AN ABSTRACT FOR THE THESIS OF

Jason S. Lusk for the degree of Honors Baccalaureate of Science in Chemistry presented on June 1, 2010. Title: Studies Toward the Synthesis of Natural Product Scaffolds.

Abstract approved:

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Rich G. Carter

Part 1: A Diels-Alder Approach to the Synthesis of Novel Analogues of the Natural Product Siamenol

Due to the prevalence of biaryl motifs in natural product synthesis, the Carter research group has been exploring the utility of a Diels-Alder approach to biaryl synthesis. The Diels-Alder approach involves a [4+2] cycloaddition between an acetylene dienophile and a cyclohexadiene, followed by subsequent [4+2] cycloreversion. This method of biaryl synthesis introduces numerous advantages compared to the traditional metal-mediated biaryl synthesis procedures, including a lack of environmentally hazardous transition metals.

The Diels-Alder approach has been used by the Carter group to synthesize the natural product siamenol. This carbazole alkaloid, isolated from the *Murraya siamensis* shrub, has been found to possess moderate activity in the inhibition of the human immunodeficiency virus (HIV). Previously, synthesis of siamenol had been based on the traditional metal-mediated cross-coupling approach. Based on this initial synthesis, a series of novel analogues of siamenol have been synthesized using the Diels-Alder approach to biaryl synthesis. This project focuses on the synthesis of four such analogues of siamenol.

Key Words: Diels-Alder reaction, siamenol, HIV inhibitors

Part 2: Advances in Proline-Based Enantioselective Organocatalysis and its Application to a Novel Synthesis of the Natural Product Aconitine

Organocatalysis, while not a novel concept, has made significant strides in the last decade with the advent of improved methods of enantioselective organocatalysis. Particular advances have been made in the use of proline-based organocatalysts in catalyzing such reactions as aldol, Mannich and Michael reactions in a highly enantioselective fashion. The Carter Group has utilized Hua Cat, a proline-based sulfonamide, to catalyze a series of [2.2.2] bicyclizations based on a Mannich reaction-related mechanism. This approach has been utilized to form a precursor to the natural product aconitine, a known analgesic and antipyretic. The key [2.2.2] bicyclization step proceeded in a high-concentration (1.0 M), room temperature reaction that produced the target [2.2.2] octane with a 57% yield and 99% e.e. Further considerations toward the synthesis of aconitine are also discussed.

Key Words: organocatalysis, asymmetric, proline, aconitine,

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Studies Toward the Synthesis of Natural Product Scaffolds

by

Jason S. Lusk

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I understand that my thesis will become part of the permanent collection of Oregon State University, University Honors College and Department of Chemistry. My signature below authorizes release of my project to any reader upon request.

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Jason S. Lusk, Author

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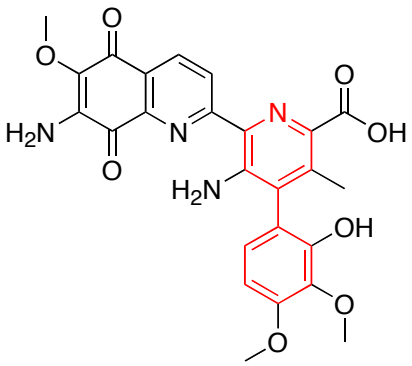
This thesis is dedicated to my wonderful parents, Scott and Debbie Lusk. Thank you for your continuous love and support.

PART 1: A DIELS-ALDER APPROACH TO THE SYNTHESIS OF NOVEL ANALOGUES OF THE NATURAL PRODUCT SIAMENOL

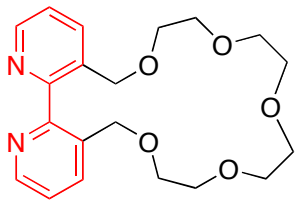
Introduction

History of Biaryl Synthesis

Biaryl compounds are ubiquitous throughout chemistry. Organic chemists commonly find biaryl motifs in natural products, such as the antitumor compound streptonigrin (**1**).[1] There has also been a great deal of interest in biaryl motifs as ligands in transition metal chemistry; for example, the biaryl ligand BINAP is used to catalyze a wide range of reactions in an asymmetric fashion.[2] More recently, biaryls have been incorporated into molecular motors and switches. For example, ditopic receptor **2** functions in an allosteric fashion, as coordination of metal ions to the bipyridine system alters the ability of the crown ether system to bind potassium ions.[3]



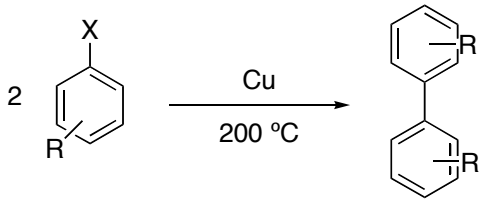
streptonigrin
(**1**)



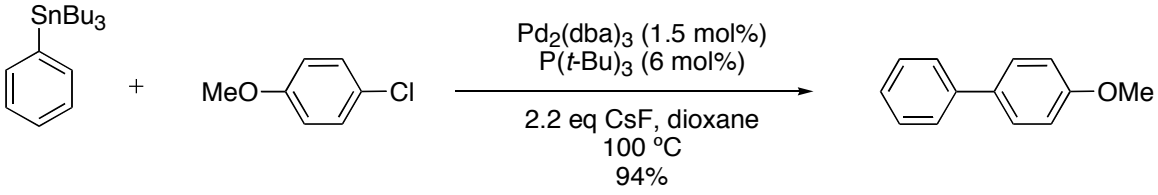
allosteric ditopic receptor
(**2**)

Figure 1: Natural product streptonigrin (1) and a ditopic receptor acting as a molecular switch (2)

Most commonly, C-C bond formation between aryl rings is achieved via metal-mediated cross-coupling. One common method for synthesizing biaryl compounds involves homocoupling reactions, in which two molecules of an aryl halide or aryl organometal compound are joined with the aid of a transition metal, such as copper (Ullman coupling, Scheme 1).[4] In another common form of biaryl cross-coupling, an aryl halide and an aryl organometallic (often an organotin or organoboron compound) combine to form a biaryl product in a reaction that is catalyzed by a transition metal complex, usually palladium or rhodium (ex. Stille coupling, Scheme 2).[4]



Scheme 1: Example of a copper-mediated biaryl homocoupling (Ullman coupling)



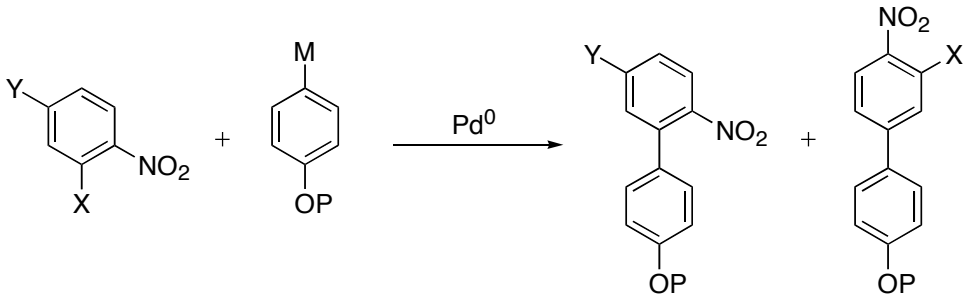
Scheme 2: Example of a biaryl cross-coupling between an aryl halide and a tin-containing aryl ring (Stille coupling)

Biaryls via the Diels-Alder Reaction

While metal-mediated cross-couplings are an indispensable tool for synthetic chemistry, there are drawbacks to their use. Often, it can be difficult to acquire the starting materials needed to produce certain biaryl compounds. The

synthesis of highly congested tri- and tetra-ortho substituted biaryls, which have shown promise as ligands in palladium chemistry, can prove challenging.[5]

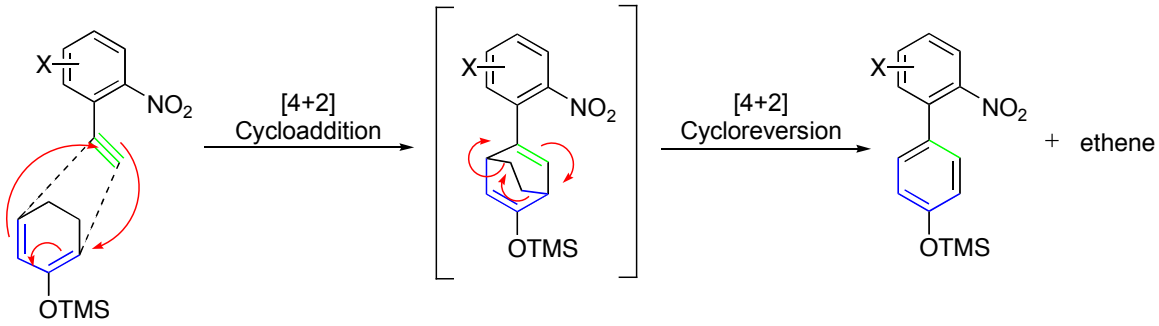
The most prominent drawback to metal-catalyzed biaryl formation in this project is a matter of orthogonality. In a later step, a Suzuki cross-coupling reaction is employed to add a methyl substituent. In order to achieve this, the starting material used contains a chloro group at the site of methylation. If a cross-coupling mechanism were to be used for the biaryl-forming step, a dihalogenated starting material would be required. As a result, a variety of unwanted side-products would be formed in addition to the desired product, with no mechanism for selectivity.



Scheme 3: In metal cross-coupling reactions where the target product is halogenated, orthogonality becomes an issue

The Diels-Alder approach to biaryl formation largely avoids this dilemma. In the Diels-Alder pathway, an acetylene acts as the dienophile, reacting with a cyclohexadiene to form a [2.2.2] bicyclic intermediate. When exposed to heat, this intermediate undergoes a [4+2] cycloreversion, liberating ethene and forming the desired aryl ring. No hazardous and expensive transition metals are used in this synthetic pathway, and orthogonality is maintained. In addition, it has been

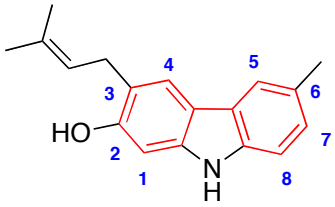
demonstrated that the Diels-Alder approach allows for the synthesis of highly-congested tri- and tetra-ortho substituted biaryls. [5]



Mechanism 1: Diels-Alder biaryl formation

Synthesis of Siamenol Analogs

Siamenol (**3**) is of a class of natural products known as alkaloids, naturally-occurring compounds containing basic nitrogen atoms. The compound was first isolated from the shrub *Murraya siamensis* in southeast Asia, along with the known compounds mahanimbilol and mahanimbine.[6] The three alkaloids were tested against the human immunodeficiency virus (HIV) in a XTT-tetrazolium assay. From this experiment, it was found that siamenol exhibited moderate anti-HIV activity, producing an EC_{50} of 2.6 μg/mL (the value for EC_{50} is the concentration of compound that produces 50% protection from the virus).[7] Due to its potential as an HIV medication, there has been an interest in a total synthetic pathway for siamenol.



Siamenol
(**3**)

Figure 2: Siamenol, (3) showing standard carbazole ring-numbering system

The synthesis of siamenol has been achieved by employing palladium catalysis at two key steps in the synthetic pathway.[8] The Carter group has since synthesized siamenol using the Diels-Alder approach to biaryls.[9] The purpose of this research project is to develop a synthetic pathway for four novel analogues of siamenol (**4**-**7**). The analogues differ from siamenol at the C_1, C_3, C_6 and C_8 of the carbazole moiety. The prenyl group at C_3 in siamenol is replaced by an allyl group at either C_3 (**4** and **6**) or C_1 (**5** and **7**). The methyl substituent at C_6 in siamenol is absent, while C_8 contains either a chloro group (**4** and **5**) or a methyl group (**6** and **7**). Eventually, these analogues are to undergo biological evaluation to determine their effectiveness at suppressing HIV (though this is beyond the scope of the current project).

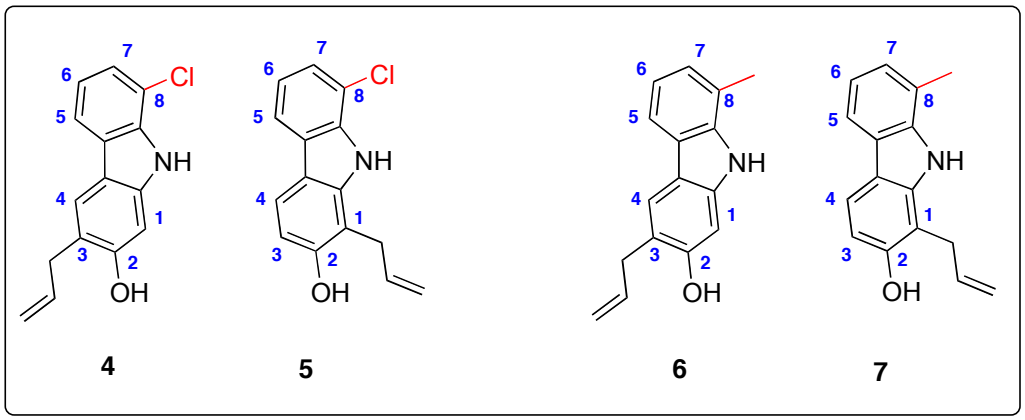
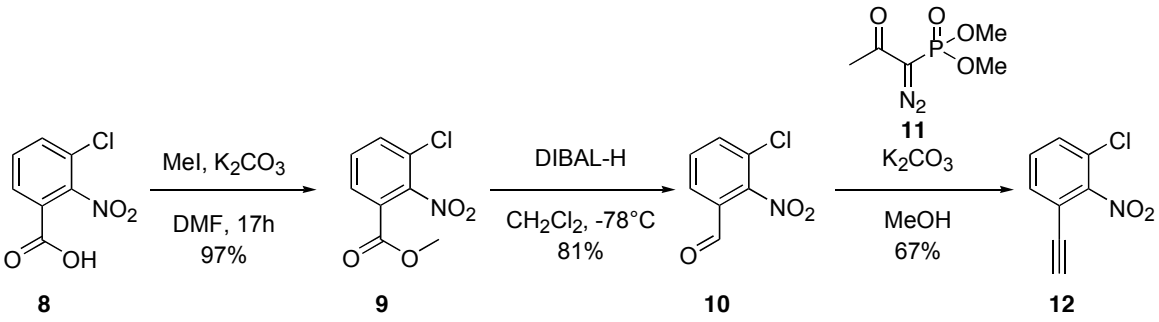


Figure 3: Target siamenol analogues 4-7

Results and Discussion

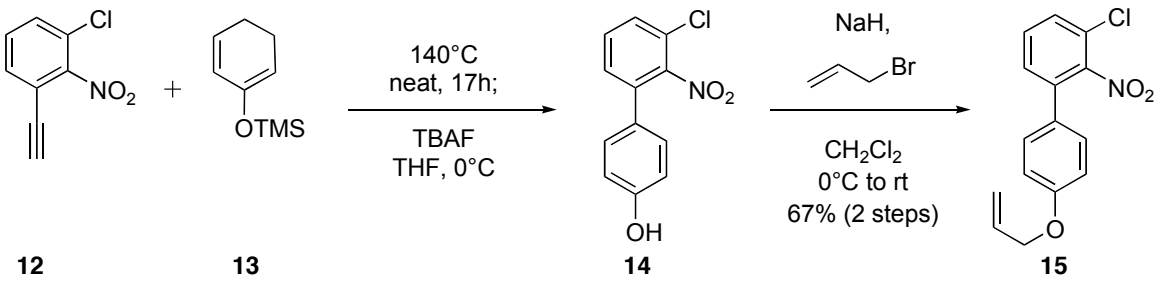
Synthesis of Acetylene Starting Material



Scheme 4: Preparation of acetylene starting material 12

The synthetic pathway began with the straightforward formation of acetylene dienophile **12**. Commercially available benzoic acid **8** was treated with methyl iodide and potassium carbonate to form the corresponding methyl ester **9**. The ester was then reduced to an aldehyde **10** using DIBAL-H. Acetylene **12** was formed by reacting **10** with Ohira-Bestmann reagent[10] (**11**) in the presence of potassium carbonate and methanol. Each of these reactions proceeded with little difficulty, producing product in at least 67% yield.

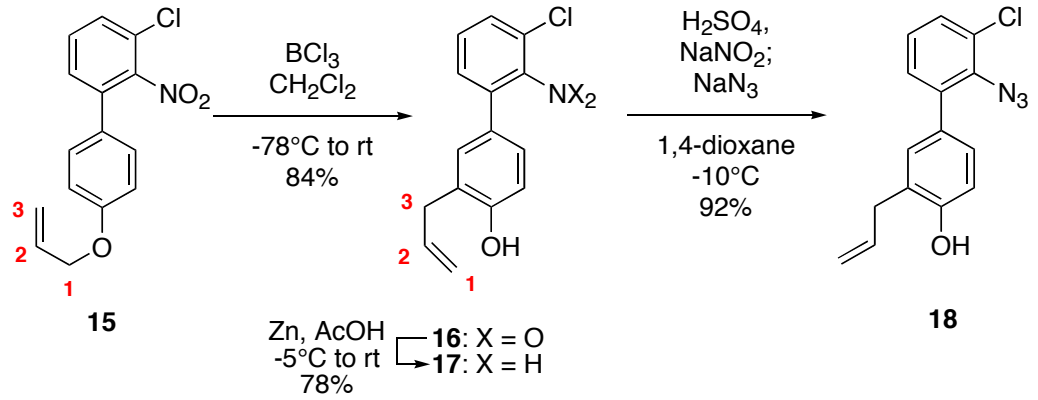
Diels-Alder Biaryl Formation and Allylation



Scheme 5: Reaction scheme depicting the Diels-Alder biaryl formation and subsequent allylation

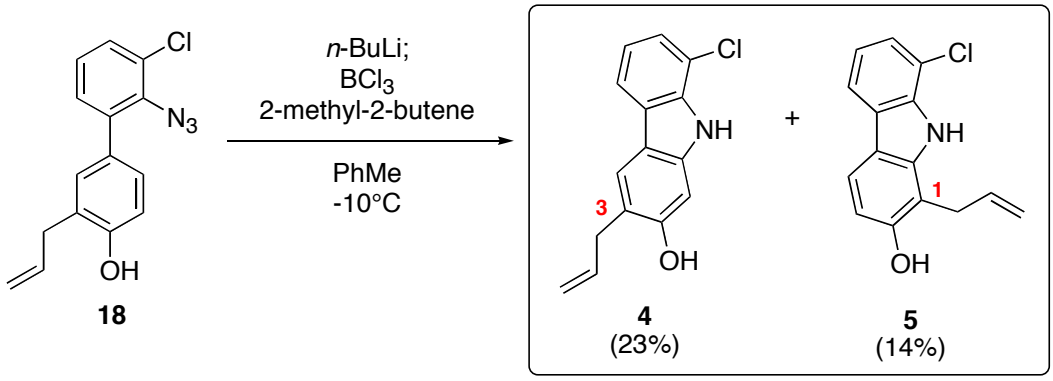
The Diels-Alder, biaryl-forming step involved the reaction of acetylene **12** with diene **13**. The reaction was run without solvent (neat), warmed to 140 °C in a pressure vessel to prevent the loss of diene. It was found to be convenient to eschew purification of **14**; the crude phenol was allylated with allyl bromide, forming ether **15**. The Diels-Alder biaryl formation step was thus deemed an effective method for forming the halogenated biaryl motif, with a combined two-step yield of 67%.

Synthesis of Chloro Analogues



Scheme 6: Claisen rearrangement to azide 18 synthesis

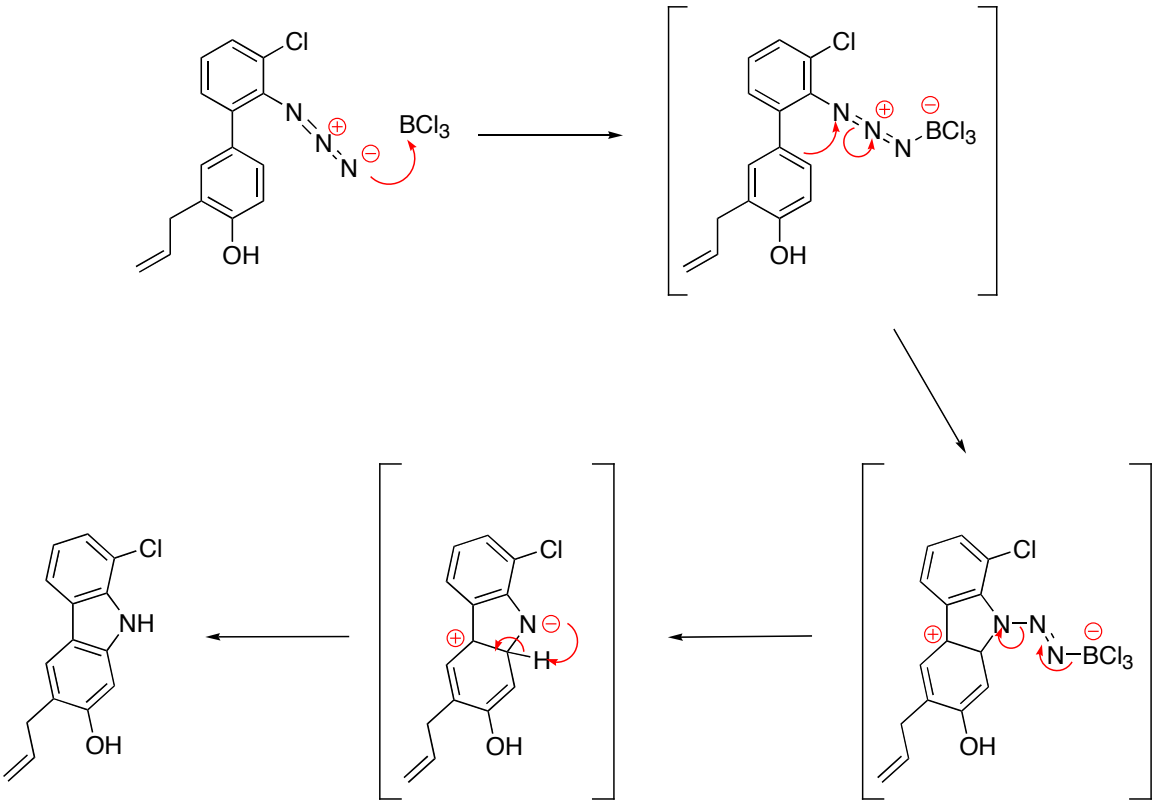
Allyl ether **15** underwent a Claisen rearrangement with BCl_3, thereby placing the allyl group ortho to the resulting phenol **16**. Starting at allyl phenol **16**, two separate methods were attempted to form the final carbazole compound. The first method involved a Cadogan cyclization with tributylphosphine, which would have led to formation of the key C-N bond. This pathway was attempted first due to the fewer steps involved (two steps between the Claisen rearrangement and the final product, as opposed to three). Unfortunately, the reaction did not progress as planned, yielding only starting material.



Scheme 7: Electrophilic aromatic substitution forming analogues 4 and 5

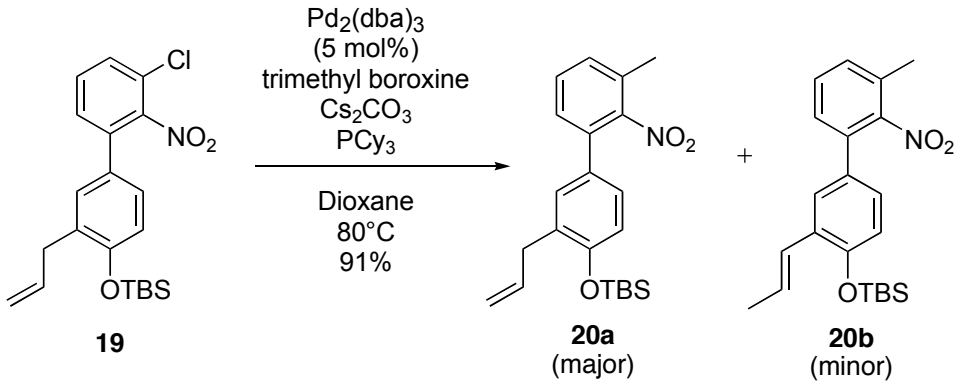
The second pathway attempted involved C-N bond formation via electrophilic aromatic substitution by an azide (M echanism 2). The nitro group was first converted to an amino group using zinc and acetic acid. The resulting aniline was converted to an azide using $NaNO_2$ and sulfuric acid, followed by sodium azide. In the aromatic substitution step, the azide was treated with BCl_3 and 2-methyl-2-butene (as a sacrificial olefin). The Lewis acidic BCl_3 attacks the

azide, causing the azide to develop a partial positive charge. This positive polarity causes an electrophilic attack by π electrons in the lower aryl ring, leading to the formation of the C-N bond. The nitrogen atom then absorbs a proton from the aryl ring, thereby restoring aromaticity. This cyclization pathway was successful, yielding target chloro analogs **4** and **5**, in a roughly 1.7:1 ratio (respectively).



Mechanism 2: Electrophilic aromatic substitution by azide

Synthesis of Methyl Analogues



Scheme 8: Pd-catalyzed Suzuki cross-coupling

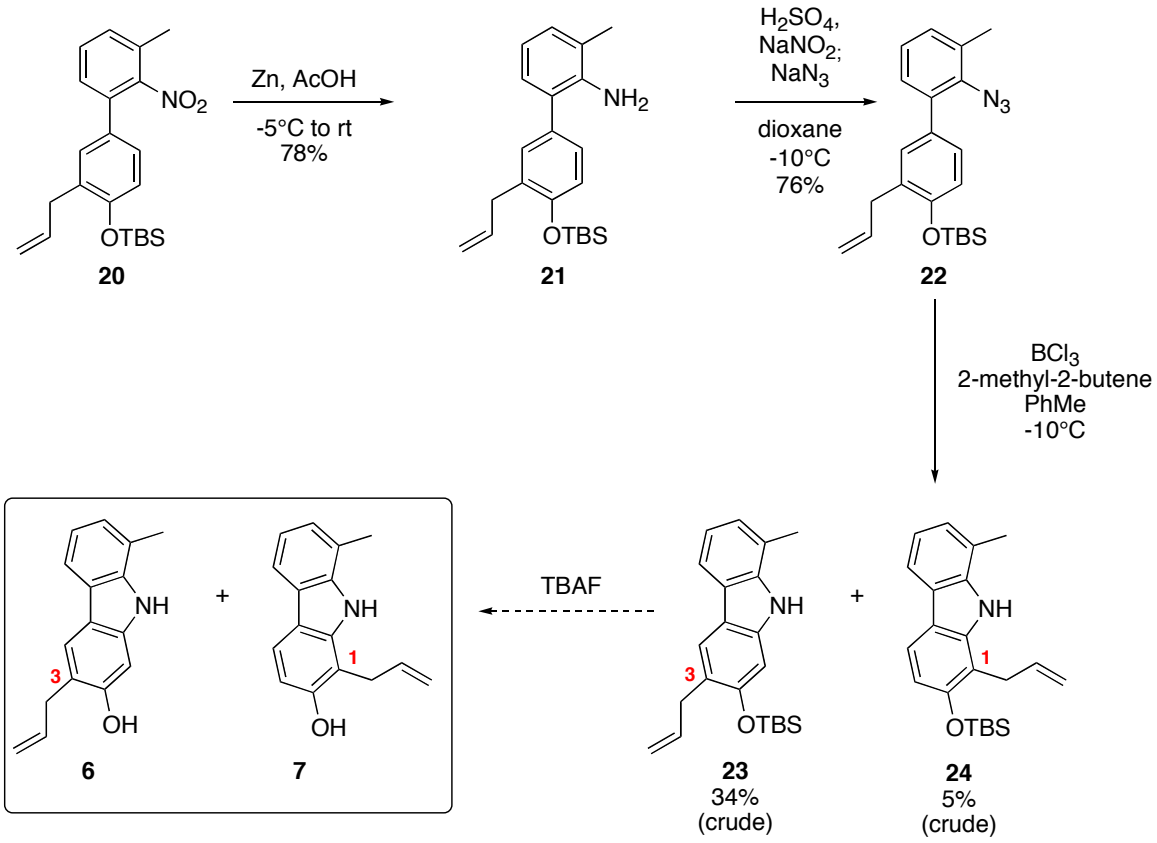
Synthesis of methyl analogues **6** and **7** began with allyl phenol **16** as a starting point. Here, a Suzuki coupling was employed to replace the chloro substituent with a methyl group. A Suzuki reaction involves the cross-coupling of an organoboron reagent with an organohalide, catalyzed by palladium. [11]

After protection of the phenol as TBS ether **19**, the Suzuki reaction was initially attempted using the palladium catalyst PEPPSI.[12] Trimethylboroxine,[13] which the Carter group has found to be a very successful reagent for methyl additions, was used as the methyl donor for this reaction. PEPPSI was unsuccessful at catalyzing the desired reaction, leading to decomposition of starting material.

Next, palladium dibenzylideneacetone $Pd_2(dba)_3$ was tried as a catalyst. Fortunately, the cross-coupling turned out to be successful, producing the methyl product **20a** with an impressive 91% yield. Upon examination of the HNMR for compound **20** it became apparent that the allyl group had interacted with the palladium catalyst, causing a small amount of the alkene to undergo

isomerization into conjugation, forming isomer **20b**. This isomer persisted through the azide formation step, at which point it was no longer discernible via HNMR.

The synthesis toward analogues **6** and **7** proceeded along the same synthetic pathway as analogues **4** and **5**. Compound **20** was converted to aniline **21**, from which was formed azide **22**. It was decided that the phenol would remain protected as a silyl ether, as this would eliminate the need for a protecting

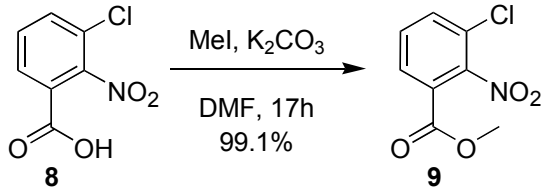


Scheme 9: Formation of methyl analogues 6 and 7

base. Azide **22** was reacted with BCl_3, forming silyl ether-protected carbazoles **23** and **24**; these may later be de-protected using TBAF to form analogues **6** and **7**. It is important to note here that while analogues **4** and **5** were synthesized in

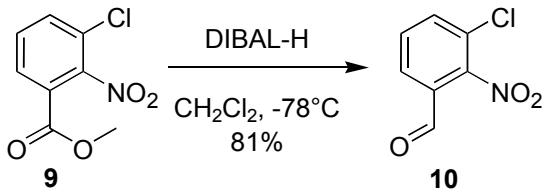
approximately a 2:1 ratio, compounds **23** and **24** formed in a nearly 7:1 ratio. This dramatic difference was most likely caused by a combination of electronic and steric factors resulting from the presence of a methyl group, as opposed to a chloro group. It is also possible that the presence of a silyl ether in place of the phenol may have contributed to the steric effects resulting in isomeric selectivity. Future studies may involve carrying out the aromatic substitution step with the unprotected alcohol.

Experimental



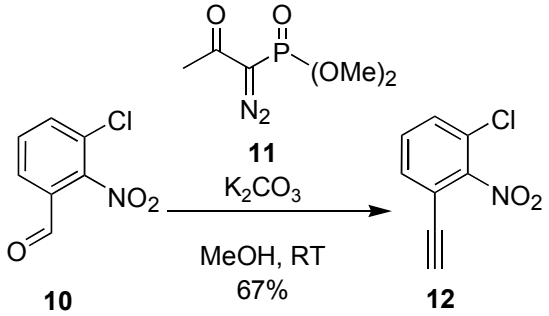
8 **9**

Methyl Ester 9: To a stirred solution of **8** (1.56 g, 7.75 mmol) and K_2CO_3 (3.05 g, 22.1 mmol) in DMF (7.8 mL) was added MeI (2.12 g, 0.93 mL, 14.9 mmol) dropwise via syringe. After 17 h, the reaction was quenched with H_2O (10 mL) and diluted with EtOAc (30 mL). The organic layer was washed with H_2O (20 mL) and sat. aq. NaCl (2 x 20 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* to yield **8** (1.66 g, 7.68 mmol, 99%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 1.1, 7.9 Hz, 1H), 7.74 (dd, *J* = 1.1, 8.1, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 3.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 134.7, 130.7, 129.7, 126.3, 124.4, 53.4.



9 **10**

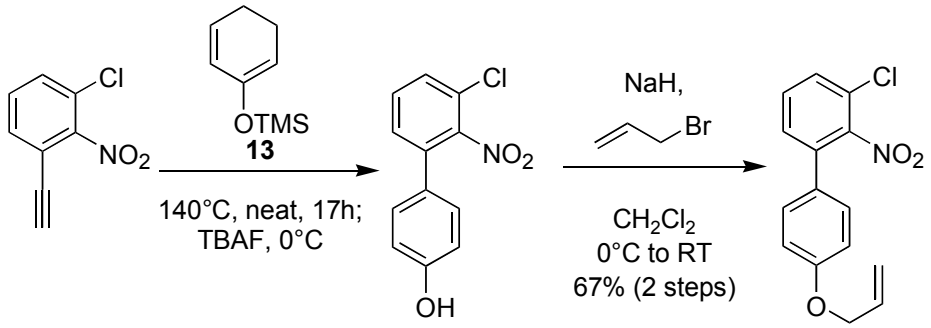
Aldehyde 10: To a stirred solution of **9** (569 mg, 2.64 mmol) in CH_2Cl_2 (26 mL) at -78˚C was added DIBAL-H (3.2 mL, 3.2 mmol, 1.0 M in CH_2Cl_2) dropwise via syringe. After 40 min, the reaction was quenched with MeOH (5 mL). Next, aq. sodium potassium tartrate (30 mL, 10% w/w) was added to the solution. After 4 h, the solution was diluted with CH_2Cl_2 (15 mL). The aqueous layer was extracted with CH_2Cl_2 (15 mL). The organic layer was washed with H-$_2$O (2 x 15 mL) and sat. aq. NaCl (60 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified via flash chromatography over silica gel, eluting with PhMe, to give **10** (430 mg, 2.32 mmol, 88%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.91 (dd, *J* = 1.4, 7.7 Hz, 1H), 7.81 (dd, *J* = 1.4, 8.1 Hz, 1H), 7.67 (dd, *J* = 7.7, 8.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.7, 148.6, 136.0, 131.6, 129.6, 128.6, 126.6.



10 **12**

Acetylene 12: To a stirred solution of **10** (724 mg, 3.90 mmol) in MeOH (40 mL) was added K_2CO_3 (1.09 g, 7.91 mmol). After 10 min, **11** (1.14 g, 5.96

mmol) was added slowly via syringe. After 50 min, the reaction was quenched with sat. aq. $NaHCO_3$ (40 mL). MeOH was removed *in vacuo*, and the solution was diluted with H_2O and EtOAc. The organic layer was washed with H_2O (2 x 20 mL), and combined aqueous layers were extracted with EtOAc (3 x 35 mL). The combined organic layers were washed with sat. aq. NaCl (2 x 20 mL). The dried extract ($MgSO_4$) was concentrated *in vacuo* and purified via flash chromatography over silica gel, eluting with PhMe to give **12** (481 mg, 2.65 mmol, 68%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56-7.51 (m, 2H), 7.42 (dd, J = 8.1, 7.7 Hz, 1H), 3.39 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 131.9, 131.0, 130.7, 125.4, 117.1, 85.0, 75.7.

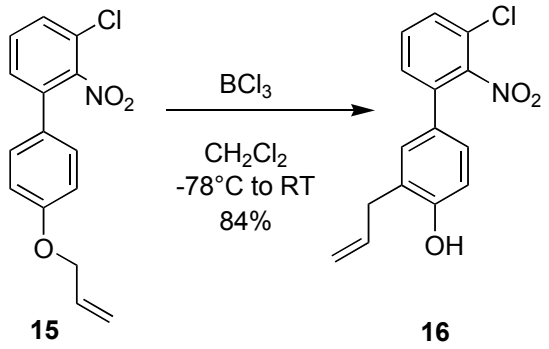


Biaryl Phenol 14: To a pressure vessel containing **12** (743 mg, 4.09 mmol) was added **13**[14] (2.57 g, 12.7 mmol) via syringe. The solution was immediately heated to 135˚C. After 14 h, the reaction was cooled to 0˚C and TBAF (12.2 mL, 12.2 mmol, 1.0 M in THF) was added via syringe. After 30 min, the reaction was quenched with sat. aq. NH_4Cl (50 mL) and diluted with EtOAc

(100 mL). The organic layer was washed with H_2O (50 mL), and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with sat. aq. NaCl (2 x 50 mL). The dried extract (Na_2SO_4) was concentrated *in vacuo* and purified via flash chromatography over silica gel, eluting with 15-50% EtOAc/PhMe, to give impure **14** (1.36 g).

Allyl Ether 15: To a stirred solution of **14** (1.36 g) in DMF (28 mL) at 0˚C was added NaH (280 mg, 6.80 mmol, 60% in mineral oil). After 25 min, allyl bromide (1.39 g, 11.5 mmol) was added slowly via syringe. After 30 min, the reaction was warmed to rt. After 30 min, the reaction was quenched with sat. aq. NH_4Cl (20 mL) and diluted with EtOAc (30 mL) and H_2O (20 mL). The organic layer was washed with H_2O (2 x 20mL), and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with sat. aq. NaCl (50 mL). The dried extract (Na_2SO_4) was concentrated *in vacuo* and purified by flash chromatography over silica gel, eluting with toluene, to give **15** (1.00 g, 3.48 mmol, 85% over two steps) as a yellow solid. MP 83-85˚C; IR (neat) 3077, 2924, 2887, 2871, 1608, 1517, 1456, 1425, 1371, 1249, 1181, 1019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.44 (m, 2H) 7.36 (dd, *J* = 2.1, 6.9 Hz, 1H), 7.30 (d, *J* = 8.7, 2H), 6.98 (d, *J* = 8.68 Hz, 2H), 6.09 (ddt, *J* = 5.3, 10.5, 15.9 Hz, 1H), 5.46 (dd, *J* = 1.28, 17.48 Hz, 1H), 5.34 (dd, *J* = 1.0, 10.5 Hz, 1H), 4.59 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 149.0, 135.8, 132.9,

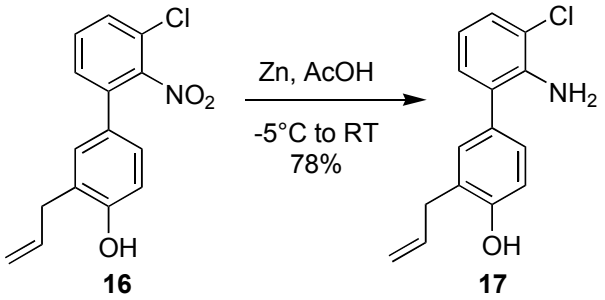
130.6, 129.5, 129.3, 128.9, 127.7, 125.2, 118.0, 115.2, 68.9; HRMS (EI+) calcd. for $C_{15}H_{12}NO_3Cl$ (M+H) 289.0500, found 289.0506.



15 **16**

Allyl Phenol 16: To a stirred solution of **15** (836 mg, 2.89 mmol) in CH_2Cl_2 (30 mL) at -78˚C was added BCl_3 (6.0 mL, 6.0 mmol, 1.0 M in heptanes) dropwise via syringe. After 15 min, the reaction was warmed to 0˚C. After 15 min, the solution was warmed to rt. After 10 min, the reaction was quenched with MeOH (3.0 mL) and diluted with CH_2Cl_2 (30 mL). The solution was washed with H_2O (2 x 15 mL) and sat. aq. NaCl (2 x 15 mL). The dried extract (Na_2SO_4 and $MgSO_4$) was concentrated *in vacuo* and purified via flash chromatography over silica gel, eluting with 10-40% EtOAc/hexanes, to give **16** (703 mg, 2.43 mmol, 84%) as a yellow solid. MP 108-109˚C; IR (neat) 3509, 3077, 2887, 1609, 1536, 1508, 1460, 1369, 1271, 1199, 1117, 1057, 915, 791 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.44 (m, 2H), 7.36 (dd, *J* = 2.1, 6.9 Hz, 1H), 7.16-7.14 (m, 2H), 6.86 (d, *J* = 8.8 Hz, 1H), 6.04 (m, 1H), 5.23 (s, 1H), 5.20 (dd, *J* = 1.2 Hz, 1H), 5.18 (d, *J* = 1.4 Hz, 1H), 3.45 (d, *J* = 6.4, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

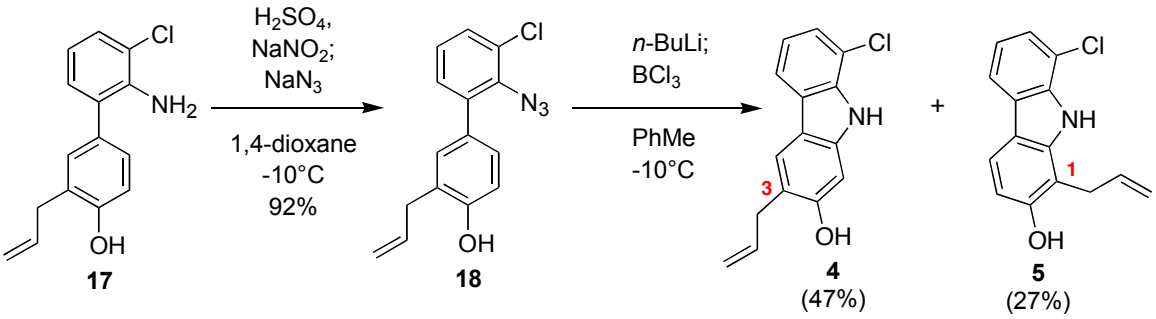
154.9, 149.0, 135.9, 135.7, 130.6, 130.2, 129.5, 128.9, 128.0, 127.6, 126.1, 125.2, 117.1, 116.3, 34.9; HRMS (EI+) calcd. for $C_{15}H_{12}NO_3Cl$ 289.0516, found 289.0506.



16 **17**

Aniline 17: To stirred solution of **16** (200 mg, 0.693 mmol) and glacial AcOH (3.5 mL) cooled to -5˚C was added Zn (459 mg, 7.02 mmol). After 15 min, the reaction was warmed to rt. After 7 h, the reaction was diluted with EtOAc (20 mL) and quenched w/ sat. aq. $NaHCO_3$ until bubbling ceased. The aqueous layer was extracted with EtOAc (20 mL), and the combined organic layers were washed with sat. aq. NaCl (20 mL). The dried solution (Na_2SO_4) was concentrated *in vacuo* and purified via flash chromatography over silica gel, eluting with 10-30% EtOAc/hexanes to give **17** (140 mg, 0.541 mmol, 78%) as a white solid. MP 87-89˚C; IR (neat) 3378, 3296, 3163, 3078, 2745, 1607, 1508, 1452, 1420, 1265, 1240, 1126, 1097, 908, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.23 (m, 3H), 7.02 (dd, *J* = 1.7, 10.0 Hz, 1H), 6.90 (dd, *J* = 3.4, 8.1, 1H), 6.75 (t, *J* = 10.3 Hz, 1H), 6.06 (ddt, *J* = 6.3, 9.9, 16.5 Hz, 1H), 5.26-5.15 (m, 3H), 4.17 (s, 2H), 3.47 (d, *J* = 8.48 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 140.5, 136.1, 131.4, 131.1, 128.8, 128.6, 128.4, 128.2, 126.0, 119.6, 118.4,

116.9, 116.3, 35.2; HRMS (EI+) calcd. for $C_{15}H_{14}NOCl$ 259.0766, found 259.0764.



Azide 18: To a stirred solution of **17** (49.4 mg, 0.191 mmol) in 1,4-dioxane (1.0 mL) at -10˚C was added H_2SO_4 (1.9 mL, 3.8 mmol, 2.0 M in H_2O). After 5 min, $NaNO_2$ (0.13 mL, 0.39 mmol, 3.0 M in H_2O) was added via syringe. After 30 min, NaN_3 (0.19 mL, 0.57 mmol, 3.0 M in H_2O) was added via syringe. After 30 min, the reaction was warmed to rt and diluted with Et_2O (10 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (5 mL). The aqueous layer was extracted with Et_2O (5 mL), and combined organic layers were washed with sat. aq. $NaHCO_3$ (2 x 5 mL). Dried extract (Na_2SO_4) was concentrated *in vacuo* to give **18** (50.1 mg, 0.176 mmol, 92%) as a white/brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (dd, J = 2.0, 7.6 Hz, 1H), 7.25-7.12 (m, 4H), 6.92 (d, J = 8.1 Hz, 1H), 6.07 (ddt, J = 6.3, 10.4, 16.8 Hz, 1H), 5.25-5.19 (m, 2H), 5.11 (s, 1H), 3.49 (d, J = 6.3 Hz, 2H).

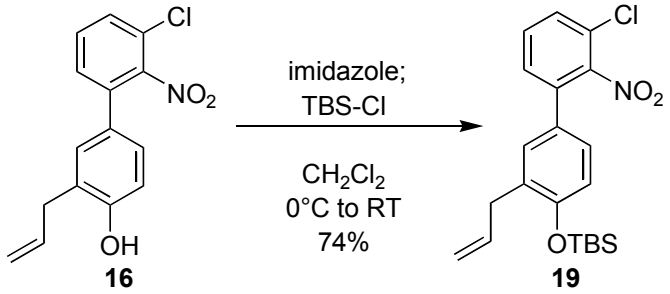
Carbazoles 4 and 5: To a stirred solution of **18** (264 mg, 0.926 mmol) in PhMe (9.5 mL) at -10˚C was added *n*-BuLi (0.64 mL, 1.0 mmol, 1.6 M in hexanes). After 20 min, BCl_3 (2.8 mL, 2.8 mmol, 1.0 M in heptane) was added

slowly via syringe. After 125 min, reaction was quenched with MeOH (10 mL) and diluted with CH_2Cl_2 (50 mL). Solution was washed with sat. aq. NH_4Cl (1 x 40 mL, 1 x 20 mL), and H_2O (30 mL). Aqueous layers were extracted with CH_2Cl_2 (25 mL) and combined organic layers were washed with sat. aq. NaCl (30 mL). Dried extract (Na_2SO_4) was concentrated *in vacuo* and purified via flash chromatography over silica gel, eluting with 0-23%EtOAc/25%CH_2Cl_2/hexanes to give **4** and **5.**

3-allyl carbazole 4: Product was purified via flash chromatography over silica gel, eluting with PhMe. Product was further purified via recrystallization in Et_2O/hexanes, to give **4** (55.6 mg, 0.216 mmol, 47%) as a white solid. MP 142-144˚C; IR (neat) 3413, 3078, 3015, 2992, 1640, 1614, 1584, 1427, 1388, 1344, 1279, 1220, 1138, 1010 cm^{-1}; ^1H NMR (300 MHz, $(CD_3)_2CO$) δ 10.29 (s, 1H), 8.70 (s, 1H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.81 (s, 1H), 7.30 (dd, *J* = 0.9, 7.8 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 7.10 (s, 1H), 6.12 (ddt, *J* = 6.6, 10.1, 23.6 Hz, 1H), 5.11 (dd, *J* = 17.1, 2.1 Hz, 1H)), 5.02 (dd, *J* = 10.0, 2.2 Hz, 1H)), 3.53 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 155.0, 140.4, 137.9, 136.8, 125.5, 123.0, 121.2, 120.4, 119.6, 119.6, 116.2, 115.2, 114.3, 96.9, 34.5; HRMS (EI+) calcd. for $C_{15}H_{12}NOCl$ 257.0606, found 257.0607.

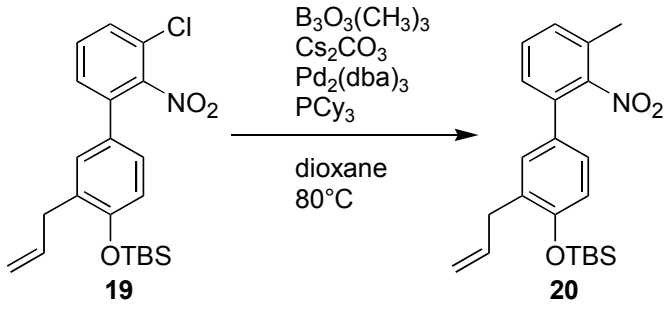
1-allyl carbazole 5: Product was purified via flash chromatography over silica gel, eluting with 0-75% CH_2Cl_2/PhMe. Product was further purified via recrystallization in Et_2O/Hex, to give **5** (32.0 mg, 0.125 mmol, 27 %) as a yellow

solid. MP 137-139˚C; IR (neat) 3428, 3283, 3070, 2965, 1610, 1488, 1433, 1368, 1289, 1209, 1162, 989 cm^{-1}; ^1H NMR (300 MHz, $(CD_3)_2CO$) δ 9.97 (s, 1H), 8.45 (s, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.31 (dd, *J* = 0.9, 7.8 Hz, 1H), 7.13 (t, J = 7.8, 1H), 6.90 (d, *J* = 8.4 Hz, lH), 6.09 (ddt, *J* = 6.0, 10.1, 17.1 Hz, 1H), 5.13 (dd, *J* = 2.1, 17.1 Hz, 1H), 4.99 (dd, *J* = 1.8, 9.9 Hz, 1H), 3.82 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 154.3, 140.9, 136.9, 136.3, 126.0, 123.4, 119.8, 118.9, 117.6, 116.5, 115.3, 114.0, 109.5, 108.2, 28.5; HRMS (EI+) calcd. for $C_{15}H_{12}NOCl$ 257.0614, found 257.0607.



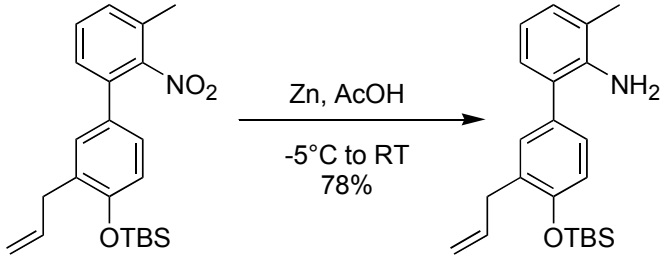
Silyl Ether 19: To a stirred solution of **16** (101 mg, 0.351 mmol) in CH_2Cl_2 (0.60 mL) was added imidazole (36.0 mg, 0.529 mmol). The reaction was cooled to 0˚C, and TBS-Cl (67.8 mg, 0.450 mmol) was added. After 5 min, the reaction was warmed to rt. After 15 min, the reaction was quenched with H_2O (2.0 mL) and diluted with CH_2Cl_2 (3 mL). The organic layer was washed with sat. aq. NaCl (2.5 mL), and the combined aqueous layers were extracted with CH_2Cl_2 (1.0 mL). The combined organic layers were washed with sat. aq. NaCl (1.0 mL). The dried extract (Na_2SO_4) was concentrated *in vacuo* and purified via flash

chromatography over silica gel, eluting with 50-100% PhMe/hexanes, to give **19** (104 mg, 0.258 mmol, 74%) as a white solid. MP 101-102˚C; IR (neat) 2953, 2930, 2857, 1607, 1536, 1499, 1458, 1370, 1257, 1111 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.43 (m, 2H) 7.35 (dd, *J* = 2.3, 6.8 Hz, 1H), 7.16 (d, *J* = 2.4 Hz, 1H), 7.11 (dd, *J* = 2.4, 8.3 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 5.98 (ddt, *J* = 6.52, 10.12, 16.72 Hz, 1H), 5.12-5.04 (m, 2H) 3.40 (d, *J* = 6.6, 2H), 1.045 (s, 9H), 0.288 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 148.9, 136.3, 136.1, 131.5, 130.5, 130.0, 129.5, 128.7, 127.9, 126.7, 125.1, 118.5, 116.2, 34.3, 25.7, 18.3, -4.1; HRMS (EI+) calcd. for $C_{21}H_{26}ClNO_3Si$ 403.1385, found 403.1371.



Silyl Ether 20: To a pressure vessel containing **19** (480 mg, 1.19 mmol) and dioxane (5.5 mL) was added $B_3O_3(CH_3)_3$ (448 mg, 3.57 mmol), $CsCO_3$ (775 mg, 2.38 mmol), $Pd_2(dba)_3$ (54.4 mg, 0.0594 mmol) and PCy_3 57.4 mg, 0.204 mmol). Solution was heated to 80°C. After 21 h, solution was filtered through Celite, washing with EtOAc (90 mL) and concentrated *in vacuo* and purified via flash chromatography over silica gel, eluting with 0-5% EtOAc/hexanes, to give **20** (416 mg, 1.09 mmol, 91%) as a yellow solid. MP 59-61˚C; IR (neat) 2956,

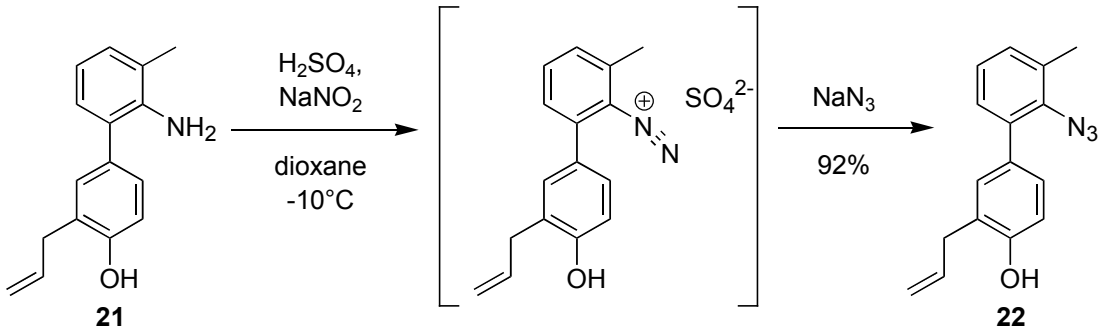
2930, 2858, 1531, 1503, 1471, 1368, 1261, 915, 840, 783, 700; ^{1}H NMR (400 MHz, CD_3Cl) δ 7.40 (dd, *J* = 7.6, 7.7 Hz, 1H), 7.29-7.25 (m, 2H), 7.15 (d, *J* = 2.3 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 5.99 (ddt, *J* = 6.5, 10.2, 16.8 Hz, 1H), 5.10-5.05 (m, 2H), 3.40 (d, *J* = 6.5 Hz, 2H), 2.38 (s, 3H), 1.04 (s, 9H), 0.29 (s, 6H); ^{13}C NMR (100 MHz, CD_3Cl) δ 153.8, 150.9, 136.5, 134.2, 131.1, 130.0, 129.8, 129.6, 129.5, 129.3, 128.7, 126.7, 118.4, 116.0, 34.3, 25.8, 18.3, 17.4, -4.1; HRMS (EI+) calcd. for $C_{22}H_{29}NO_3Si$ 383.1917, found 383.1921.



20 **21**

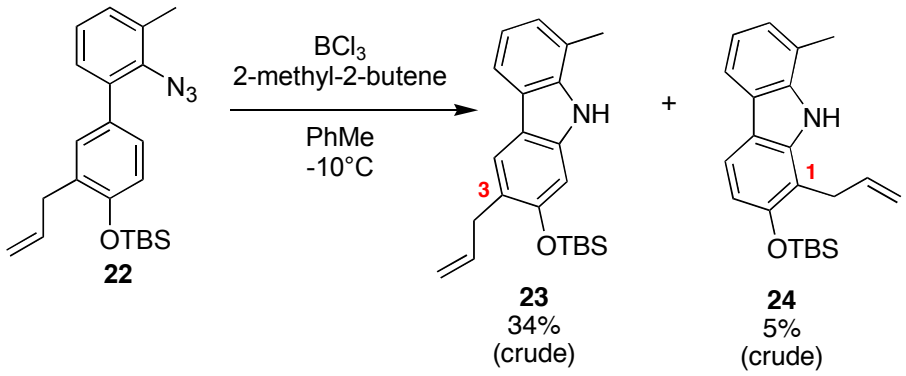
Aniline 21: To a stirred solution of **20** (23.9 mg, 0.0624 mmol) in AcOH (0.35 mL) at -5°C was added Zn (42.0 mg, 0.642 mmol). Reaction was immediately warmed to rt. After 17 h, reaction was diluted with EtOAc (2 mL) and quenched with sat. aq $NaHCO_3$ (6 mL). Solution was diluted with EtOAc (15 mL) and H_2O (10 mL). Organic layer was washed with sat. aq. NaCl (20 mL). Dried extract ($MgSO_4$) was concentrated *in vacuo* and purified via flash chromatography over silica gel, eluting with 0-5% EtOAc/hexanes, to give **21** (17.1 mg, 0.0485 mmol, 78%) as a yellow oil. IR (neat) 3477, 3387, 3074, 3023, 2957, 2930, 2857, 1612, 1500, 1474, 1436, 1254, 1120, 995, 917, 841, 805, 780, 744, 675; ^{1}H NMR (300 MHz, CD_3Cl) δ 7.24 (d, *J* = 2.2 Hz, 1H), 7.18 (dd, *J* = 2.3, 8.2 Hz, 1H), 7.07-7.00 (m, 2H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H),

6.01 (ddt, *J* = 6.6, 10.3, 16.8 Hz, 1H), 5.12-5.04 (m, 2H), 3.73 (s, 2H), 3.43 (d, *J* = 6.6 Hz, 2H), 2.24 (s, 3H), 1.06 (s, 9H), 0.30 (s, 6H); ^{13}C NMR (100 MHz, CD_3Cl) δ 164.1, 152.5, 141.8, 136.9, 132.4, 131.1, 129.3, 128.3, 127.8, 127.5, 122.4, 118.5, 118.0, 115.7, 34.5, 25.8, 18.3, 17.9, -4.07; HRMS (EI+) calcd. for $C_{22}H_{31}NOSi$ 353.2175, found 353.2188.



Azide 22: To a stirred solution of **21** (17.1 mg, 0.0485 μmol) in 1,4-dioxane (0.25 mL) at -10°C was added H_2SO_4 (0.49 mL, 0.98 mmol, 2.0 M in H_2O) via syringe. After 10 min, $NaNO_2$ (0.032 mL 0.096 mmol, 3.0 M in H_2O) added via syringe. After 30 min, NaN_3 (0.049 mL, 0.15 mmol, 3.0 M in H_2O) added to yellow solution of salt **24** via syringe. After 40 min, solution warmed to rt and diluted with Et_2O (15 mL) and H_2O (20 mL). Solution was treated with $NaHCO_3$ (15 mL). Aqueous layer was extracted with Et_2O (20 mL), and combined organic layers were washed with $NaHCO_3$ (20 mL). Dried solution ($MgSO_4$) concentrated *in vacuo* and purified via flash chromatography, eluting with 0-10% EtOAc/hexanes, to give **22** (14.0 mg, 0.0369 mmol, 76%) as a yellow oil. IR (neat) 2956, 2929, 2857, 2127, 2096, 1501, 1469, 1255, 914, 839, 806, 780; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 2.8 Hz, 1H), 7.21 (dd, *J* = 2.4, 8.2 Hz, 1H),

7.18-7.11 (m, 3H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.03 (ddt, *J* = 6.5, 9.5, 17.8 Hz, 1H), 5.13-5.08 (m, 2H), 3.45 (d, *J* = 6.5 Hz, 2H), 2.40 (s, 3H), 1.07 (s, 9H), 0.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 136.8, 136.3, 135.9, 132.0, 131.2, 131.1, 130.7, 129.7, 129.0, 127.9, 125.2, 118.4, 115.8, 34.4, 25.8, 18.4, 18.3, -4.1; HRMS (EI+) calcd. For $C_{22}H_{29}ON_3Si$ 379.2080, found 379.2085.



Carbazoles 23 and 24: To a stirred solution of **22** (121 mg, 0.319 mmol) in PhMe (3.2 mL) and 2-methyl-2-butene (0.49 mL) at -10°C was added BCl_3 (0.96 mL, 0.96 mmol, 1.0 M in heptane) slowly via syringe. After 50 min, reaction was quenched with MeOH (4 mL). The solution was diluted with EtOAc (20 mL) and H_2O (10 mL). The organic layer was washed with H_2O (5 mL), sat. aq. NH_4Cl (20 mL) and sat. aq. NaCl (30 mL). Dried solution ($MgSO_4$) was concentrated *in vacuo* and purified via flash chromatography over silica gel, eluting with 0-50% PhMe/Hex, to give **23** (crude; 19 mg, 54 μmol, 34%) as a white solid and **24** (crude; 2.8 mg, 8.0 μmol, 5%) as a yellow oil.

3-Allyl Carbazole 23: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84-7.79 (m, 3H), 7.17-7.10 (m, 2H), 6.91 (s, 1H), 6.11 (ddt, *J* = 6.5, 9.5, 17.6 Hz, 1H), 5.14-5.08 (m,

2H), 3.53 (d, *J* = 6.5 Hz, 2H), 2.55 (s, 3H), 1.08 (s, 9H), 0.308 (s, 6H); IR, ^{13}C NMR, HRMS currently unavailable.

1-Allyl Carbazole 24: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.85-7.78 (m, 2H), 7.17-7.11 (m, 2H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.10 (ddt, *J* = 6.0, 10.1, 16.1 Hz, 1H), 5.26-5.17 (m, 2H), 3.77 (d, *J* = 6.0 Hz, 2H), 2.55 (s, 3H), 1.07 (s, 9H), 0.28 (s, 6H); IR, ^{13}C NMR, HRMS currently unavailable.

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PART 2: ADVANCES IN PROLINE-BASED ENANTIOSELECTIVE ORGANOCATALYSIS AND ITS APPLICATION TO A NOVEL SYNTHESIS OF THE NATURAL PRODUCT ACONITINE

Introduction

A Brief History of Organocatalysis

The use of enantioselective catalysis is ubiquitous throughout organic chemistry, as nature provides a virtually inexhaustible array of stereochemically complex molecules.[1] Indeed, the vast majority of the fundamental organic compounds in biochemistry—sugars, peptide chains, and nucleic acids, to name a few—contain multiple stereocenters that, if altered, would disrupt the biological function of the compound. In addition, there are a wide variety of stereochemically complex organic compounds that act upon biological pathways, many of which are the targets of synthetic chemistry. It is therefore not surprising that a great deal of focus on methodological studies in organic chemistry should be concerned with the catalysis of reactions that produce products with high enantioselectivity.

During the 20th century, asymmetric catalysis in organic chemistry was dominated by two classes of compounds: organometallic catalysts and enzymes. In organometallic catalysis, a chiral organic ligand forms a complex with a metal center, usually a transition metal. Metal ions in complex with chiral ligands such as BINAP have been used to catalyze a wide range of asymmetric organic reactions, such as hydrogenations, aldol reactions and Diels-Alder reactions.[2,3]

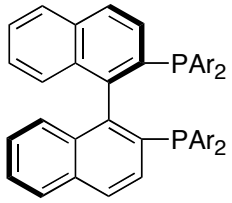
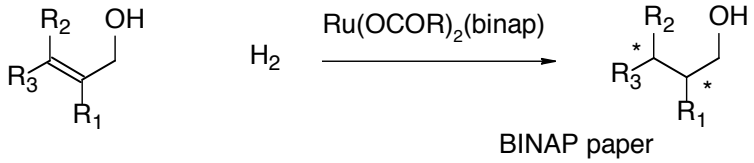


Figure 4: R-BINAP



Scheme 10: Ru-BINAP complex used to catalyze an asymmetric hydrogenation

Despite the extreme utility of organometallic catalysis throughout organic chemistry, the high cost and potential toxicity of many metal ions made alternative, metal-free alternatives an attractive goal.[4] Enzyme catalysis was one common solution to this dilemma. Due to the high degree of stereospecificity found in biological molecules, enzymes (naturally occurring protein catalysts) have evolved to catalyze reactions in a highly enantioselective fashion. For example, there are a wide variety of aldolase enzymes that are able to catalyze many of the types of reactions discussed in this thesis, such as aldol and Mannich reactions.[5] Though enzymes often avoid the problem of toxicity and high cost common with metal ions, enzyme catalysis is limited in its scope in that many enzymes can be prohibitively selective in terms of substrates.

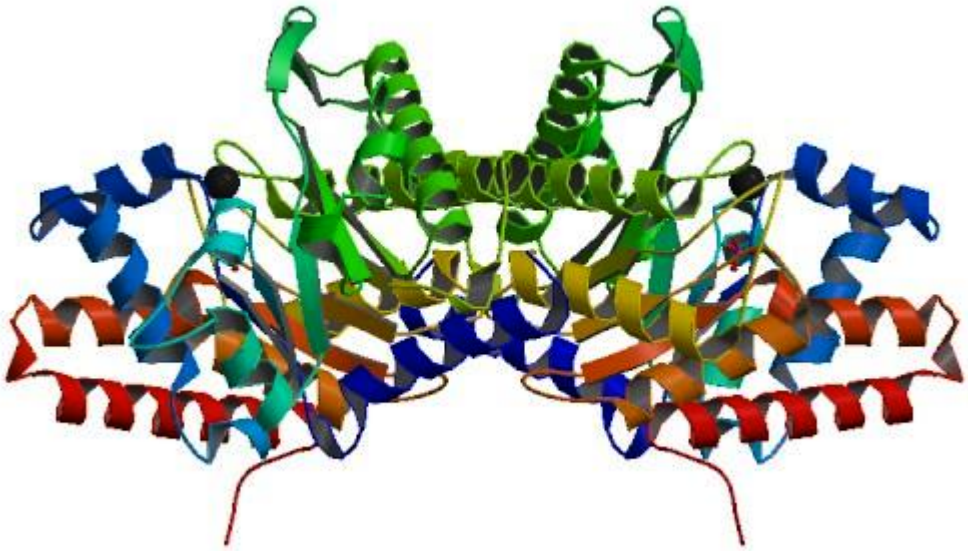


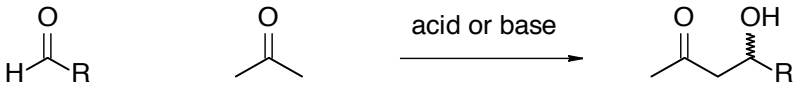
Figure 5: Structure of fructose bisphosphate aldolase, found in *Encephalitozoon cunicui*[a]

The last decade has seen the use of relatively small, chiral organic molecules emerge as a third pillar of asymmetric catalysis. Organocatalysis is an old concept in organic chemistry. Indeed, Emil Knoevenagel realized over a century ago that amines were able to catalyze the condensation of aldehydes and ketones with malonates or β-ketoesters, a process known today as the Knoevenagel condensation.[6] Since Knoevenagel's initial discovery, little attention was paid to organocatalysis until 1974, when Hajos and Parrish discovered that by employing proline as the catalyst, asymmetric aldol reactions could take place in an enantioselective fashion.[7] This monumental discovery paved the way for enantioselective organocatalysis, though despite a few isolated advancements, enantioselective organocatalysis would not truly begin to flourish until the turn of the millennium.

[a] http://www.pdb.org/pdb/images/3mbd_bio_r_500.jpg

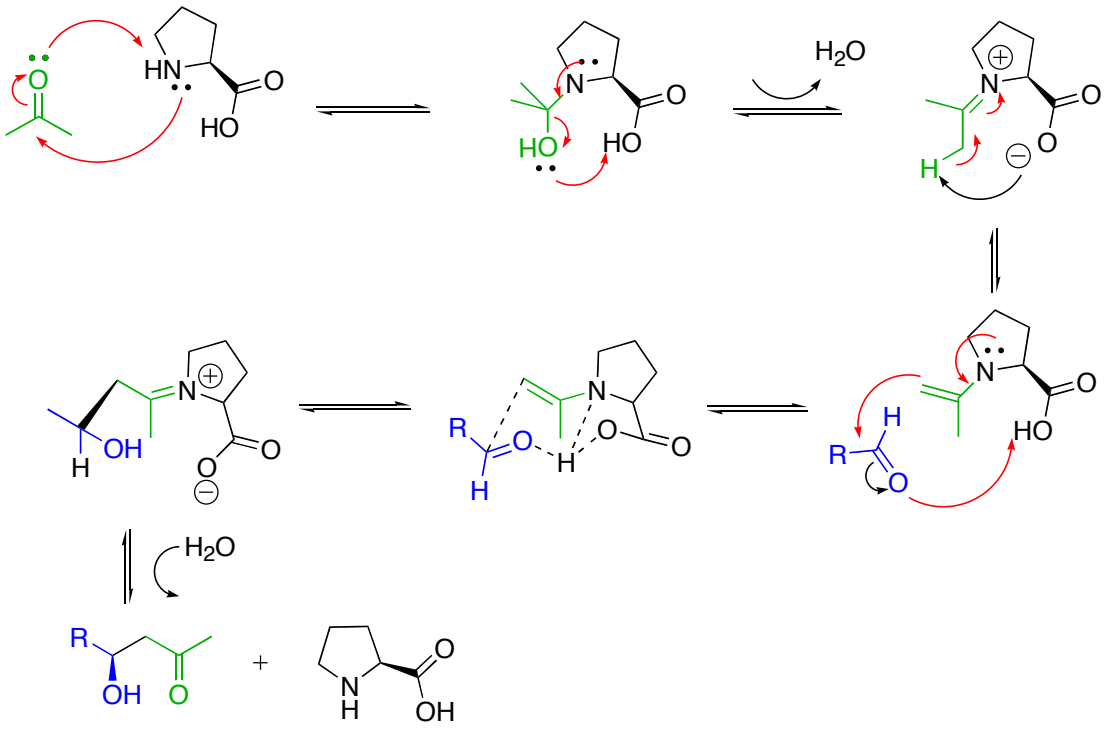
Organocatalysis Today

The current renaissance in organocatalysis began in 2000, when the Benjamin List group published its research in using an array of proline derivatives to catalyze aldol reactions.[8] In an aldol reaction, an aldehyde and ketone react to form a β-hydroxy ketone.



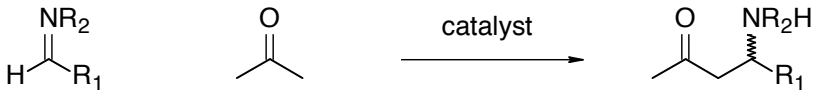
Scheme 11: Basic aldol reaction example

List proposed a mechanism for aldol catalysis by which the proline catalyst reacts with a ketone to form an enamine, which then attacks the aldehyde. List's initial studies reported the formation of a variety of ß-hydroxy ketones with as much as 96% ee.[8]



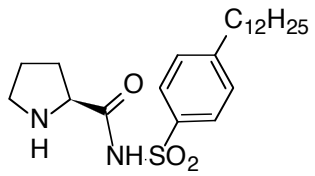
Mechanism 3: Proline-catalyzed aldol reaction[7]

Since List's seminal work, proline-based organocatalysis has come to the forefront of modern asymmetric catalysis. In the process, the scope of organocatalysis has expanded greatly. Among the most prevalent examples (including the subject of this Thesis) are Mannich reactions, in which an imine replaces the aldehyde in the aldol mechanism as the electron acceptor,[5] leading to a primary amine product. The Mannich reaction proceeds with a similar mechanism as the Aldol reaction.



Scheme 12: Basic Mannich reaction example

One problem commonly faced in proline catalysis is that polar solvents, such as methanol or DMSO, are commonly needed to dissolve the catalyst.[4] Such solvents can often cause difficulties at the industrial level, such as problems with their miscibility with water.[9] In response to the demand for catalysts that will function in nonpolar solvents, a variety of tetrazole and sulfonamide catalysts have been developed, allowing for the asymmetric catalysis of aldol- and Mannich-type reactions in such nonpolar solvents as dichloromethane.[4] The Carter group has developed a proline-based sulfonamide known as Hua Cat, a proline-based sulfonamide containing a long, nonpolar dodecane tail.[9] The catalyst was named after Hua Yang, a post-doctoral research assistant in the Carter group who has been exploring applications of the catalyst.



25

Figure 6: Hua Cat (25)

ent-*Hua Cat and Aconitine Synthesis*

The purpose of this research has been to examine the utility of organocatalysis, particularly the catalyst *ent*-Hua Cat (**26**), in catalyzing Mannich-related [2.2.2] bicyclizations. The project focuses on the synthesis of the core of the natural product aconitine, an Na^+ ion channel activator. Aconitine has been used worldwide due to its antipyretic and analgesic properties. It is utilized to this day to treat ailments ranging from snakebites to coughing and asthma.[10] However, the compound is a highly potent cardiotoxin and presents significant medical issues in parts of the world where herbal medicines are widely used.[10] Though the toxic nature of aconane alkaloids such as aconitine limit their use in traditional medicine, their myriad therapeutic properties have attracted significant attention in the realm of natural product synthesis.

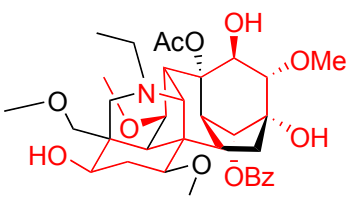
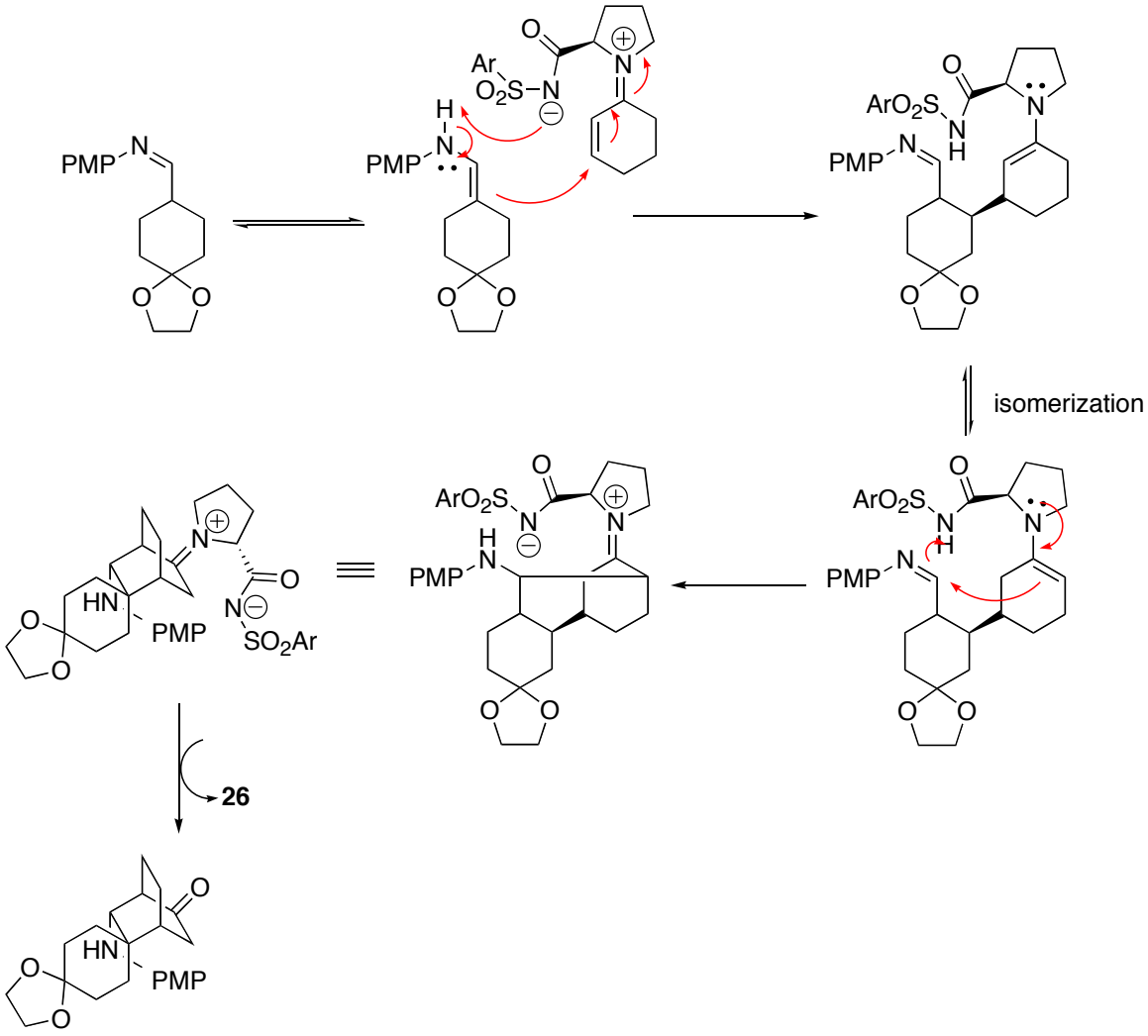


Figure 7: Structure of target product aconitine

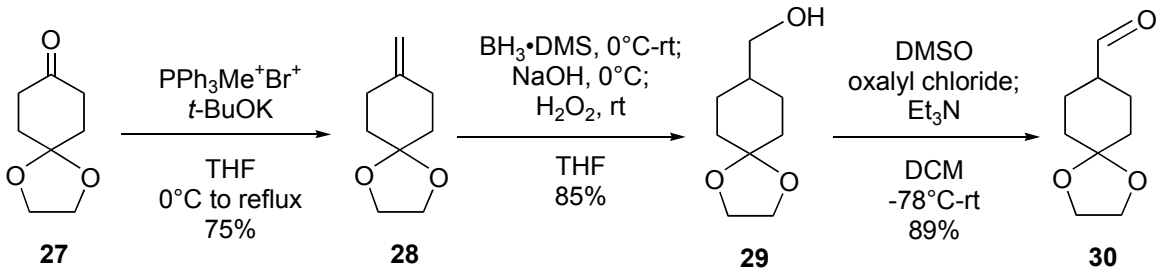
The key asymmetric step toward aconitine synthesis is a [2.2.2] bicyclization involving an imine and a cyclohexenone and is catalyzed by *ent*-Hua Cat (**26**). The proposed mechanism for this reaction involves a tandem Mannich-Michael bicyclization.[11]



Mechanism 4: Tandem Mannich-Michael [2.2.2] Bicyclization[11]

Results and Discussion

Synthesis of Aldehyde Starting Material



Scheme 13: Synthesis of aldehyde 30

The synthesis of aldehyde **30** began with the commercially available ketone **27**. The proposed three-step pathway depicted in Scheme **11** involves the Wittig conversion of ketone **27** into olefin **28**, followed by hydroboration to alcohol **29** and then further oxidation to known aldehyde **30**.[12]

The preparation of starting material proceeded with little trouble. The Wittig olefination was carried out using trimethylphenylphosphonium bromide as a methyl group donor and potassium *tert*-butoxide as a base. The reaction was initially warmed to 90 ^{o}C after base addition at 0 ^{o}C, based on a literature source that had reported a yield of 91%.[13] It was later found that allowing the reaction to warm to room temperature was sufficient to allow the reaction to proceed to completion, giving a slightly higher yield (72% versus 66%).

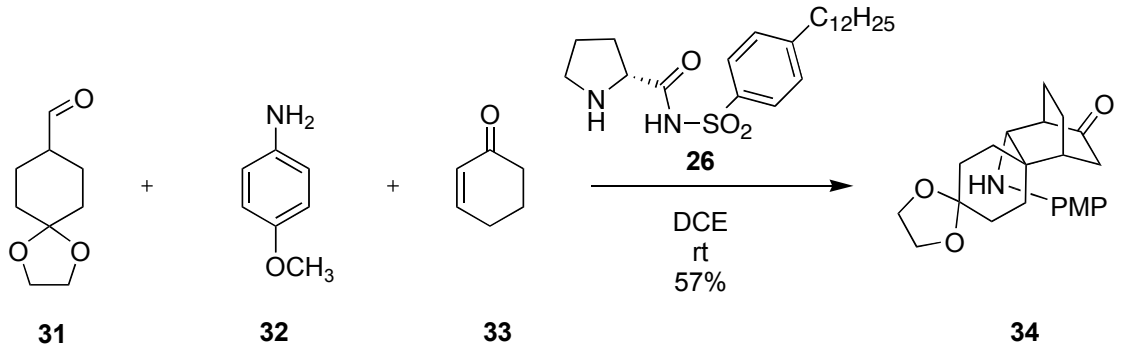
Hydroboration was next used to form alcohol **29** from olefin **28**. Two hydroboration reagents, 9-BBN and BH_3•DMS, were tested for this step. The results of the hybroboration experiments were acceptable, though disappointing.

While 9-BBN led to starting material decomposition, BH_3•DMS performed the hydroboration with a modest 68% yield.

The oxidation of alcohol **29** to aldehyde **30** was initially attempted using pyridinium chlorochromate (PCC). This method was initially preferred over a Swern oxidation due to the multiple distillations needed to perform the latter procedure, as well as the unpleasant odor of sulfur-based compounds. When the PCC oxidation produced the target aldehyde with only a 29% yield, the Swern oxidation was employed for the oxidation. Swern oxidations have a reputation for producing compounds in high yields; as expected, this procedure produced aldehyde **30** with yields as high as 85%.

Upon synthesizing aldehyde **30**, it became immediately apparent that the compound was very unstable when concentrated. It is believed that at high concentration, the aldehyde undergoes a spontaneous aldol condensation. For this reason, after the oxidation, the Hua Cat-catalyzed [2.2.2] bicyclization was carried out with as little delay as possible. Eventually, it was discovered that storing aldehyde **30** in benzene at -78 °C prevented the aldol condensation, though it is recommended that the starting material be stored for long periods of time as the stable alcohol **29**.

Hua Cat-Catalyzed [2.2.2] bicyclization



Scheme 14: [2.2.2] bicyclization step with ent-Hua Cat

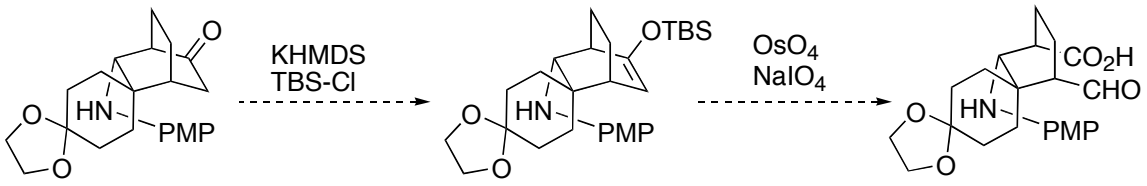
The *ent*-Hua Cat catalyzed [2.2.2] bicyclization step was a relatively low-maintenance reaction. Aldehyde **30** and aniline **31** were stirred in dichloroethane for 30 minutes to form an imine. Cyclohexenone **32** and *ent*-Hua Cat (**26**) were then added to the reaction, which was allowed to stir at room temperature for three days. The lack of need for heating and cooling, as well as the high reaction concentration (and, by extension, the low reaction volume) are among the attributes of this reaction that make Hua Cat an attractive catalyst for industrial applications.

Purification of product **34** is a more difficult and time-consuming procedure. A TLC of the product showed significant streaking, and as this predicted, separating pure product from waste compounds and decomposed starting material was a tiresome process. This difficulty was compounded by the fact that aniline **31**, which was still present in the product, elutes at an Rf that is virtually indiscernible from the product. Eventually, multiple flash

chromatography columns, with varying solvent systems, were used to purify the product (as well as to separate it from the catalyst, which was recovered from the reaction with a 52% mass recovery). Once the product had been sufficiently purified in this manner, the product was recrystallized in ethyl acetate and dichloromethane. This solvent system was employed under the hypothesis that ethyl acetate, in which **34** is only marginally soluble, would likely provide high solubility for the more polar impurities that were present in the product. Indeed, the recrystallization worked very well, producing pure white crystals of **34** with an overall yield of 57%. The stereochemical purity of the compound was determined via HPLC, using a chiral C_{18} column. It was found that *ent*-Hua Cat demonstrated excellent enantioselectivity, synthesizing **34** with 99% enantiomeric excess (ee).

Recent Work and Future Considerations

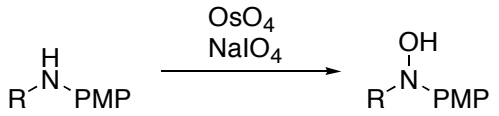
Currently, two major hurdles in the progression of product **34** to aconitine are being considered. The majority of recent efforts have been focused on the next step of the procedure, the oxidation of **34** to form aldehyde **36**. Originally, it was proposed that **34** would be “trapped’ in its enol form as silyl ether **35**, which would then undergo oxidation with OsO_4 and $NaIO_4$ to form **36**.



34 **35** **36**

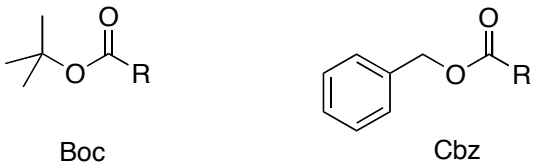
Scheme 15: Proposed steps toward aldehyde 36

This procedure is hindered by the second obstacle: protection from oxidation of the protic nitrogen in **34**. Without proper protection of the nitrogen, an oxidation reaction would likely oxidize the amine to a hydroxylamine.



Scheme 16: Possible oxidation of amine to hydroxylamine

A variety of procedures have been tried to protect the amine. Initially, protection with an N-tert-butyloxycarbonyl (Boc) group was tried as a protecting group. After Boc-ON and Boc_2O were both unsuccessful at protecting the amine, a carboxybenzyl (Cbz) was tried. Unfortunately, Cbz-Cl was also unsuccessful at amine protection.



Boc Cbz

Figure 8: N-*tert*-butylcarbonyl (Boc) and carboxybenzyl (Cbz) protecting groups

The proposed cause of difficulty in protection of the secondary amine lies in the high level of steric hindrance surrounding the amine. The amine is already bonded to two fairly bulky groups (a PMP and the large [2.2.2] octane). Coupled

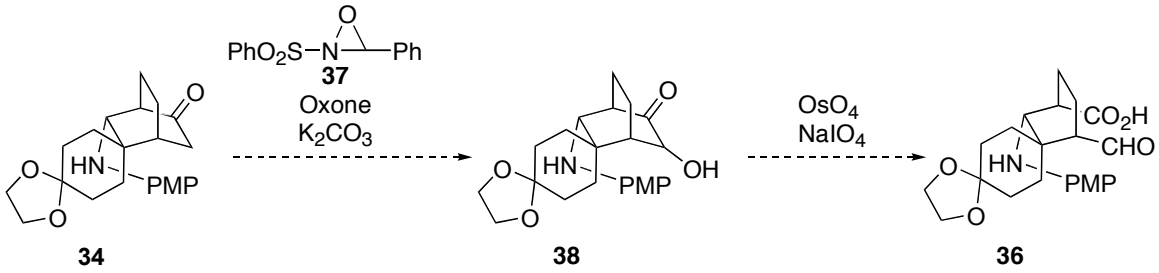
with the fact that it sits very near the large cyclohexanone ring (with the ketone protected as the larger ketal), there is very little room for yet another large group, such as Boc or Cbz.

One proposed solution to this dilemma has been to replace the PMP group with a much smaller ethyl group. Using the smaller substituent should relieve some steric hindrance. Replacing the PMP group with an ethyl group would also be more convenient in later steps, as the PMP would eventually need to be replaced by an ethyl group.

It had been proposed that the oxidation step be attempted without protecting the amine. Given the significant troubles faced in protecting the amine, it may be easier to simply perform the oxidation (oxidizing the amine in the process), followed by a simple reduction of the resulting hydroxylamine. This procedure was briefly attempted, though not enough experiments have been run to conclusively decide whether this procedure will work.

Silyl ether **35** has been successfully synthesized using TBS-OTf and 2,6-lutidine. Unfortunately, the stability of **35** is limited; after only a few days of storage at -20 °C, about half of the silyl ether had reverted back to ketone **34** (as evidenced by TLC). Two solutions to this dilemma have been proposed. The first (and simplest) solution would be to synthesize **35** and perform the oxidation in the same day, as had been done with the aldehyde. It may even be more convenient to attempt the oxidation without isolating the silyl ether.

The second option would be to forego the use of a silyl ether, forming instead α-hydroxy ketone **37** using Davis oxiziridine. It is expected that **37** would be more stable than silyl ether **35**, allowing for its isolation and storage in mild conditions.

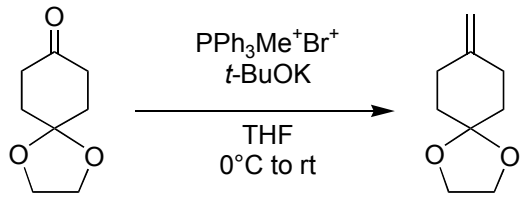


Scheme 17: Proposed oxidation pathway via α-hydroxyketone 38

Conclusion

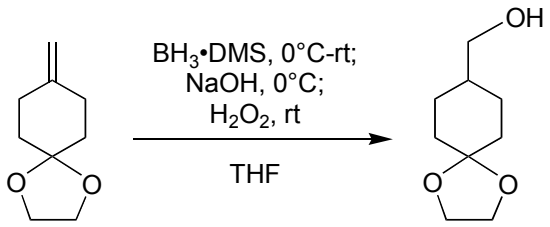
While recent experiments have proven to be mostly fruitless at this point, the the enantioselective [2.2.2] cyclization catalyzed by *ent*-Hua Cat (which was the primary focus of this research project) was very successful. Though yields were modest at best, the high enantiomeric purity of the final product, the ability to recover the catalyst with modest mass recovery, the ability to use low volumes of a non-polar solvent and the mild reaction conditions are exciting developments in the field of enantioselective organocatalysis. If it can be shown (through success in subsequent steps toward the synthesis of the core of aconitine) that this procedure for catalyzing tandem Mannich-Michael reactions in an asymmetric fashion is effective in natural product synthesis, it is anticipated that this procedure will find utility in industrial application.

Experimental



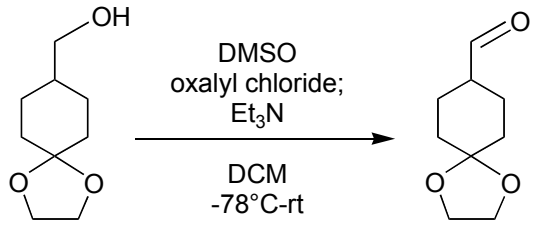
27 **28**

Methylene 28: To stirred solution of $PPhMe^+Br^-$ (9.27 g, 25.9 mmol, previously dried in vacuo at 60°C) in THF (30 mL) at 0°C was added t-BuOk (2.91 g, 25.94 mmol, in 26 mL THF) via cannula. After 5 min, the bright yellow solution was allowed to warm to rt. After 25 min, **27** (2.03 g, 13.0 mmol, in 50 mL THF) was added via cannula. After 20 min, solvent was remived in vacuo. The resulting oil was diluted with Et_2O (150 mL) and H_2O (30 mL). The organic layer was washed with sat. aq. NaCl (100 mL). Dried extract ($MgSO_4$) was concentrated in vacuo and purified via flash chromatography over silica gel, eluting with 10-30% EtOAc/Hex, to give **28** (1.44 g, 9.306 mmol, 72%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.69 (s, 2H), 3.99 (s, 4H), 2.31 (t, J = 6.64 Hz, 4H), 1.73 (t, J = 6.72 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 108.5, 108.2, 64.3, 35.8, 32.0.



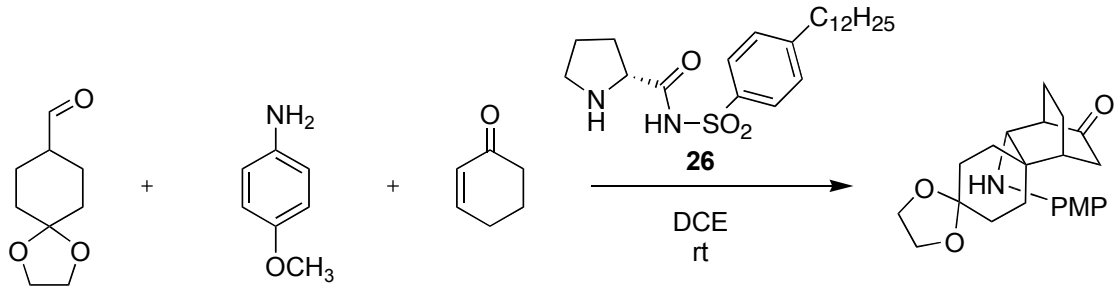
28 **29**

Alcohol 29: To stirred solution of **28** (302 mg, 1.96 mmol) in THF (20 mL) at 0°C was added BH_3•DMS (0.27 mL, 2.9 mmol) dropwise via syringe. Reaction immediately warmed to rt. After 110 min, additional BH_3•DMS (0.050 mL, 0.53 mmol) added dropwise via syringe. After 15 min, reaction cooled to 0°C. After 5 min, NaOH (9.8 mL, 3 M in H_2O) added via syringe. After 15 h, H_2O_2 (9.5 mL, 30% in H2O) added via syringe. Reaction was allowed to warm to rt. After 3 h, K_2CO_3 (1.03 g) added to solution. Solution diluted with Et_2O (30 mL). Aqueous layer extracted Et2O (2 x 25 mL), and combined organic layers washed with sat. aq. NaCl (50 mL). Dried solution ($MgSO_4$) concentrated in vacuo. Product purified via flash chromatography over SiO_2, eluting with 20-100% EtOAc/hexanes, to give **30** (302 mg, 1.75 mmol, 89%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (t, *J* = 2.1 Hz, 4H), 3.49 (d, *J* = 6.4 Hz, 2H), 1.79 (d, *J* = 9.2 Hz, 4H), 1.59-1.49 (m, 3H), 1.33-1.23 (m, 2H); ^{13}C NMR (100 MHz, CDC_{l3}) δ 109.0, 67.7, 64.2, 39.1, 34.1, 26.7.



29 **30**

Aldehyde 30: To stirred solution of oxalyl chloride (1.8 mL, 21 mmol) in DCM (280 mL) at -78°C was added DMSO (3.0 mL, 42 mmol) dropwise via syringe. After 40 min, **29** (2.29 g, 13.3 mmol) in DCM (140 mL) was added via cannula. After 90 min, Et_3N (6.0 mL, 43 mmol) added to cloudy-white solution via syringe. After 25 min, reaction diluted with DCM (200 mL). Organic layer washed with H_2O (3 x 100 mL) and sat. aq. NaCl (2 x 350 mL). Dried solution ($MgSO_4$) concentrated in vacuo. Product purified via flash chromatography over SiO_2, eluting with 50-100% EtOAc/hexanes, to give **30** (1.93 g, 11.3 mmol, 85%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (d, *J* = 1.2 Hz, 1H), 3.96 (t, *J* = 2.8 Hz, 4H), 2.27 (dtt, *J* = 1.3, 4.1, 9.7, 1H), 1.99-1.92 (m, 2H), 1.81-1.71 (m, 4H), 1.65-1.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 108.1, 64.3 (d, *J* = 5.7 Hz), 48.2, 33.4, 23.3.



31 **32** **33** **34**

Ketone 34: To stirred solution of **30** (1.77 g, 10.4 mmol) in DCE (10 mL) was added **31** (1.41 g, 11.4 mmol). After 30 min, **32** (10.0 mL, 9.93 g, 103 mmol) and ent-Hua cat **26** (0.873 g, 2.07 mmol) added to solution. After 3 days, DCE revoved in vacuo. Product purified via flash chromatography over SiO_2, eluting with 0-20% EtOAc/DCM, to give **34** (2.20 g, 10.4 mmol, 57%) as a white solid. IR

(neat) 3360, 2936, 2904, 2874, 1709, 1514, 1443; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, *J* = 8.8 Hz, 2H), 6.56 (d, *J* = 8.7 Hz, 2H), 3.94 (s, 4H), 3.75 (s, 3H), 3.39 (d, *J* = 22.1 Hz, 1H), 2.575-2.442 (m, 2H), 2.338-2.128 (m, 2H), 2.03-1.55 (m, 13H); HRMS (EI+) calcd. for $C_{22}H_{29}NO_4$ 371.20966, found 371.20831; ^{13}C NMR currently unavailable.

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