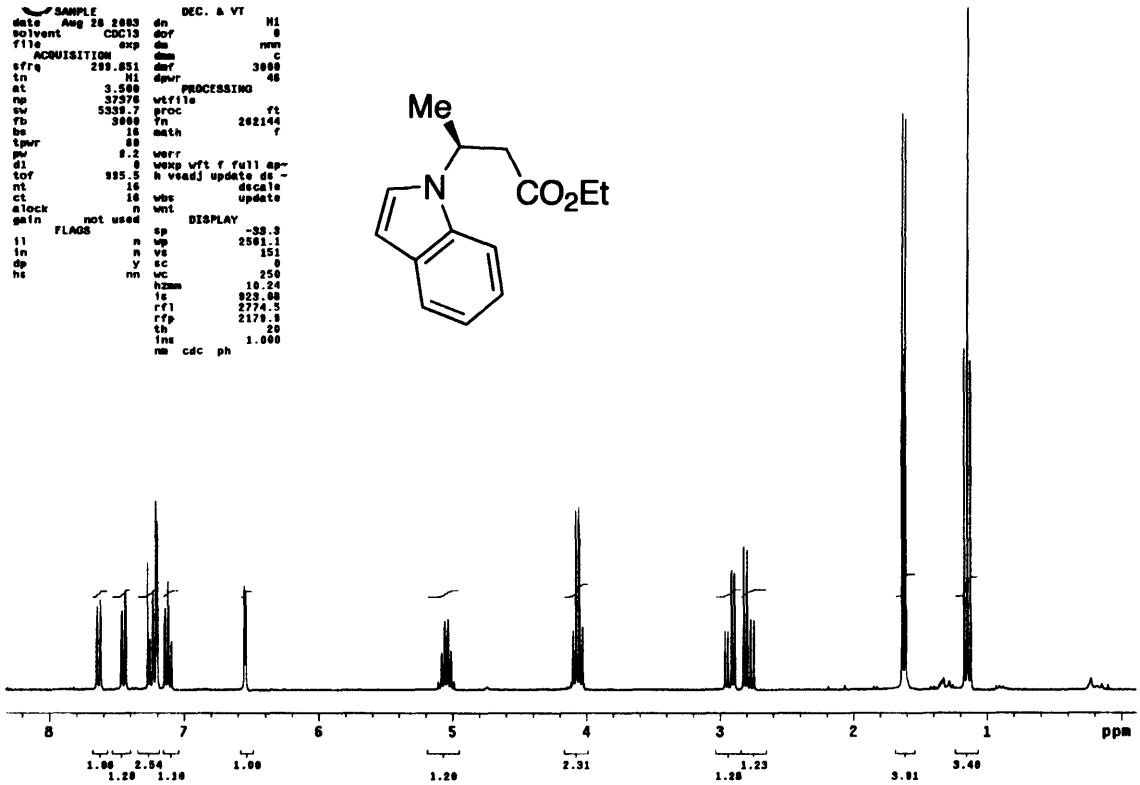
The general procedure was followed using 10 equivalents of PMHS and the reaction was allowed to stir for 24 h. Workup B, eluting with 1 : 9 ethyl acetate : hexane gave 52 mg (83%) of the title compound as a colorless oil. Chiral HPLC analysis (Daicel Chiralpak® OD column (0.46cmØ x 25 cm), 0.6 mL/ min, 4% *i*-PrOH/ Hexane, 254 nm, 280 nm, retention times: 8.11 min (major), 9.34 min (minor)) showed 86% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.39 (s, 1H), 5.69 (s, 1H), 4.54 (sx, J = 7 Hz, 1H), 4.12 (q, J = 7 Hz, 2H), 2.70 (ABX, ddd, J = 15 Hz, 7 Hz, 2H), 2.23 (s, 3H), 2.06 (s, 3H), 1.43 (d, J = 7 Hz, 3H), 1.23 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.0, 128.2, 118.2, 113.2, 108.0, 60.8, 47.8, 42.8, 22.0, 14.3, 12.2, 12.1; IR (cm^{-1}): 2981, 1725, 1376, 1096, 1081, 1038, 904, 731; HRMS calc: 209.1410; Found: 209.1415. α_D (589 nm, 0.10 g/ 100 mL $CHCl_3$) = -2.3.

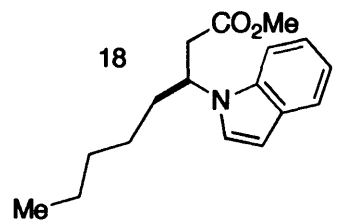




3-Indol-1-yl-butyric acid ethyl ester

The general procedure was followed and the reaction was allowed to stir for 1.25 h. Workup B, eluting with 1 : 9 ethyl acetate : hexane gave 111 mg (96%) of the title compound as a colorless oil. Chiral HPLC analysis (Daicel Chiralpak® OD column (0.46cmØ x 25 cm), 0.7 mL/ min, 5% *i*-PrOH/ Hexane, 254 nm, 280 nm, retention times: 13.3 min (major), 21.66 min (minor)) showed 90% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.64 (m, 1H), 7.43 (m, 1H), 7.21 (m, 2H), 7.11 (m, 1H), 6.54 (m, 1H), 5.04 (sext, J = 7 Hz, 1H), 4.06 (q, J = 7 Hz, 2H), 2.84 (ABX, ddd, J = 15 Hz, 7 Hz, 2H), 1.64 (d, J = 7 Hz, 3H), 1.15 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.9, 135.7, 128.7, 124.1, 121.7, 121.2, 119.7, 109.7, 102.2, 60.9, 48.5, 42.2, 21.0, 14.2; IR (cm^{-1}): 2956, 1750, 1397, 1245, 1206, 1169, 1011; HRMS calc: 231.1254; Found: 231.1257. α_D (589 nm, 0.11 g/ 100 mL $CHCl_3$) = +16.8.

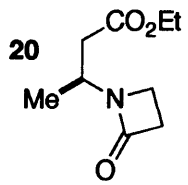




3-Indol-1-yl-octanoic acid methyl ester

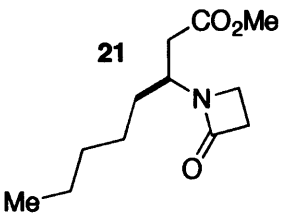
The general procedure was followed 10 mol% catalyst and 10 equivalents of PMHS, and the reaction was allowed to stir for 23 h. Workup B, eluting with 1 : 9 ethyl acetate : hexane gave 110 mg, 96% of the title compound as a colorless oil. Chiral HPLC analysis (Daicel Chiralpak® OD column (0.46cmØ x 25 cm), 0.7 mL/ min, 5% *i*-PrOH/ Hexane, 254 nm, 280 nm, retention times: 10.17 min (major), 20.77 min (minor)) showed 85% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62 (m, 1H), 7.44 (m, 1H), 7.18 (m, 3H), 6.53 (m,

1H), 4.84 (m, 1H), 3.54 (s, 3H), 2.84 (m, 2H), 1.92 (m, 2H), 1.21 (m, 6H), 0.81 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.5, 136.3, 128.6, 124.5, 121.7, 121.1, 119.6, 109.8, 102.4, 53.2, 52.0, 40.9, 35.3, 31.5, 25.9, 22.6, 14.1; IR (cm^{-1}): 2931, 1737, 1459, 1306, 1194, 1167, 737; Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48. Found: C, 74.67; H, 8.43. α_D (589 nm, 0.10 g/ 100 mL $CHCl_3$) = -2.2.



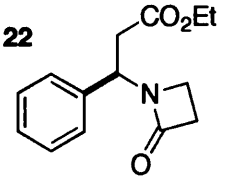
3-(2-Oxo-azetidin-1-yl)-butyric acid ethyl ester

The general procedure was used with 10 mol% catalyst and 8 equivalents of PMHS, and the reaction was allowed to stir for 24 h. Workup A, eluting with 1 : 3 ethyl acetate : hexane gave 80 mg (86%) of the title compound as a light yellow oil. Chiral HPLC analysis (Daicel Chiralpak® OD column (0.46cmØ x 25 cm), 0.7 mL/ min, 5% *i*-PrOH/ Hexane, 254 nm, 280 nm, retention times: 24.29 min (minor), 26.25 min (major)) showed 84% ee. ^1H NMR (300 MHz, $CDCl_3$) δ: 4.14 (m, 3H), 3.23 (m, 2H), 2.85 (t, J = 4 Hz, 2H), 2.55 (ABX, ddd, J = 15 Hz, 7 Hz, 2H), 1.24 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.8, 166.9, 60.8, 45.2, 39.6, 36.5, 35.7, 18.4, 14.2; IR (cm^{-1}): 2977, 1750, 1719, 1393, 1374, 1246, 1206, 1183, 1028; Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.36; H, 8.16. Found: C, 58.5; H, 7.89. α_D (589 nm, 0.10 g/ 100 mL $CHCl_3$) = -8.3.



3-(2-Oxo-azetidin-1-yl)-octanoic acid methyl ester

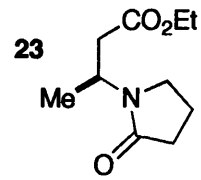
The general procedure was followed using 10 mol% catalyst with 10 equivalents of PMHS, and the reaction was allowed to stir for 24 h. Workup B, eluting with 1 : 1 ethyl acetate : hexane gave 110 mg (98%) of the title compound as a colorless oil. Chiral HPLC analysis (Daicel Chiralpak® OD column (0.46cmØ x 25 cm), 0.6 mL/ min, 2% *i*-PrOH/ Hexane, 254 nm, 280 nm, retention times: 42.55 min (minor), 44.24 min (major)) showed 94% ee ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.02 (m, 1H), 3.65 (s, 3H), 3.24 (m, 2H), 2.87 (m, 2H), 2.55 (ABX, ddd, J = 15 Hz, 7 Hz, 2H), 1.57 (m, 2H), 1.23 (m, 6H), 0.87 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.6, 167.6, 52.1, 49.7, 38.1, 36.9, 35.9, 32.7, 31.5, 26.1, 22.6, 14.1; IR (cm^{-1}): 2979, 1737, 1727, 1461, 1306, 1289, 1179, 1038, 1025, 737; Anal. Calcd. for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31. Found: C, 63.44; H, 9.33. α_D (589 nm, 0.10 g/ 100 mL $CHCl_3$) = +8.3.



3-(2-Oxo-azetidin-1-yl)-3-phenyl-propionic acid ethyl ester

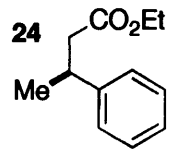
The general protocol was followed using 10 equivalents of PMHS and the reaction was allowed to stir for 24 h. Workup B, eluting with 1 : 9 ethyl acetate : hexane gave 118 mg (96%) of the title compound as a yellow oil. Chiral HPLC analysis (Daicel Chiralpak® OD column (0.46cmØ x 25 cm), 0.7 mL/ min, 5% *i*-PrOH/ Hexane, 254 nm, 280 nm,

retention times: 33.50 min (minor), 34.75 min (major)) showed 99% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 (m, 5H), 5.07 (m, 1H), 4.13 (q, J = 7 Hz, 2H), 3.24 (m, 2H), 3.11 (m, 1H), 2.86 (m, 3H), 1.22 (t, J = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.7, 167.4, 138.7, 129.1, 128.3, 127.2, 61.1, 54.5, 38.4, 37.7, 36.2, 14.3; IR (cm^{-1}): 2979, 1752, 1719, 1389, 1245, 1165, 1030, 700; Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93. Found: C, 67.71; H, 6.91. α_D (589 nm, 0.10 g/ 100 mL $CHCl_3$) = -16.3.



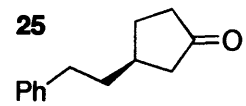
3-(2-Oxo-pyrrolidin-1-yl)-butyric acid ethyl ester

The general procedure was followed using 10 mol% catalyst with 10 equivalents of PMHS and the reaction was allowed to stir for 9 h. Workup B, eluting with ethyl acetate gave 56 mg (92%) of the title compound as a yellow oil. Chiral HPLC analysis (Daicel Chiralpak® OD column (0.46cmØ x 25 cm), 0.7 mL/ min, 5% *i*-PrOH/ Hexane, 254 nm, 280 nm, retention times: 28.35 min (minor), 29.57 min (major)) showed 81% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.54 (sext, J = 7 Hz, 1H), 4.07 (q, J = 7 Hz, 2H), 3.32 (m, 2H), 2.50 (ABX, ddd, J = 15 Hz, 7 Hz, 2H), 2.32 (m, 2H), 1.96 (m, 2H), 1.19 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.5, 170.8, 60.6, 44.4, 42.6, 39.0, 31.4, 18.1, 17.9, 14.1; IR (cm^{-1}): 2979, 1729, 1686, 1422, 1285, 1177, 1094, 1042, 1028; Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60. Found: C, 60.44; H, 8.58. α_D (589 nm, 0.11 g/ 100 mL $CHCl_3$) = -1.6.



3-Phenyl-butyric acid ethyl ester

The general procedure was followed and the reaction was allowed to stir for 3 h. Workup A, eluting with 5 : 95 ethyl acetate : hexane gave 62 mg (85%) of the title compound as a colorless oil. Chiral HPLC analysis (Daicel Chiralpak® OB column (0.46cmØ x 25 cm), 0.5 mL/ min, 0.5% *i*-PrOH/ Hexane, 254 nm, 280 nm, retention times: 20.32 min (minor), 21.64 min (major)) showed 92% ee. Spectral data were the same as those previously reported.[9e]



3-Phenethyl-cyclopentanone

The general procedure was followed and the reaction was allowed to stir for 1 h. Workup A, eluting with 1 : 10 ethyl acetate : hexane gave 47 mg (82%) of the title compound as a colorless oil. Chiral HPLC analysis (Daicel Chiralpak® OB column (0.46cmØ x 25 cm), 0.5 mL/ min, 0.5% *i*-PrOH/ Hexane, 254 nm, 280 nm, retention times: 6.49 min (minor), 7.34 min (major)) showed 92% ee. Spectral data were the same as those previously reported.[19]

References

(1) For reviews on the biology of β-amino acids see: (a) Juaristi, E. *Enantioselective Synthesis of β-Amino Acids,* **1997**, (Wiley-VCH, New York). (b) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173. (c) Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015.

(2) For reviews on the synthesis of β-amino acids see: (a) Ma, J. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290. (b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (c) Juaristi, E. *Enantioselective Synthesis of β-Amino Acids,* **1997**, (Wiley-VCH, New York).

(3) (a) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964. (b) Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, *4*, 143. (c) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866.

(4) For recent examples of catalytic asymmetric conjugate addition see: (a) Sibi, M. P.; Chen, J. *Org. Lett.* **2002**, *4*, 2933. (b) Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442. (c) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959.

(5) For recent reviews on asymmetric conjugate additions see: (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033.

(6) For a recent review on the synthesis of β-amino acid derivatives via asymmetric hydrogenation see: Drexler, H. J.; You, J.; Zhang, S.; Fischer, C.; Baumann, W.; Spannenberg, A.; Heller, D. *Org. Process Res. Dev.* **2003**, *7*, 355.

(7) For other catalytic enantioselective syntheses of β-amino acid derivatives see: (a) Davies, H. M. L.; Venkataramani, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2197. (b) Nelson,

S. G.; Spencer, K. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 1323. (c) Zhou, Y. G.; Tang, W.; Wang, W. B.; Li, W.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 4952. (d) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578. (e) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.

(8) For a recent example of hydrogenation of unprotected β-enamine esters and amides see: Hsiao, Y.; Rivera, N. R.; Rosner, T.; Krska, S. W.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, III, J. D.; Grabowski, E. J. J.; Tillyer, R. D.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918.

(9) (a) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253. (b) Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *14*, 2417. (c) Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 2892. (d) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797. (e) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473. (f) Yun, J.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1129.

(10) For other recent examples employing chiral copper hydride catalysts see: (a) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352. (b) Lipshutz, B. H.; Shimizu, H. *Angew. Chem., Int. Ed. Eng.* **2004**, *43*, 2228. (c) Lipshutz, B. H.; Servesko, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4789. (d) Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4793. (e) Lipshutz, B. H.; Caires, C. C.; Kuipers, P.; Chrisman, W. *Org. Lett.* **2003**, *5*, 3085.

(11) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667.

(12) Synthesis of the vinyl iodides: (a) Piers, E.; Wong, T.; Coish, P. D.; Rogers, C. *Can. J. Chem.* **1994**, *72*, 1816. (b) Rossi, R.; Bellina, F.; Mannina, L. *Tetrahedron* **1997**, *53*, 1025.

(13) (a) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684. (b) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.

(14) For examples of Pd-catalyzed coupling of nitrogen heterocycles with vinyl halides see: Lebedev, A. Y.; Izmer, V. V.; Kazyul'kin, D. N.; Beletskaya, I. P.; Voskoboynikov, A. Z. *Org. Lett.* **2002**, *4*, 623.

(15) (a) Lipshutz, B. H. in *Modern Organocopper Chemistry*, ed. Krause, N. (Wiley-VCH, Weinheim), 2002, pp. 175-179. (b) Stryker, J. M.; Mahoney, W. S.; Daeuble, J. F.; Brestensky, D. M. in *Catalysis in Organic Synthesis*, ed. Pascoe, W. E.; (Marcel Dekker, New York), 1992, pp. 29-44. (c) Daeuble, J. F.; Stryker, J. M. in *Catalysis of Organic Reactions*, eds. Scaros, M.; Prunier, M. L. (Marcel Dekker, New York), 1995, pp. 235-247. (d) Chen, J. X.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron*, **2000**, *56*, 2153. (e) Chen, J. X.; Daeuble, D. M.; Stryker, J. M. *Tetrahedron,* **2000**, *56*, 2789.

(16) Sirol, S.; Courmarcel, J.; Mostefai, N.; Riant, O. *Org. Lett.* **2001**, *3*, 4111.

(17) For deprotection of pyrrole to the corresponding amine: (a) Kashima, C.; Maruyama, T.; Fujioka, Y.; Harada, K. *J. Chem. Soc., Perkin Trans. 1*, **1989**, 1041. (b) Convery, M. A.; Davis, A. P.; Dunne, C. J.; MacKinnon, J. W. *Tetrahedron Lett.* **1995**, *36*, 4279.

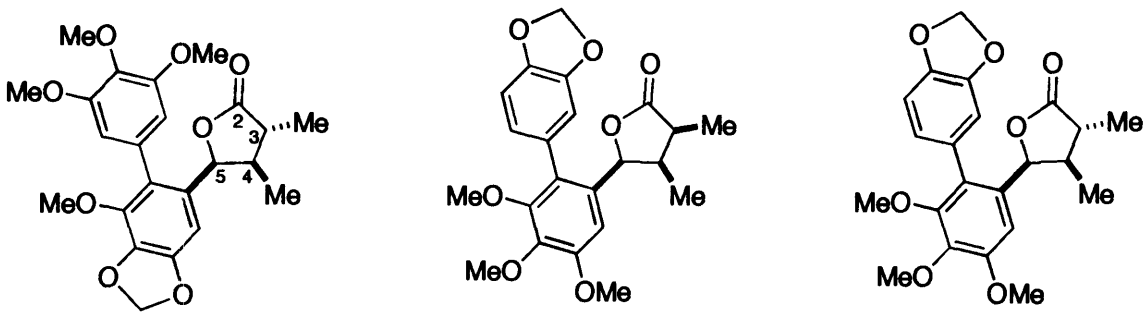
(18) (a) Pangborn, A.B.; Giardello, M.A.; Grubbs, R.H.; Rosen, R.K.; Timmers, F.J. *Organometallics* **1996**, *15*, 1518. (b) Alaimo, P.J.; Peters, D.W.; Arnold, J.; Bergman, R.G. *J. Chem. Ed.* **2001**, *78*, 64.

(19) Gadwood, R.C.; Mallick, I. M.; DeWinter, A. J. *J. Org. Chem.* **1987**, *52*, 774.

Chapter 4.
Dynamic Kinetic Resolution of α,β-Unsaturated Lactones Via Asymmetric Copper-Catalyzed Conjugate Reduction: Application in the Total Synthesis of Eupomatilone-3

Introduction

Eupomatilones 1-7 are a family of lignans[1] isolated from the Australian shrub *Eupomatia bennettii,* found in the tropical and subtropical forests of New South Wales and Queenland.[2] This family of lignans is considered "degraded" due to the unique cleavage of the Cα-linkage in one of the phenylpropanoid units. All seven members of this family contain a highly oxygenated biaryl motif, as well as the C4-C5 *cis* stereochemistry in the butyrolactone ring. While the biological activity of the members of this family remain unknown, there are structural components similar to known antimitotics such as colchicines.[1]



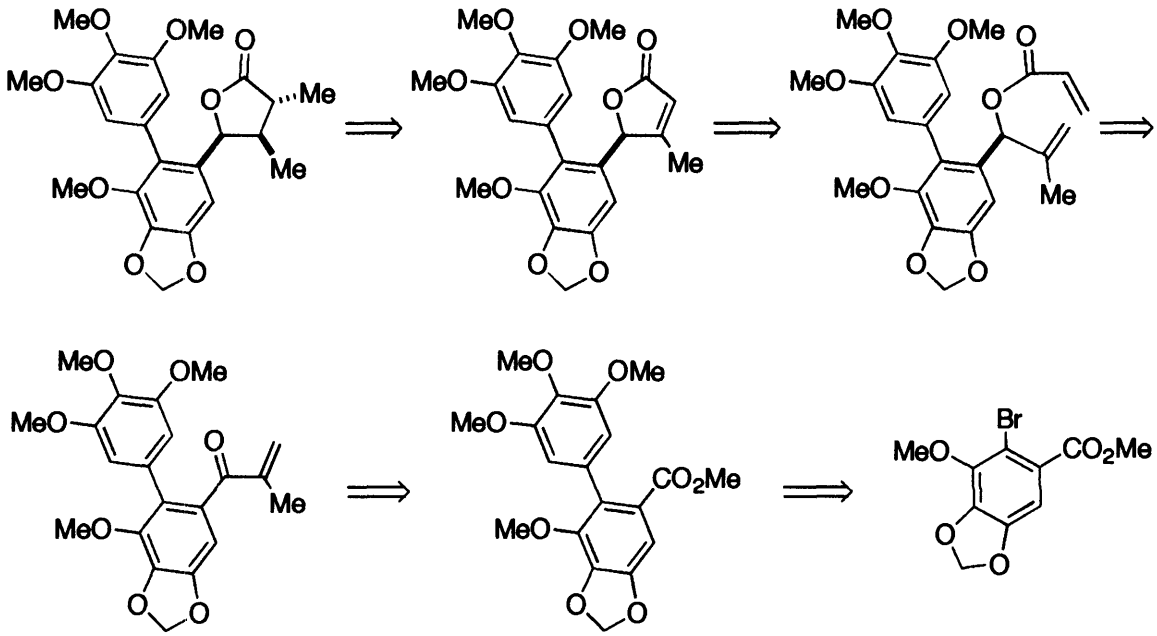
eupomatilone-3 | 3-*epi*-eupomatilone-6 (Gurjar) | eupomatilone-6 (revised by Coleman)

Figure 1. Some members of the Eupomatilone family of lignans

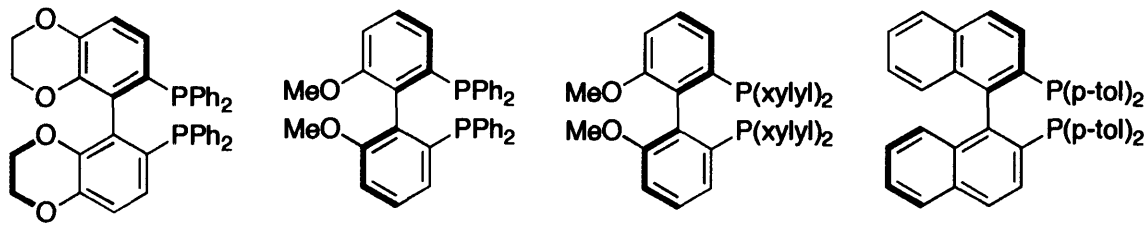
Of all the members of the eupomatilone family, there are only three reported total syntheses, all of which were directed toward the synthesis of Eupomatilone-6.[3] In 2004, Gurjar and co-workers reported the synthesis of Eupomatilone-6 as originally proposed by Carroll and Taylor.[3c] However, the spectroscopic data for synthetic Eupomatilone-6 was not in agreement with the data gathered on the natural material. More recently, Coleman and Gurrala have revised the structure of Eupomatilone-6, along with the product produced by Gurjar (now believed to be 3-*epi*-Eupomatilone-6).[3d] They also

disclosed the synthesis of Eupomatilone-4 in this work. Despite this research, the total synthesis of the enantiomerically enriched members of the Eupomatilone family has remained an unsolved problem.

We became interested in the synthesis of Eupomatilone-3 due to its interesting structural features, in particular the biaryl motif, along with the *cis*-orientation of the C4-C5 substituents on the lactone portion of the molecule. Our retrosynthesis of this compound is shown below. It was envisioned that a diastereoselective alkylation could



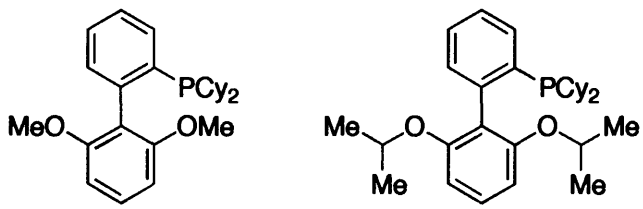
occur at C2 as the final step in the synthesis. The necessary precursor containing the *cis*-geometry of the C4-C5 substituents could be formed by a diastereoselective copper-catalyzed conjugate reduction of the corresponding α,β-unsaturated lactone.[4b] The selectivity of this reaction can be tuned based on appropriate ligand choice, as shown by the elegant work of Lipshutz,[5] as well as our own research.[4] The unsaturated lactone could be prepared via ring closing metathesis



SYNPHOS **1** | MeO-BIPHEP **2** | MeO-xylylBIPHEP **3** | p-tolBINAP **4**

Figure 2. Chiral ligands commonly employed in copper-catalyzed conjugate reduction chemistry

as described by Hughes and Buchwald.[4b] Subsequently, preparation of the requisite chiral alcohol could be accomplished utilizing an asymmetric reduction of the corresponding enone.



SPhos **5** | RuPhos **6**

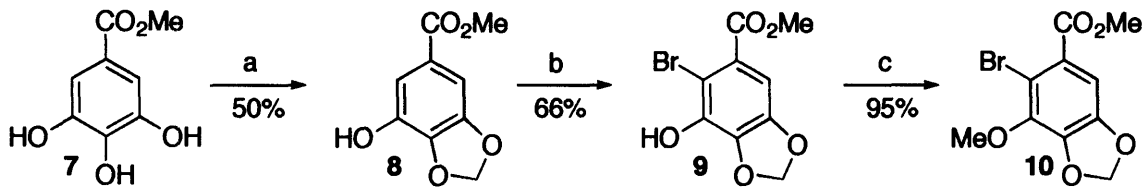
The enone should be available in a few synthetic steps from the biaryl ester. Our recent progress in palladium-catalyzed cross-coupling technology utilizing the monophosphino biaryl ligands shown above led us to predict the rapid and efficient synthesis of the desired biaryl compound employing one of these methods.[6]

Results and Discussion

Initial investigation in this synthesis was begun by Dr. J. Milne, who sought to synthesize the highly substituted aryl bromide **10**. While there have been several reports on the preparation of this material, a combination of several routes was chosen in order to

optimize yield while minimizing the number of steps.[7] Methylenation of the commercially available methyl gallate **7**, followed by bromination gave bromophenol **9**. Alkylation of this material then

Scheme 1.

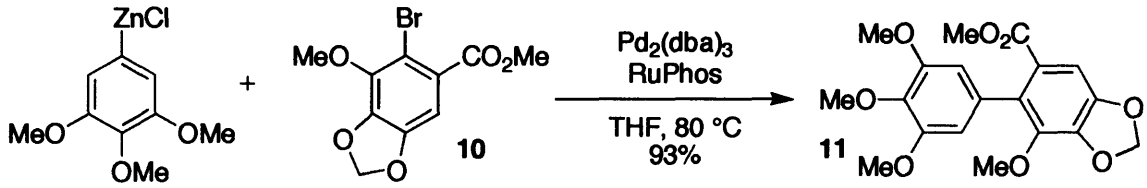


Experiments performed by Dr. J. Milne. Isolated yield average of two runs determined to be >95% purity by ^{1}H NMR or GC. a) CH_2I_2 (1 equiv), K_2CO_3 (1.2 equiv), DMSO, 120 °C. b) NBS (1.1 equiv), MeOH, CH_2Cl_2, -78 °C to RT. c) 1) NaH, THF. 2) Me_2SO_4.

gave the aryl bromide **10** that is required for the cross-coupling reaction. With an expedient route to the aryl bromide, investigation of the palladium-catalyzed cross-coupling reaction could commence.

Emanating from our interest in palladium catalyzed cross-coupling reactions, we recently reported a highly efficient catalyst system derived from the biaryl phosphine ligand RuPhos for the Negishi cross-coupling of a variety of arylzinc reagents (including electron-rich arylzinc reagents) with a number of aryl bromides and chlorides.[6b] It was believed that this system would allow us to efficiently cross-couple aryl bromide **10** with the arylzinc reagent derived from 3,4,5-trimethoxybromobenzene. In fact, using 0.5% $Pd_2(dba)_3$ / 1% **6** in THF at 80 °C for 24 hours gave the desired product in 93% isolated yield. While this reaction was quite efficient with a catalyst loading of 1 mol% palladium, attempts to lower the loading below this level were unsuccessful.[8] In this manner, significant quantities of the biaryl **11** necessary for the completion of the synthesis could be obtained.

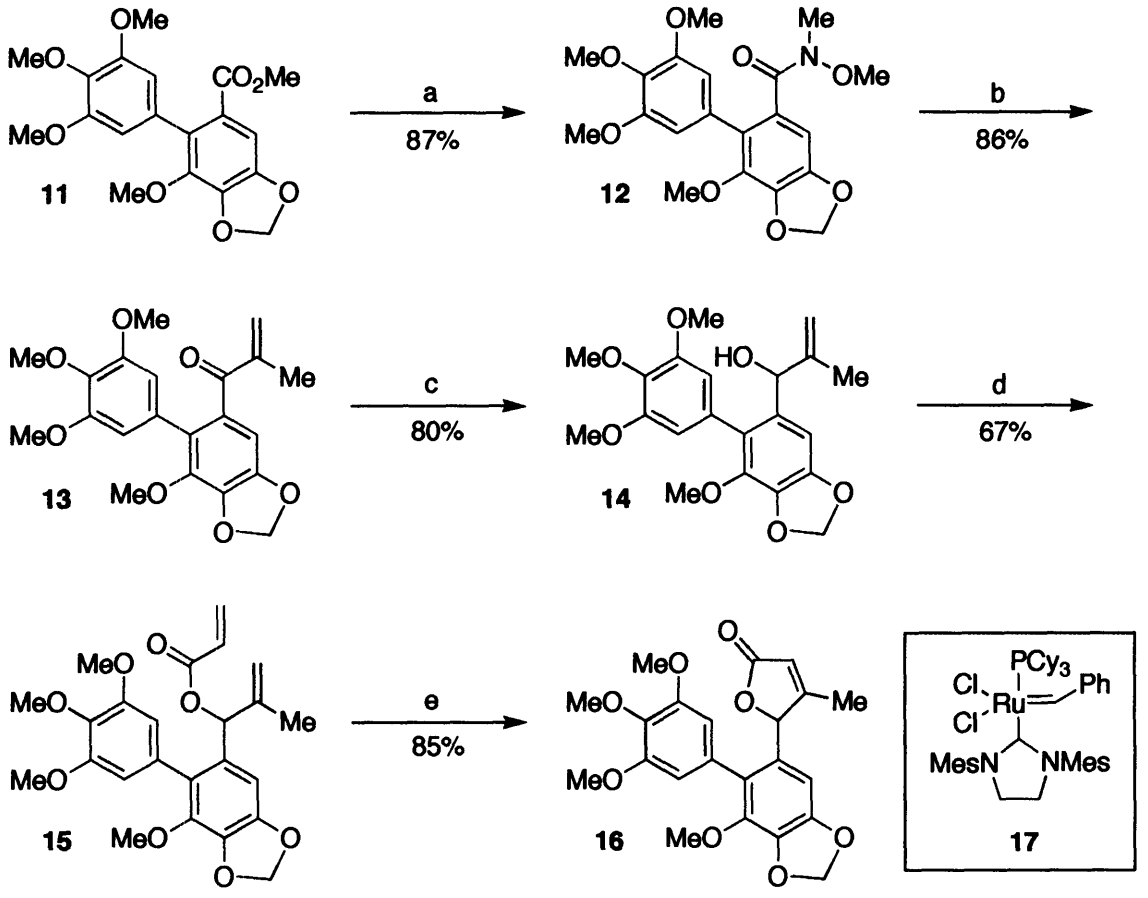
Scheme 2.



Experiment performed by Dr. J. Milne

With the biaryl ester synthesis complete, the next step required preparation of the corresponding enone **13**. This process was begun by preparing Weinreb amide **12** from the methyl ester. Initial results employing Grabowski's procedure for the formation of Weinreb amides from esters were disappointing.[9] However, by employing the less hindered base methylmagnesium bromide (instead of *i*-propylmagnesium chloride), increasing the concentrations of each reagent, and allowing the reaction to warm to room temperature, a good yield of the desired amide was obtained. Initially, 4 equivalents of the Grignard reagent were added to a suspension of the starting ester (1 equiv) and amine (2 equiv). Additional *N,O*-dimethylhydroxylamine hydrochloride and base were added if thought to be necessary after the reaction was analyzed by TLC. Unfortunately, it was observed that the multiple addition of excess reagents led to the formation of an unidentified byproduct. Therefore, if only a small amount of ester remained, it was preferred to stop the reaction and recover the starting material to avoid formation of the byproduct. Subsequent treatment of the Weinreb amide with isoprenyllithium at 0 °C and warming to room temperature provided the desired enone **13** in 86% yield.

Scheme 3.



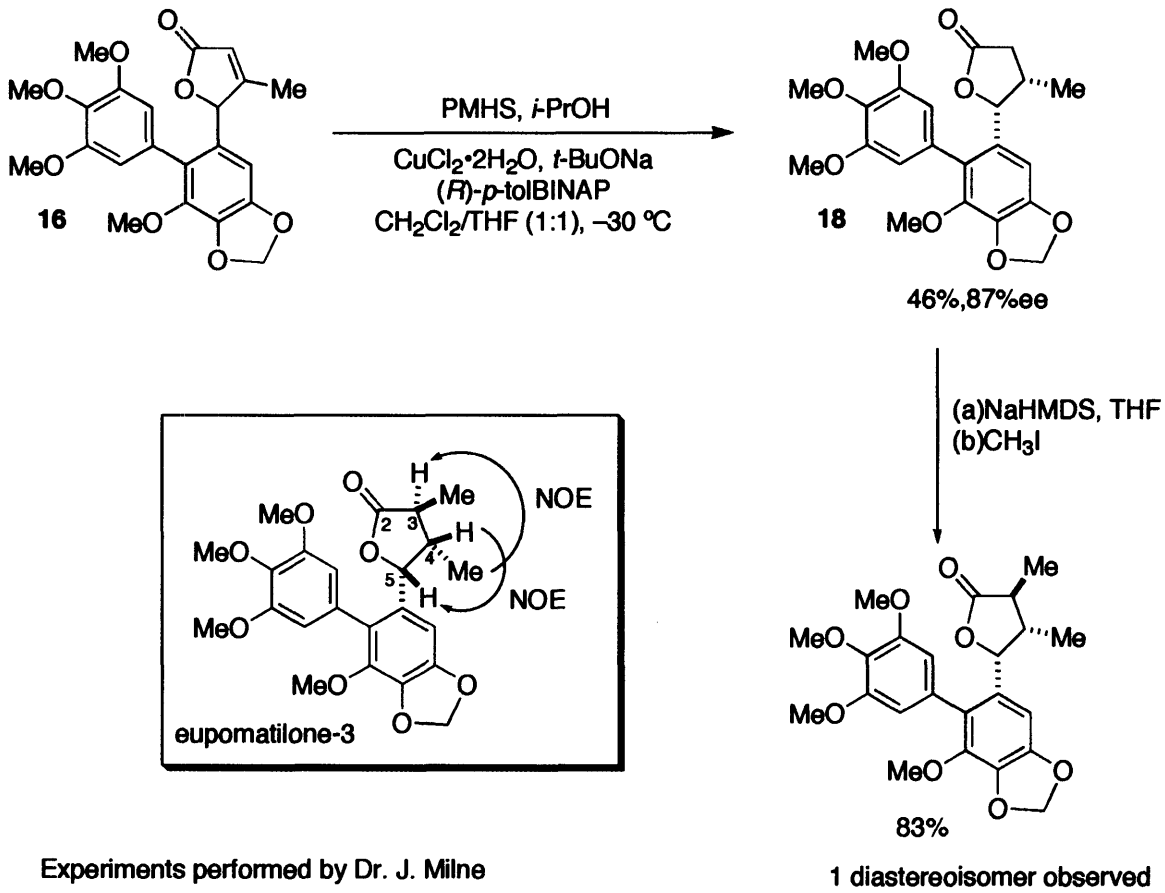
Experiments carried out by Dr. J. Milne. Isolated yield average of two runs determined to be >95% purity by ^{1}H NMR or GC. a) Me(MeO)NH•HCl (3 equiv), MeMgBr (6 equiv), -20 °C, THF. b) isoproprenyllithium (2 equiv), 0 °C, THF. c) $NaBH_4$, $CeCl_3$, MeOH, 0 °C. d) 1) *n*-BuLi, 0 °C, THF. 2) acryloyl chloride, 0 °C. e) **17** (0.05 equiv), CH_2Cl_2, reflux.

Next, the biaryl enone needed to be converted to the corresponding chiral secondary alcohol **14**. A variety of chiral ketone reduction conditions were attempted including CBS reduction and ruthenium catalyzed transfer hydrogenation.[10,11] Unfortunately, in all cases attempted, no desired alcohol was observed. In most attempts, there was no conversion of the starting ketone. Under forcing conditions, decomposition products began to be formed, with still no desired product detected. To try to circumvent this problem, the enone was subjected to a Luche reduction to provide the racemic allylic

alcohol.[12] A kinetic resolution via palladium-catalyzed oxidation was then attempted following the procedure described by Stoltz.[13] However, despite varying temperature, solvent, and catalyst loadings, no conversion of the alcohol was ever observed. At this point, it was decided to carry on this racemic alcohol in the hopes of generating the desired stereochemistry in the lactone through the use of a kinetic resolution via copper conjugate reduction of the unsaturated lactone.[4d] The racemic alcohol was then acylated with acryloyl chloride to give the diene **15** in 67% yield. This material was then treated with the 2nd generation Grubb's catalyst **17** to generate the desired unsaturated lactone **16** in 85% yield.[4b] It should be noted that the best results for the ring closing metathesis were obtained when the catalyst was added slowly over a period of eight hours.

With the ability to synthesize the unsaturated lactone, the asymmetric conjugate reduction reaction was explored. The reduction reaction was attempted employing our standard conjugate reduction conditions at –30 °C in a 1:1 mixture of THF : CH_2Cl_2 (dichloromethane was necessary due to the poor solubility of the lactone in THF).[4] It was observed that at 50% conversion, the desired *cis*-compound was isolated in 46% yield and 87% ee. It is interesting to note that only the *cis*-isomer was ever detected. To conclude the synthesis, the enantiomerically enriched conjugate reduction product **18** was deprotonated with NaHMDS, followed by treatment with iodomethane to give the target natural product eupomatilone-3 in 83% yield. NOE experiments were carried out on synthetic eupomatilone-3 and confirmed the desired relative stereochemistry. In addition, the spectra for synthetic Eupomatilone 3 were in agreement with those obtained from the natural material.[1]

Scheme 4.



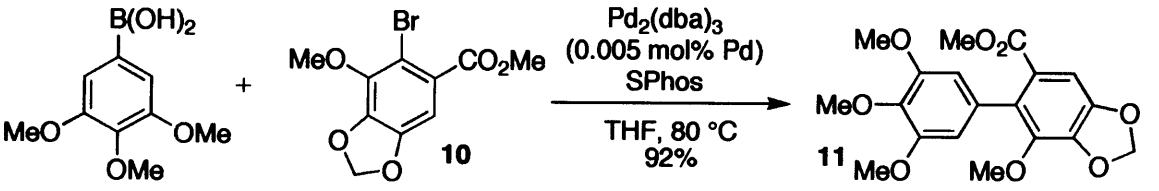
Isolated yield average of two runs determined to be >95% purity by ^{1}H NMR or GC.

Utilizing this synthetic route, we were able to achieve our goal of synthesizing Eupomatilone-3. While the target was obtained in 8 steps from the known aryl bromide **10** in 12% overall yield, the synthesis still required additional attention. In particular, three points needed to be addressed: 1) lowering the amount of palladium catalyst required for the cross-coupling reaction; 2) reducing the overall length of the synthesis; and 3) overcoming the severe limitation of performing a kinetic resolution at a late stage in the synthesis.

Work began by addressing the first problem with the synthesis: lowering the catalyst loading for the cross-coupling reaction. As previously mentioned, earlier

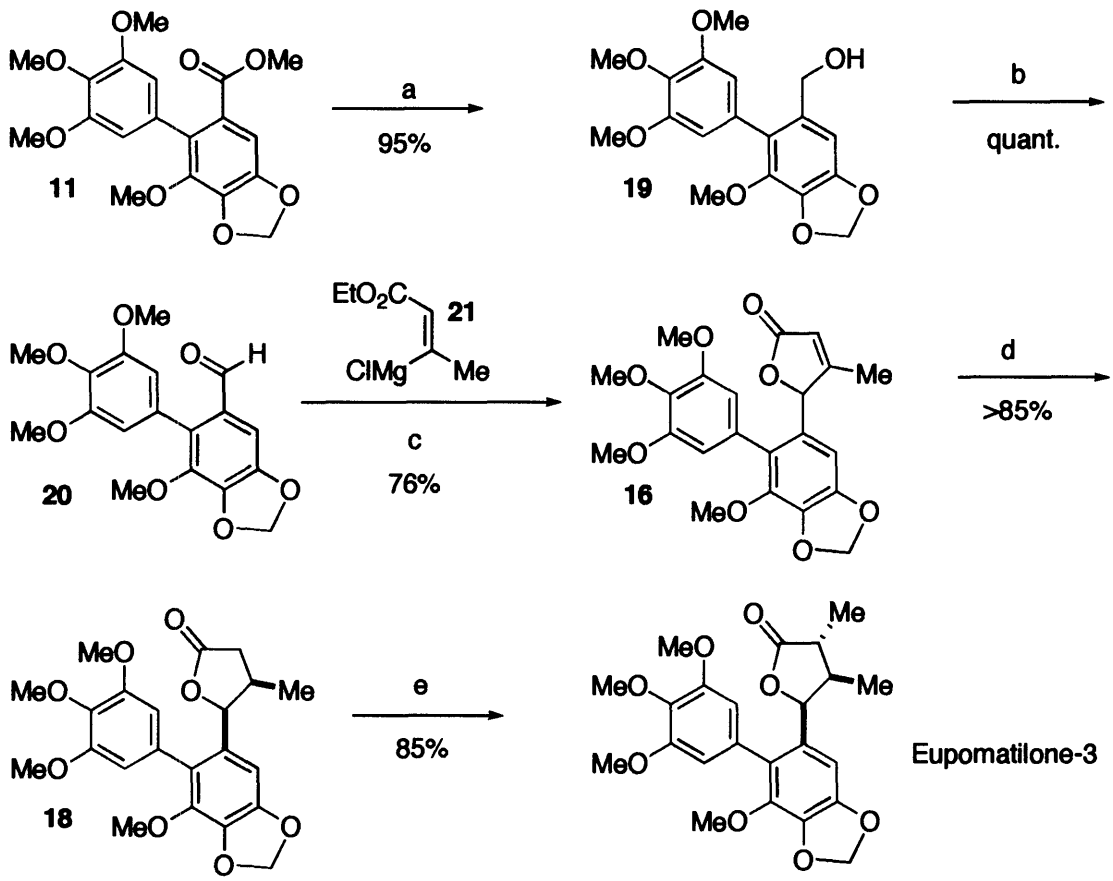
attempts at lowering the catalyst loading in the Negishi cross-coupling reaction had proven unsuccessful. Therefore, other possible cross-coupling reactions that would allow for this reaction to be successfully carried out at lower catalyst loadings were investigated. In particular, the Suzuki-Miyaura cross-coupling reaction utilizing a catalyst based on the recently reported monophosphino biaryl SPhos was examined.[6a,c] To this goal, the cross-coupling of aryl bromide **10** with the commercially available 3,4,5-trimethoxybenzeneboronic acid was attempted in THF at 80 °C with 1 mol % palladium catalyst. It was found that this reaction was indeed successful, and the desired product was obtained in 93% isolated yield. After obtaining this result, the efficiency of this reaction at lower catalyst loadings was examined. In fact, this reaction still proceeded at 0.1 mol% palladium. As the catalyst loading was continued to be lowered down to 0.01 mol%, it was found that after 18 hours, the reaction had failed to reach complete conversion. However, by increasing the ligand : palladium ratio from 2 : 1 to 4 : 1, the reaction was then found to reach complete conversion not only at 0.01 mol%, but as low as 0.005 mol% (50 ppm) palladium.[6a,c] Attempts at performing this reaction at even lower catalyst loadings were less successful, giving incomplete coversion after 24 hours even in the presence of excess ligand. With the ability to form biaryl **11** in high yield using a Suzuki-Miyaura cross-coupling reaction, we chose to proceed with the synthesis.

Scheme 5.



With the ability to rapidly construct the biaryl portion of Eupomatilone-3, investigation began into how to transform this material to the natural product in a more efficient manner. The next objective was to improve the preparation of the butenolide precursor **16** to be used as the substrate for the copper-catalyzed asymmetric conjugate reduction reaction. When examining this motif, we were inspired by the work of Knochel and his synthesis of a variety of butenolides from the reaction of stabilized vinyl Grignard reagents with aldehydes.[14] To apply his method to our synthesis, the material first needed to be transformed from the methyl ester to the corresponding aryl aldehyde. This was achieved by borane reduction of ester **11** to the benzyl alcohol **19**, followed by oxidation with MnO_2 to give the desired benzaldehyde derivative **20** in essentially quantitative yield. Reaction of this aldehyde in THF at -40 °C with the vinyl Grignard reagent **21** (formed in situ from the corresponding vinyl iodide[15]) provided the desired unsaturated lactone in 75% yield.

Scheme 6.



Isolated yield average of two runs determined to be >95% purity by ^{1}H NMR or GC. a) BH_3•THF, THF, 60 °C. b) MnO_2, CH_2Cl_2, RT. c) THF, -40 °C. d) $CuCl_2$•$2H_2O$, (R)-SYNPHOS, NaO*t*-Bu, PMHS, *t*-BuOH, THF, CH_2Cl_2, RT. e) NaHMDS, THF, 0 °C, then MeI.

With the ability to rapidly access the unsaturated lactone **16**, the next problem to address was how to circumvent the requirement to use the late-stage kinetic resolution. The optimal solution would be one in which all of the racemic unsaturated lactone could be converted to the desired *cis*-saturated lactone with high enantioselectivity and diastereoselectivity; namely to establish a dynamic kinetic resolution as shown in Figure 3.[16] Previously, success had been found employing 3,5-substituted unsaturated cyclopentenones in a dynamic kinetic resolution, however, no progress was made with 3,4-substituted cyclopentenone substrates.[4d] However, we believed that the γ proton in

our system would be sufficiently acidic that by performing this reaction in the presence of excess base (sodium *tert*-butoxide) racemization at that center would be viable. Thus, the dynamic kinetic resolution was first attempted utilizing the conditions

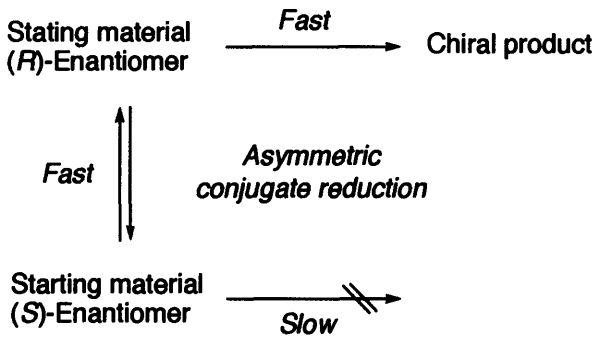


Figure 3. Principle of dynamic kinetic resolution

conditions previously found successful for the kinetic resolution, only now the reaction was performed in the presence of excess base. Unfortunately, no racemization was obtained when 1.2 equivalents of NaO*t*-Bu were used at –30 °C, even after prolonged reaction times. However, when the same experiment was repeated at room temperature, complete conversion of the starting material to the desired product was observed. Just as in the kinetic resolution, the product was again obtained as a single diastereomer and in 83% enantiomeric excess. With this promising result, we sought to optimize the enantioselectivity for this transformation. It was found that replacing *p*-tol-BINAP with MeO-BIPHEP allowed for the conjugate reduction to be carried out at room temperature and provide the desired compound, again as a single diastereomer, but now in 93% enantiomeric excess (when the kinetic resolution was carried out at –30 °C with MeO-BIPHEP, the product was produced in 95% ee). With the synthesis of the *cis*-lactone accomplished, all that remained to complete the synthesis was to install the final methyl group in the alpha-position on the lactone ring. This was accomplished as in the previous

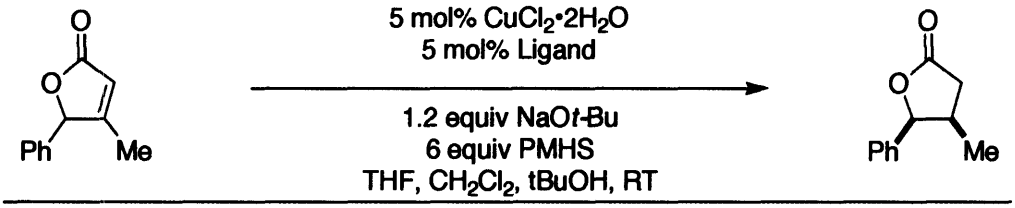
route by enolization of lactone **18** with NaHMDS, followed by alkylation with iodomethane to give Eupomatilone-3 in 85% yield.

Through re-examination of the synthesis, the problems associated with the first generation synthesis were all able to be addressed. By switching to a Suzuki-Miyaura cross-coupling reaction, the biaryl synthesis was able to be completed utilizing only 0.005 mol% of palladium catalyst. Furthermore, taking advantage of the Knochel butenolide synthesis, along with the development of a dynamic kinetic resolution of the butenolide via asymmetric copper-catalyzed conjugate reduction, the natural product was produced in 6 steps from the known aryl bromide **10**, and in 48% overall yield.

The scope of this reaction with other substrates was of interest based on our success with the dynamic kinetic resolution in the synthesis of Eupomatilone-3. The investigation was initiated by examining a simpler substrate than the one used in the total synthesis. The simplest substrate would be a lactone containing an unsubstituted phenyl ring in the gamma position. This material was again readily prepared from reaction of vinyl Grignard **21** with benzaldehyde in THF at –40 °C. This material was then subjected to the conjugate reduction reaction conditions we found to be optimal for the synthesis of Eupomatilone-3. The material was again converted to the saturated lactone in high yield and as a single diastereomer. However, the enantioselectivity observed for this product was only 41% ee. Based on this result, we decided to re-examine the effect of various chiral bisphoshine ligands on the enantioselectivity of the conjugate reduction reaction. The results of this study are shown in Table 1. After screening several chiral ligands, it was found that the observed enantioselectivity for this reaction was highest (67%) when utilizing the commercially available SYNPHOS ligand **1**.[17] The observed

trend seems to follow the trend of decreasing bite angle of the bisphosphine ligand.[18] Presumably, this allows for more interaction of the ligand with the substrate, causing improved selectivity. Next, a variety of experiments were carried out to determine the optimal solvent system for this reaction. After examining a number of solvents and solvent mixtures, we found that the

Table 1. Effect of Ligand on Enantioselectivity in the Conjugate Reduction Reaction

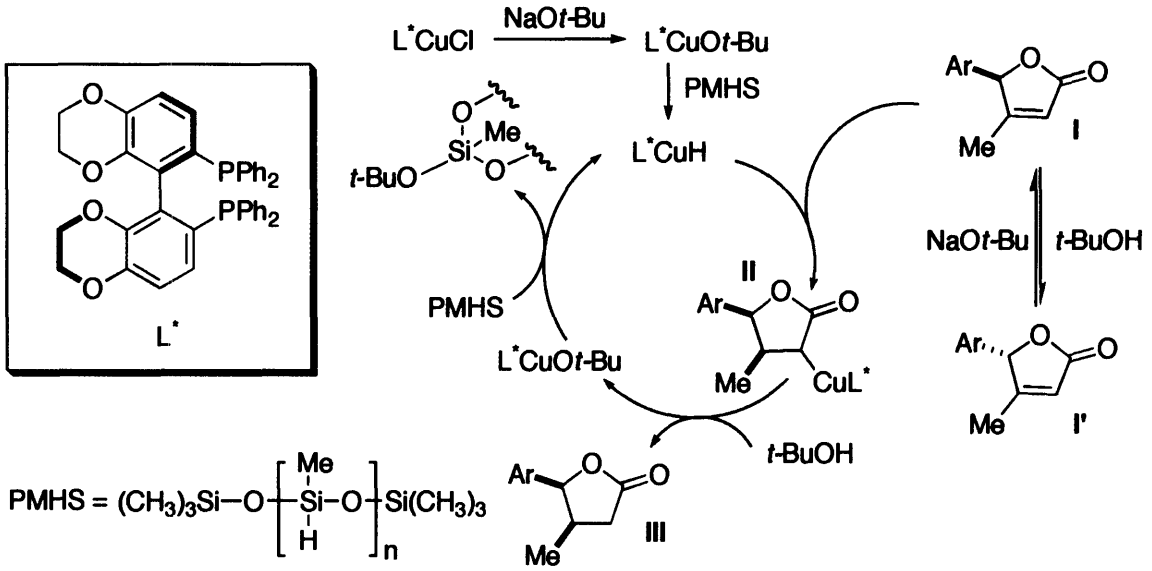


Ligand	BINAP	BIPHEP	xylylBIPHEP	SYNPHOS
ee	41%	35%	58%	67%

original solvent system used in the synthesis of Eupomatilone-3 was optimal. Simple replacement of the dichloromethane with an equal volume of THF still gave the desired product, however with a significantly decreased level of enantiomeric excess. Moreover, as previously observed, reactions carried out in the absence of *t*-BuOH lead to lower reaction rates (however the enantioselectivity remained unchanged). A proposed catalytic cycle for this reaction that accounts for these phenomena is shown below. It is believed the active copper hydride catalyst is formed by reaction of a copper alkoxide with the silane. This can then preferentially react with one of the two equilibrating enantiomers of the starting material **I** or **I'** from the face opposite the arene substituent. This would generate a copper enolate **II**, which can then be protonated by the alcohol to release the desired product **III** and generate another copper alkoxide. This species can

then undergo reaction with the silane to regenerate the active copper hydride catalyst and turn the cycle over.

Scheme 7.

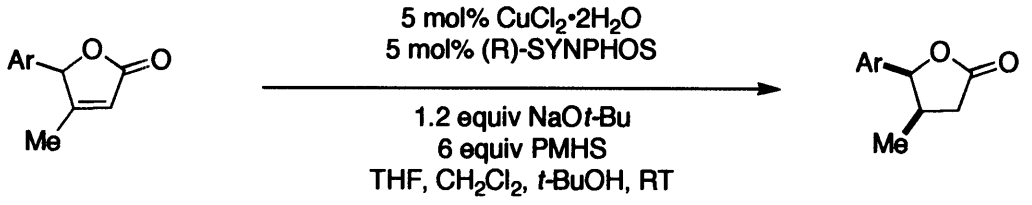


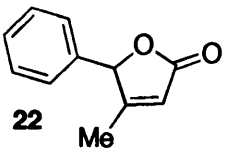
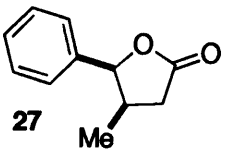
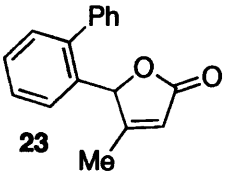
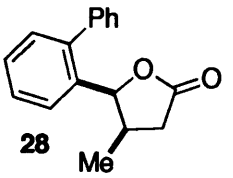
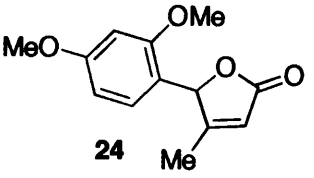
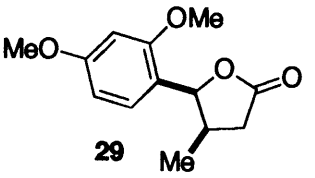
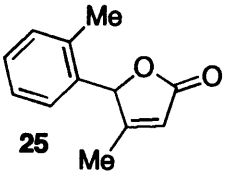
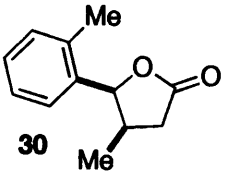
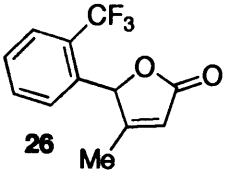
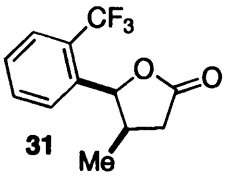
After finding the optimal reaction conditions, other lactone substrates were examined in this transformation. Several γ-aryl containing lactones were prepared, again all from the reaction of vinyl Grignard **21** with the corresponding aryl aldehyde. The results of this examination are shown in Table 2.

It was found that a substrate containing a methyl group in the *ortho* position of the arene gave the product again a single diastereomer, however now in slightly higher selectivity (77% ee). Changing the substituent on the aromatic ring from a methyl group to a phenyl ring gave the product in 82% ee. When a lactone containing an electron rich arene (derived from 2,4-dimethoxy-benzaldehyde) in the γ-position was reduced, the product was produced in 87% ee. Additionally, a lactone containing an arene with an *ortho* electron-withdrawing substituent (trifluoromethyl group) gave the reduced product in nearly identical selectivity (78% ee) as for the lactone containing the methyl group.

This suggests that the enantioselectivity of the conjugate reduction reaction is independent of the electronic nature of the arene, however, the selectivity is sensitive to the size of the arene. Interestingly, the enantioselectivity for the conjugate reduction of γ-aryl lactones was highest when employing SYNPHOS as the supporting ligand in all cases except for the substrate in the synthesis of Eupomatilone-3 (here MeO-BIPHEP gave slightly higher selectivity, ~3%). This implies that one cannot assume that the ligand with the smallest dihedral angle will give the highest selectivity. Instead, there needs to be a match between the dihedral angle of the ligand and the size of the substrate in order to maximize selectivity.

Table 2. Dynamic kinetic resolution of unsaturated lactones



Entry	Substrate	Product	ee	yield
1	 **22**	 **27**	67%	95%
2	 **23**	 **28**	81%	92%
3	 **24**	 **29**	87%	85%
4	 **25**	 **30**	77%	91%
5	 **26**	 **31**	78%	94%

Isolated yield average of two runs determined to be >95% purity by ^{1}H NMR or GC.

Unfortunately, employing the same reaction conditions for the dynamic kinetic resolution on lactones containing simple alkyl substituents in the γ-position have failed to give >50% conversion of the starting material. This is presumably due to poor racemization of the starting lactone. Additionally, the reaction provided both the *cis*- and

trans-isomers of the product. Furthermore, the enantioselectivity of the *cis*-product was found to be low (<25% ee).

Conclusions

Reaction conditions have bee developed that allow for a variety of γ-aryl containing α,β-unsaturated butenolides to be reduced in both high enantiomeric and diastereomeric excess. While a number of catalysts based on chiral bisphosphines were found to successfully promote this transformation, optimal enantioselectivity was obtained when employing the commercially SYNPHOS ligand. Through the use of this transformation, the total synthesis of Eupomatilone-3 was achieved in 6 steps and in 48% overall yield.

Experimental Procedures

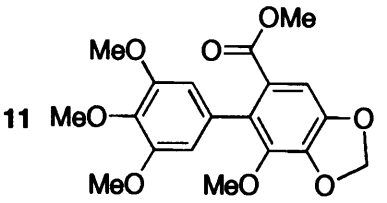
I. General Considerations.

Unless otherwise noted, THF and toluene were purchased from J.T. Baker in CYCLE-TAINER® solvent-delivery kegs and vigorously purged with argon for 2 h. The solvents were further purified by passing them under argon pressure through two packed columns of neutral alumina (for THF) or through neutral alumina and copper (II) oxide (for toluene).[19] Starting materials for substrate synthesis were purchased from commercial sources and used as is. PMHS (polymethylhydrosiloxane) and *t*-BuOH were purchased from Aldrich and used as is. SYNPHOS was purchased from Strem Chemicals, Inc.

Yields refer to isolated yields of compounds of greater than 95% purity as estimated by capillary GC and ^{1}H NMR. Yields reported in this section refer to a single experiment, while those reported in the tables are the average of two or more runs.

All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy, in addition to elemental analysis (Atlantic Microlabs, Inc) or HRMS. Nuclear Magnetic Resonance spectra were recorded on a Varian Mercury 300 of Varian 500 instrument. Infrared spectra were recorded on a Perkin-Elmer Model 2000 FTIR instrument. All ^{1}H NMR experiments are reported in δ units, parts per million (ppm) downfield from tetramethylsilane. All ^{13}C NMR spectra are reported in ppm relative to residual solvent, and all were obtained with ^{1}H decouling. Melting points (uncorrected) were obtained on a Mel-Temp capillary melting point apparatus. Optical rotations were taken on a Jasco Model-1010 Polarimeter at 21 °C. Gas Chromatographic analyses were performed on a Hewlett-Packard 6890 gas chromatography instrument with an FID detector using 25m x 0.20 mm capillary column with cross-linked methyl siloxane as a stationary phase. Chiral High Performance Liquid Chromatography analyses were performed on a Hewlett-Packard 1100 system with an HP 1100 Diode Array Detector, using the columns and wavelengths mentioned in sections II and IV.

Part II. Total Synthesis of Eupomatilone-3

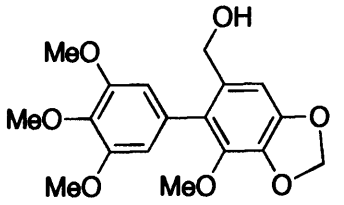


7-Methoxy-6-(3,4,5-trimethoxy-phenyl)-benzo[1,3]dioxole-5-carboxylic acid methyl ester

A flame-dried 5 mL screw cap vial equipped with a Teflon-coated magnetic stir bar was charged with $Pd(OAc)_2$ (1 mg, 0.005 mmol) and SPhos (8.2 mg, .02 mmol), then sealed with a Teflon centered screw cap. The flask was then evacuated, backfilled with argon, and this process was repeated one additional time. THF (1 mL) was then added to the flask via syringe and the resulting solution was allowed to stir at room temperature for 5 minutes. Seperately, a flame-dried 15 mL Schlenk flask equipped with a Teflon-coated magnetic stir bar was charged with aryl bromide **4** (145 mg, 0.5 mmol), 3,4,5-trimethoxy benzeneboronic acid (159 mg, 0.75 mmol), and tripotassium phosphate (212 mg, 1.0 mmol). The flask was then capped with a rubber septum, evacuated, backfilled with argon, and this process was repeated one additional time. THF (1 mL) was then added to the Schlenk flask while under argon via syringe. Then 5 μL of the catalyst solution generated in the vial; as described above, was added to the Schlenk flask via syringe, followed by an additional 0.5 mL of THF that was added to the Schlenk flask to wash down the sides of the flask. The septum was then replaced with a Teflon screw cap and the flask was sealed and placed in a 80 °C oil bath for 20 h. Upon complete conversion of the starting aryl bromide (as assessed by both TLC and GC) the reaction mixture was allowed to cool to room temperature, then filtered through a small plug of silica gel eluting with EtOAc. This was then concentrated to dryness with the aid of a rotary

evaporator. The resulting residue was purified by flash chromatography on silica gel eluting with 3:1 to 2:1 EtOAc : Hexane to give 173 mg (92%) of the title compound as a white solid. M.p. : 145-146 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.02 (s, 1H), 6.44 (s, 2H), 6.06 (s, 2H), 3.90 (s, 3H), 3.84 (s, 6H), 3.83 (s, 3H), 3.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.1, 152.5, 148.2, 141.0, 140.0, 137.0, 132.0, 130.1, 125.9, 106.8, 104.2, 102.0, 60.8, 60.0, 56.0, 52.0; IR (cm^{-1}): 1728, 1612, 1583, 1434, 1326, 1281, 1240, 1126, 1086, 1044; Anal. Calcd. for $C_{19}H_{20}O_8$: C, 60.63; H, 5.36. Found: C, 60.61; H, 5.33.

19

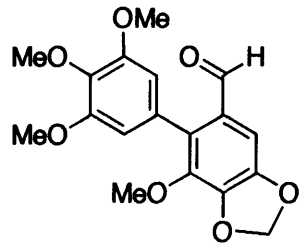


[7-Methoxy-6-(3,4,5-trimethoxy-phenyl)-benzo[1,3]dioxol-5-yl]-methanol

A flame dried 25 mL round bottom flask equipped with a Teflon-coated magnetic stir bar was charged with **5** (850 mg, 2.26 mmol) and THF (5 mL). Then, 11.3 mL of a solution of BH_3•THF in THF (1M) (10 mmol) was carefully added dropwise to the stirring solution. When addition was complete, the flask was equipped with a reflux condenser and then placed in a 80 °C oil bath and allowed to stir for 14 h. The reaction mixture was allowed to cool to room temperature, then carefully quenched with water. This mixture was then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, then concentrated with the aid of a rotary evaporator. The resulting residue was then purified by flash chromatography on silica gel eluting with 1:1 to 2:1 EtOAc : Hexane to give 724 mg (92%) of the title comound as a white solid. M.p. : 106-108 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.74 (s, 1H), 6.43 (s, 2H), 5.95 (s, 2H), 4.30 (s, 2H), 3.86

(s, 3H), 3.80 (s, 9H), 2.09 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.9, 148.6, 141.0, 136.9, 136.4, 133.6, 131.5, 127.4, 107.3, 102.9, 101.3, 62.9, 60.9, 60.1, 56.1; IR (cm^{-1}): 3481, 1584, 1507, 1457, 1410, 1238, 1126, 1059; Anal. Calcd. for $C_{18}H_{20}O_7$: C, 62.06; H, 5.79. Found: C, 62.06; H, 5.82.

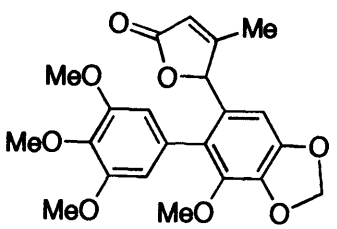
20



7-Methoxy-6-(3,4,5-trimethoxy-phenyl)-benzo[1,3]dioxole-5-carbaldehyde

A 100 mL round bottom flask equipped with a Teflon-coated magnetic stir bar was charged with **13** (660 mg, 1.9 mmol) and CH_2Cl_2 (28 mL). To the stirring solution was added MnO_2 (1.65g, 19 mmol) in one portion. This suspension was allowed to stir at room temperature for 2 h (at which time complete conversion of the starting material was confirmed by TLC and ^1H NMR). The reaction mixture was filtered through a plug of celite, eluting with CH_2Cl_2. The solution was then concentrated to dryness with the aid of a rotary evaporator, then used in the next reaction without further purification.

16

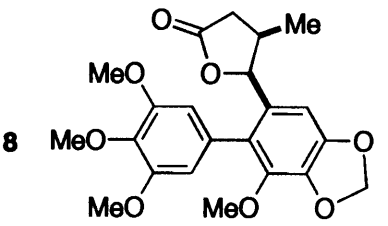


5-[7-Methoxy-6-(3,4,5-trimethoxy-phenyl)-benzo[1,3]dioxol-5-yl]-4-methyl-5*H*-furan-2-one

A flame-dried 100 mL round bottom flask equipped with a Teflon-coated magnetic stir bar was charged with 3-iodo-but-2-enoic acid ethyl ester (684 mg, 2.85 mmol), then

sealed with a rubber septum. The flask was then evacuated, backfilled with agon, and the process was repeated one additional time. The flask was finally fit with a balloon of argon. THF (15 mL) was then added to the flask, that was then cooled to –20 °C. A solution of *i*-PrMgCl (1.4 mL, 2M in Et_2O) was then slowly added dropwise to the stirring solution of vinyl iodide maintaining a temperature of –20 °C. When addition was complete, the reaction was allowed to stir an additional 2 h at –20 °C. This solution was then added via cannula to a stirring solution of **14** in THF (15 mL) in a flame dried flask under argon at –40 °C. The reaction was allowed to stir at –40 °C for 1 h, then quenched with saturated aqueous ammonium chloride and allowed to warm to room temperature. The reaction mixture was then extracted three times with EtOAc. The combined organic layers were then washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness with the aid of a rotary evaporator. The resulting residue was then purified by flash chromatography on silica gel eluting with 2:1 to 1:1 Hexane:EtOAc to give 600mg (76%) of the title compound as a white solid. M.p. : 166-168 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.52 (d, *J*=2Hz, 1H), 6.39 (d, *J*=2Hz, 1H), 6.23 (s, 1H), 5.97 (dd, *J*=2Hz, 4Hz, 2H), 5.87 (m, 1H), 5.56 (m, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 1.83 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ:173.5, 168.5, 153.7, 153.3, 153.1, 151.7, 143.3, 131.0, 130.7, 127.6, 117.2, 107.8, 107.7, 104.7, 83.5, 79.0, 61.5, 61.1, 56.4, 14.6; IR (cm^{-1}): 2940, 2252, 1760, 1583, 1477, 1411, 1237, 1127; Anal. Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 63.66; H, 5.33.

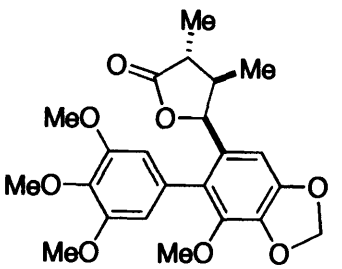
18



5-[7-Methoxy-6-(3,4,5-trimethoxy-phenyl)-benzo[1,3]dioxol-5-yl]-4-methyl-dihydro-furan-2-one

An oven-dried screw cap test tube equipped with a Teflon-coated magnetic stir bar was charged with copper (II) chloride dihydrate (2.1 mg, 0.013 mmol), (S)-BIPHEP (7.3 mg, 0.013 mmol), and sodium *tert*-butoxide (29 mg, 0.30 mmol). The tube was then sealed with a Teflon-centered screw cap, then evacuated, backfilled with argon, and the cycle was repeated. THF (2 mL) was then added to the tube and the mixture was allowed to stir at room temperature for 5 minutes. PMHS (90 μL, 1.5 mmol) was then added dropwise and allowed to stir for 5 minutes. Following this, **10** was added as a solution in THF / CH_2Cl_2 / *t*-BuOH (1.75 mL / 1.25 mL / 375 μL) and allowed to stir at room temperature for 24 h, at which point TLC indicated complete conversion of the starting material. At this point, an equal volume of 3N Hcl was carefully added to the reaction and allowed to stir for 15 minutes. This was then extracted 3 times with EtOAc. The combined organics were dried over $MgSO_4$, filtered, and concentrated to dryness with the aid of a rotary evaporator. The resulting residue was then purified by flash chromatography on silica gel eluting with 1:6 to 1:1 EtOAc:Hexane to give 89 mg (85%) of the title compound a white solid. M.p. : 52-54 °C. Chiral HPLC analysis (Daicel Chiralpak® AD column (0.46cm x 25 cm), 1 mL/ min, 50% *i*-PrOH/ Hexane, 254 nm, 210 nm, 225 nm, retention times: 9.29 min (major), 20.3 min (minor)) showed 92% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.73 (s, 1H), 6.41 (d, *J*=2Hz, 1H), 6.30 (d, *J*=2Hz, 1H), 6.00 (s, 2H), 5.37 (d, *J*=6Hz, 1H), 3.91 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H),

2.68 (dd, *J*=8Hz, 17Hz, 1H), 2.26 (m, 2H), 0.74 (d, *J*=7Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.5, 153.5, 153.2, 148.9, 141.1, 137.4, 136.5, 131.3, 129.1, 126.5, 107.7, 106.4, 101.6, 101.0, 82.1, 61.1, 60.2, 56.3, 56.2, 37.9, 34.4, 15.7; IR (cm^{-1}): 2360, 1780, 1583, 1479, 1410, 1238, 1165, 1058; Anal. Calcd. for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81. Found: C, 63.32; H, 5.45. α_D (589 nm, 2.2 g/ 100 mL $CHCl_3$) = -10.9°.



Eupomatilone-3

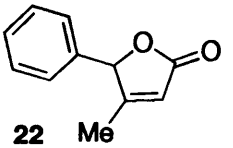
A flame-dried 25 mL round bottom flask equipped with a Teflon-coated magnetic stir bar was brought into a drybox and charged with sodium hexamethylsilazide (66 mg, 0.36 mmol). The flask was sealed with a rubber septum and then removed from the drybox. A balloon filled with argon was inserted through the septum, then THF (2 mL) was added. The flask was then cooled to –78 °C. **12** (75 mg, 0.18 mmol) was then added slowly as a solution in THF (10 mL) over 30 minutes, and then allowed to stir for an additional 4 h. Iodomethane (224 μL, 3.6 mmol) was added dropwise, then allowed to stir for 1 h. The reaction was then allowed to gradually warm to –20 °C. The reaction was then quenched with water (3 mL) and allowed to warm to room temperature. The reaction mixture was then extracted three times with EtOAc. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated to dryness with the aid of a rotary evaporator. The resulting residue was then purified by flash chromatography on

silica gel eluting with 5:1 to 1:1 Hexane:EtOAc to give 66 mg (85%) of the title compound as a colorless oil. Chiral HPLC analysis (Daicel Chiralpak® AD column (0.46cmØ x 25 cm), 1 mL/ min, 50% *i*-PrOH/ Hexane, 254 nm, 210 nm, 225 nm, retention times: 5.9 min (major), 7.9 min (minor)) showed 93% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.54 (s, 1H), 6.41 (d, *J*=2Hz, 1H), 6.32 (d, *J*=2Hz, 1H), 5.99 (s, 2H), 5.48 (d, *J*=7.3Hz, 1H), 5.89 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 2.38 (quintet, *J*=7.3Hz, 1H), 2.04 (sextet, *J*=7.3Hz, 1H), 1.16 (d, *J*=7.3Hz, 3H), 0.77 (d, *J*=7.3Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 179.6, 153.4, 153.1, 149.0, 141.1, 137.3, 136.6, 131.2, 129.2, 127.5, 108.2, 106.7, 101.5, 100.8, 79.9, 61.0, 60.1, 56.3, 41.9, 41.7, 35.2, 15.3, 14.8; IR (cm^{-1}): 1772, 1583, 1507, 1479, 1410, 1238, 1127, 1086; Anal. Calcd. for $C_{23}H_{26}O_8$: C, 64.18; H, 6.09. Found: C, 64.35; H, 6.23. α_D (589 nm, 2.1 g/ 100 mL $CHCl_3$) = -27.4°.

Part III. Synthesis of unsaturated lactones

General procedure for the synthesis of α,β-unsaturated lactones:

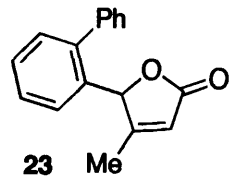
All unsaturated lactones examined were prepared following the procedure described by Knochel[13].



22

4-Methyl-5-phenyl-5*H*-furan-2-one

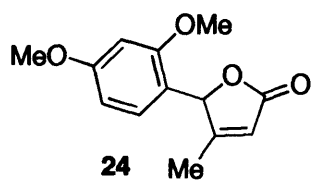
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (m, 3H), 7.25 (m, 2H), 5.93 (m, 1H), 5.71 (m, 1H), 1.91 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.6, 168.7, 134.4, 129.6, 129.2, 126.9, 116.4, 86.7, 14.2; IR (cm^{-1}): 2360, 1761, 1646, 1456, 1290, 1147, 1023, 978; Anal. Calcd. for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.76; H, 5.91.



23

5-Biphenyl-2-yl-4-methyl-5*H*-furan-2-one

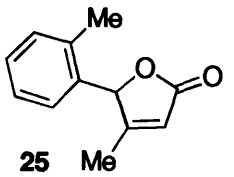
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (m, 8H), 7.11 (m, 1H), 5.91 (m, 1H), 5.87 (m, 1H), 1.81 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.6, 168.7, 143.3, 139.7, 131.3, 130.7, 129.6, 129.3, 128.6, 128.3, 127.8, 126.7, 117.1, 83.3, 14.4; IR (cm^{-1}): 1762, 1646, 1481, 1437, 1290, 1149, 1021, 974; Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.32; H, 5.44.



24

5-(2,4-Dimethoxy-phenyl)-4-methyl-5*H*-furan-2-one

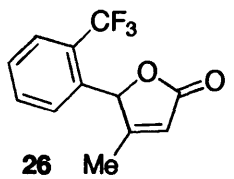
^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.94 (m, 1H), 6.46 (m, 2H), 6.16 (s, 1H), 5.86 (m, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 1.91 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.1, 169.7, 161.7, 158.6, 128.2, 116.3, 114.8, 105.1, 98.8, 81.1, 55.7, 55.6, 14.2; IR (cm^{-1}): 2941, 1758, 1612, 1508, 1303, 1210, 1159, 1031; Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.32; H, 5.84.



25

4-Methyl-5-*o*-tolyl-5*H*-furan-2-one

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24 (m, 3H), 7.01 (m, 1H), 6.02 (m, 1H), 5.96 (m, 1H), 2.43 (s, 3H), 1.94 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.6, 168.8, 136.8, 132.3, 131.3, 129.4, 126.8, 126.6, 117.2, 83.6, 19.4, 14.3; IR (cm^{-1}): 2980, 1761, 1289, 1173, 1029; Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.63; H, 6.38.



26

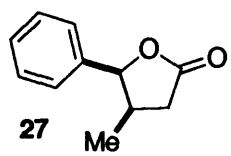
4-Methyl-5-(2-trifluoromethyl-phenyl)-5*H*-furan-2-one

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.74 (d, *J*=7Hz, 1H), 7.54 (ddd, *J*=7Hz, 2H), 7.21 (d, II=7Hz, 1H), 6.18 (m, 1H), 6.02 (m, 1H), 1.89 (m, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ: -57.3; 13C NMR (75 MHz, $CDCl_3$) δ: 173.2, 168.6, 133.2, 132.9, 129.7, 127.7, 126.3, 126.2, 117.4, 81.2, 81.1, 14.2; IR (cm^{-1}): 1767, 1315, 1285, 1161, 1114, 1028; Anal. Calcd. for $C_{12}H_9F_3O_2$: C, 59.51; H, 3.75. Found: C, 59.74; H, 3.74

Part IV. Asymmetric reduction of unsaturated lactones

General Procedure:

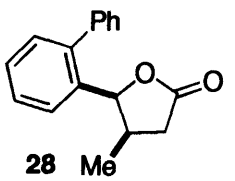
An oven-dried screw cap test tube equipped with a Teflon-coated magnetic stir bar was charged with copper(II) chloride dihydrate (5 mol%), (R)-SYNPHOS (5 mol%), and sodium tert-butoxide (1.2 equiv). The tube was then sealed with a Teflon centered screw cap. Next, the tube was evacuated, backfilled with argon, and this process was repeated. THF (2.5 mL) was then added to the tube via syringe and the mixture was allowed to stir at room temperature for 5 minutes. To this mixture was then added PMHS (6 equiv) dropwise, and then the mixture was allowed to stir for an additional 5 minutes. The unsaturated lactone (0.3 mmol) was then added to the reaction as a solution in THF (2 mL), CH_2Cl_2 (1.5 mL) and *t*-BuOH (450 μL). The reaction was allowed to stir at room temperature until complete conversion of the starting material was obtained (as judged by TLC or GC). The reaction was then carefully quenched with an equal volume of 3N HCl, and allowed to stir for 15-30 minutes. The mixture was then extracted three times with EtOAc. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated to dryness with the aid of a rotary evaporator. The crude residue was purified by flash chromatography on silica gel to give the desired compound.



4-Methyl-5-phenyl-dihydro-furan-2-one

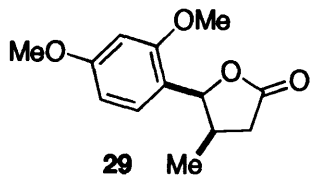
The general procedure was employed using 52 mg (0.3 mmol) of **16**. Purification via flash chromatography on silica gel eluting with 1:9 EtOAc:Hexane gave 50 mg (95%) of the title compound as a colorless oil. Chiral HPLC analysis (Daicel Chiralpak® OJ column (0.46cm x 25 cm), 1.2 mL/ min, 2% *i*-PrOH/ Hexane, 254 nm, 210 nm, 225 nm,

retention times: 25.9 min (minor), 30.1 min (major)) showed 68% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33 (m, 3H), 7.21 (m, 2H), 5.56 (d, *J*=6Hz, 1H), 2.79 (m, 2H), 2.30 (dd, *J*=4Hz, 17Hz, 1H), 0.65 (d, *J*=7Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.0, 136.2, 128.6, 128.2, 125.5, 84.2, 37.2, 35.1, 15.3; IR (cm^{-1}): 1780, 1456, 1157, 913, 749; Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.22; H, 6.94. α_D (589 nm, 1.3g/ 100 mL $CHCl_3$) = 16.9°.



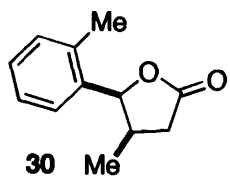
5-Biphenyl-2-yl-4-methyl-dihydro-furan-2-one

The general procedure was employed using 75 mg (0.3 mmol) of **17**. Purification via flash chromatography on silica gel eluting with 1:9 EtOAc:Hexane gave 69 mg (91%) of the title compound as a colorless oil. Chiral HPLC analysis (Daicel Chiralpak® OJ column (0.46cm x 25 cm), 1 mL/ min, 8% *i*-PrOH/ Hexane, 254 nm, 210 nm, 225 nm, retention times: 17.4 min (major), 20.8 min (minor) showed 79% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53 (m, 1H), 7.40 (m, 5H), 7.25 (m, 2H), 7.2 (m, 1H), 5.67 (d, *J*=6Hz, 1H), 2.67 (dd, *J*=8Hz, 17Hz, 1H), 2.21 (m, 2H), 0.64 (d, *J*=7Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.6, 140.5, 140.2, 133.7, 130.0, 128.8, 128.6, 127.8, 127.7, 127.6, 125.8, 82.2, 37.9, 33.9, 15.7; IR (cm^{-1}): 1783, 1479, 1306, 1213, 1164, 987, 756; Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 81.21; H, 6.45. α_D (589 nm, 5.2g/ 100 mL $CHCl_3$) = 28.9°.



5-(2,4-Dimethoxy-phenyl)-4-methyl-dihydro-furan-2-one

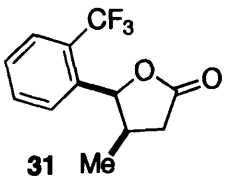
The general procedure was employed using 70 mg (0.3 mmol) of **18**. Purification via flash chromatography on silica gel eluting with 1:3 EtOAc:Hexane gave 60 mg (85%) of the title compound as a colorless oil. Chiral HPLC analysis (Daicel Chiralpak® OD column (0.46cm x 25 cm), 1 mL/ min, 10% *i*-PrOH/ Hexane, 254 nm, 210 nm, 225 nm, retention times: 9.66 min (minor), 26.0 min (major) showed 87% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.21 (d, *J*=8Hz, 1H), 6.49 (dd, *J*=2Hz, 8Hz, 1H), 6.46 (d, *J*=2Hz, 1H), 5.75 (d, *J*=6Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 2.97 (m, 1H), 2.82 (dd, *J*=8Hz, 17Hz, 1H), 2.31 (dd, *J*=4Hz, 17Hz, 1H), 0.67 (d, *J*=7Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.3, 160.7, 157.0, 127.1, 117.2, 103.9, 98.4, 81.2, 55.5, 55.4, 37.4, 33.6, 15.3; IR (cm^{-1}): 1780, 1616, 1590, 1508, 1287, 1210, 1160, 1033, 987; Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.39; H, 6.87. α_D (589 nm, 3.9g/ 100 mL $CHCl_3$) = 30.5°.



4-Methyl-5-*o*-tolyl-dihydro-furan-2-one

The general procedure was employed using 56 mg (0.3 mmol) of **19**. Purification via flash chromatography on silica gel eluting with 1:4 EtOAc:Hexane gave 52 mg (91%) of the title compound as a colorless oil. Chiral HPLC analysis (Daicel Chiralpak® OJ column (0.46cm x 25 cm), 1 mL/ min, 10% *i*-PrOH/ Hexane, 254 nm, 210 nm, 225 nm,

retention times: 12.7 min (major), 13.9 min (minor) showed 80% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.4 (m, 1H), 7.23 (m, 3H), 5.76 (d, *J*=6Hz, 1H), 2.95 (m, 2H), 2.33 (m, 4H), 0.64 (d, *J*=7Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.7, 134.4, 133.7, 130.4, 128.0, 126.2, 125.3, 82.1, 37.8, 33.2, 19.3, 15.6; IR (cm^{-1}): 1783, 1462, 1305, 1212, 1163, 987, 912, 750; Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.46; H, 7.23. α_D (589 nm, 2.1g/ 100 mL $CHCl_3$) = 37.2°.



31

4-Methyl-5-(2-trifluoromethyl-phenyl)-dihydro-furan-2-one

The general procedure was employed using 69 mg (0.3 mmol) of **20**. Purification via flash chromatography on silica gel eluting with 1:4 EtOAc:Hexane gave 69 mg (93%) of the title compound as a colorless oil. Chiral HPLC analysis (Daicel Chiralpak® AD column (0.46cm x 25 cm), 1 mL/ min, 10% *i*-PrOH/ Hexane, 254 nm, 210 nm, 225 nm, retention times: 5.63 min (minor), 6.46 min (major) showed 78% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68 (m, 3H), 7.47 (m, 1H), 5.97 (d, *J*=6Hz, 1H), 3.00 (m, 2H), 2.38 (m, 1H), 0.66 (d, *J*=7Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ: -59.5; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.5, 136.2, 132.9, 128.7, 127.5, 126.3, 126.2, 117.4, 81.2, 37.5, 35.4, 14.2; IR (cm^{-1}): 1791, 1457, 1315, 1273, 1162, 1037, 990, 771; Anal. Calcd. for $C_{12}H_{11}F_3O_2$: C, 59.02; H, 4.54. Found: C, 59.32; H, 4.67. α_D (589 nm, 2.8g/ 100 mL $CHCl_3$) = 24.9°.

References:

(1)For a review on lignans: Ward, R. S. *Nat. Prod. Rep.* **1997**, 14, 43.

(2) Carroll, A. R.; Taylor, W. C. *Aust. J. Chem.* **1991**, 44, 1705.

(3) For recent synthetic efforts: (a) Hong, S.-P.; McIntosh, M. C. *Org. Lett.* **2002**, *4*, 19. (b) Hutchison, J. M.; Hong, S. P.; McIntosh, M. C. *J. Org. Chem.* **2004**, *69*, 4185. (c) Gurjar, M. K.; Cherian, J.; Ramana, C. V. *Org. Lett.* **2004**, *6*, 317. (d) Coleman, R. S.; Gurrala, S. R. *Org. Lett.* **2004**, *6*, 4025.

(4) For examples of copper catalyzed asymmetric conjugate reductions see: (a) Rainka, M. P.; Aye, Y.; Buchwald, S. L. *Proc. Natl. Acad. Sci., USA,* **2004**, *101*, 5821. (b) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253. (c) Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *14*, 2417. (d) Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 2892. (e) Moritani, Y.; Appella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797. (f) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473. (g) Yun, J.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1129.

(5) (a) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352. (b) Lipshutz, B. H.; Shimizu, H. *Angew. Chem., Int. Ed. Eng.* **2004**, *43*, 2228. (c) Lipshutz, B. H.; Servesko, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4789. (d) Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4793. (e) Lipshutz, B. H.; Caires, C. C.; Kuipers, P.; Chrisman, W. *Org. Lett.* **2003**, *5*, 3085.

(6) (a) Barder, T.E.; Walker, S.D.; Martinelli, J.R.; Buchwald, S.L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. (b) Milne, J.E.; Buchwald, S.L. *J. Am. Chem. Soc.* **2004**, *126*, 13028. (c) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed. Eng.* **2004**, *43*, 1871.

(7) (a) Alam, A.; Takaguchi, Y.; Ito, H.; Yoshida, T.; Tsuboi, S. *Tetrahedron*, **2005**, *61*, 1909. (b) Keseru, G. M.; Nogradi, M. Kajtar-Peredy, M. *Liebigs Ann. Chem.* **1994,** 361. (c) Chang, J.; Guo, X.; Cheng, S.; Guo, R.; Chen, R.; Zhao, K. *Biorg. Med. Chem. Lett.* **2004**, *14*, 2131. (d) Chang, J.; Chen, R.; Guo, R.; Dong, C.; Zhao, K. *Helv. Chim. Acta.* **2003**, *86*, 2239.

(8) Employing a technique that had previously been found to aid reactions at low catalyst loadings (NMP added as co-solvent) also lead to incomplete conversion of the aryl bromide as well as to production of side products (including homocoupling of the aryl zinc reagent).

(9) Williams, J.M.; Jobson, R.B.; Yasuda, N.; Marchesini, G.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.

(10) (a) Leblanc, Y.; Roy, P.; Wang, Z.; Li, C. S.; Chauret, N.; Nicoll-Griffith, D. A.; Silva, J. M.; Aubin, Y.; Yergey, J. A.; Chan, C. C.; Riendeau, D.; Brideau, C.; Gordon, R.; Xu, L.; Webb, J.; Visco, D. M.; Prasit, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3317. (b) Simpson, A. F.; Szeto, P.; Lathbury, D. C.; Gallagher, T. *Tetrahedron: Asymmetry* **1997**, *8*, 673.

(11) (a) Haack, K. J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Eng.* **1997**, *36*, 285. (b) Hashiguchi, S.; Fujii, A.; Haack, K. J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Eng.* **1997**, *36*, 288.

(12) Ogata, M,; Matsumoto, H.; Takahashi, K.; Shimizu, S.; Kida, S.; Murabayashi, A.; Shiro, M.; Tawara, K. *J. Med. Chem.* **1987**, *30*, 1054.

(13) Bagdanoff, J. T.; Ferreira, E. M.; Stoltz, B. M. *Org. Lett.* **2003**, *5*, 835.

(14) Sapountzis, I.; Dohle, W.; Knochel, P. *Chem. Commun.* **2001**, 2068.

(15) Piers, E.; Wong, T.; Coish, P. D.; Rogers, C. *Can. J. Chem.* **1994**, *72*, 1816.

(16) (a) Pellissier, H. *Tetrahedron*, **2003**, *59*, 8291. (b) Ward, R.S. *Tetrahedron: Asymmetry*, **1995**, *6*, 1475. (c) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134.

(17) (a) Pai, C. –C.; Li, Y. –M.; Zhou, Z. –Y.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 2789. (b) de Paule, S. D.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genêt, J. –P.; Champion, N.; Dellis, P. *Tetrahedron Lett.* **2003**, *44*, 823. (c) SYNPHOS was purchased from Strem Chemicals, Inc.

(18) Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. *Chem. Rev.* **2005**, **ASAP**.

(19) (a) Pangborn, A.B.; Giardello, M.A.; Grubbs, R.H.; Rosen, R.K.; Timmers, F.J. *Organometallics* **1996**, *15*, 1518. (b) Alaimo, P.J.; Peters, D.W.; Arnold, J.; Bergman, R.G. *J. Chem. Ed.* **2001**, *78*, 64.

Curriculum Vitae
Matthew P. Rainka

Education

Ph.D. in Organic Chemistry. *Massachusetts Institute of Technology* June 2005
Research Advisor: Prof. Stephen L. Buchwald.
Research Project: "Development of Transition-Metal Mediated Processes in Organic Chemistry".

B.S. in Chemistry. *University of Rochester.* May 2000

Professional Experience

Graduate Research with Prof. Stephen L. Buchwald. 2000-present
Massachusetts Institute of Technology.

Undergraduate Research with Prof. Robert K. Boeckman, Jr. 1999-2000
University of Rochester.

Undergraduate Research with R. Jason Herr, Ph.D. Summers of 1998 and 2000
Albany Molecular Research, Inc.

Teaching Assistant
Massachusetts Institute of Technology. 2000-2001
University of Rochester. 1998-2000

Affiliations

American Chemical Society, Member.

Awards

Bausch & Lomb / Xerox Metal. 1996-2000

Publications

"Copper-Catalyzed Asymmetric Conjugate Reduction as a Route to Novel β-Azaheterocyclic Acid Derivatives." Rainka, M. P.; Aye, Y.; Buchwald, S. L. *Proc. Natl. Acad. Sci., USA,* **2004,** *101,* 5821.

"An Annulative Approach to Highly Substituted Indoles: Unusual Effect of Phenolic Additives on the Success of the Arylation of Ketone Enolates." Rutherford, J. L.; Rainka, M. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002,** *124,* 15168.

"A Highly Active Suzuki Catalyst for the Synthesis of Sterically Hindered Biaryls: Novel Ligand Coordination." Yin, J.; Rainka, M. P.; Zhang, X. –X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002,** *124,* 1162.