THE DEVELOPMENT OF FREE RADICAL-MEDIATED ARYL AMINATION AND ITS APPLICATION TOWARD THE TOTAL SYNTHESIS OF AMBIGUINE G NITRILE

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Submitted to the faculty of the University Graduate School

in partial fulfillment of the requirements

for the degree

Doctor of Philosophy

in the Department of Chemistry,

Indiana University

March 2005

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Accepted by the Graduate Faculty, Indiana University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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March 24, 2005

ACKNOWLEDGEMENTS

I would like to take this opportunity to thank all those who have helped and supported me throughout my graduate school. I would like to express my heartfelt gratitude to Prof. Johnston. It was his enthusiasm and eagerness to do excellent research that inspired me all along. If not for his open minded encouragement of independent ideas from me, this work would not be in its current shape. I thank Prof. Williams, for his inspiring teaching and encouraging group meeting sessions. I learnt quite a bit during those sessions. I also thank, Prof. Gajewski for his patience in teaching physical organic chemistry and also for encouraging independent ideas from me. I am grateful to him for serving on my committee during my fifth semester. Thanks to Prof. Montgomery for his thoughtful discussions during my C500 project. Thanks to Prof. Crandall and Prof. Widlanski for teaching me various aspects of organic chemistry that are so fundamental for doing synthetic organic chemistry. Thanks to Prof. Andrew Evans for serving in my committee during the final stages. My AI's, especially, Dr. Michael Clark, Cheri Stowell, Dr. Rich Heidebrecht were superb, and thanks to their patience while teaching me.

I am deeply indebted to Dr. David Kammler, Dr. David Ihle, and Samarjit Patnaik for their valuable help during my fifth semester exam. I consider it as a gift to have worked with Dr. Amie Williams, whose wonderful support and energy was so pervasive in the group. I thank Dr. E. N. Prabhakaran who was of immense support during the early years of my independent research. Among others who took special interest in my research, I thank Ben Nugent for discussions and proofreading parts of this document, Ryan Yoder for his technical support, Julie, Dr. Joe Mahoney, Jayasree for proof reading this document, Mike, Colin and Bo. Thanks to Dr. Sarah Cortright who helped me through some tough experiments and also documentation. I was lucky to guide Heather Burks along her undergraduate work, and I will cherish that experience forever. Teaching the undergraduates was an invaluable experience and I thank the department for providing me the opportunity. Work of this nature is simply impossible without the technical support of staff at IU, especially in the NMR and Mass spectrometry division, my sincere thanks to them.

Life as an international graduate student is a unique experience where friends become family (well, almost!). I am gifted to have gained some life long friendship at IU. Thanks Dayal, Doss, Sam, Khalida, Hari, Bhanu and Manami. Thanks a ton to my sister, whose love and affection has been of immense value during this endeavor. Finally I would like to not just thank but also like to dedicate this work to my Amma and Appa, whose love and constant encouragement gives me a sense of purpose.

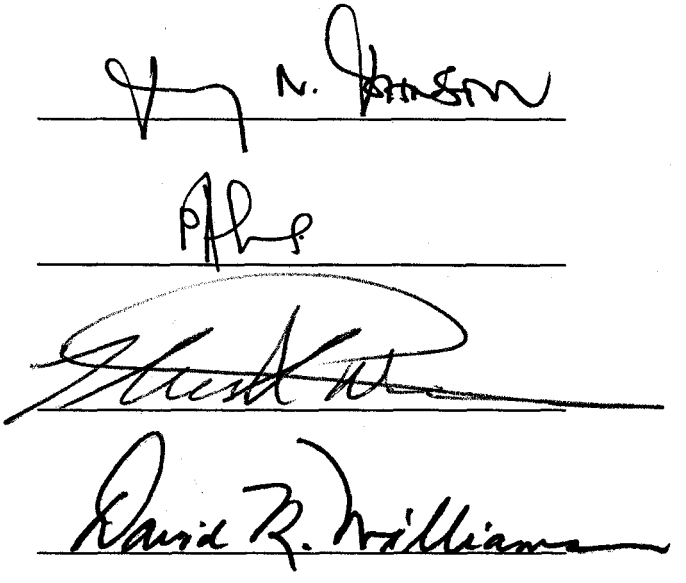
ABSTRACT

Rajesh Viswanathan

THE DEVELOPMENT OF FREE RADICAL-MEDIATED ARYL AMINATION AND ITS APPLICATION TOWARD THE TOTAL SYNTHESIS OF AMBIGUINE G NITRILE

Free radical-mediated aryl amination was developed as a conceptually unique approach toward the construction of aryl-nitrogen bond. The reaction was optimized to produce indolines in high yields. The scope and generality of this free radical-mediated cyclization was established by applying it to the synthesis of a diverse array of indolines. Aryl amination was found to be a very mild process for the synthesis of an indoline with a highly sensitive functional group. Aryl amination was then applied to the enantioselective synthesis of indoline α-amino acids. A modular annulation strategy employing O'Donnell's enantioselective glycine alkylation followed by aryl amination provided access to protected indoline α-amino acids in excellent % ee. Absolute configuration of the indoline α-amino acid was confirmed by comparison of the specific rotation after appropriate deprotection. This modular annulation approach was then extended to a stereoselective synthesis of substituted indoline α-amino acids by replacing the alkylation with a Michael addition step. (+)-ambiguine G is a nitrile-containing indole alkaloid isolated from the cyanobacterium *Hapalosiphon delicatulus* possessing anti-fungal activity. (+)-ambiguine G, has a novel pentacyclic framework and, is structurally related to the hapalindoles, fischerindoles and welwitindolinones. However, no synthesis of this natural product has been reported yet. The proposed biosynthetic pathway to the ambiguine family of natural products is discussed. The indole moiety of ambiguine G was constructed using our conceptually unique aryl amination methodology. The stereochemically dense D ring bearing the neo-pentyl chloride was synthesized using a Diels-Alder reaction between Cohen's diene and a β-chloro-α-methyl dienophile. An enolate C-arylation strategy has been attempted for the construction of the C ring. The

first *A*zaCyclopentenyl *C*arbinyl *R*adical *I*somerization (ACCRI) was identified, and documented. This process was found to be operative under aryl amination conditions. The ring-chain isomerization was gated using the steric and electronic aspects of the process. Use of a sterically demanding substrate led to the isolation of the chain isomer constituting a 1,4-imino transfer process. Relevance of ACCRI to biochemical enzyme-mediated isomerization processes is noted.



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Chapter 1. Ambiguine G and Related Alkaloids: Isolation, Structure, Biosynthesis and Synthetic Efforts

1.1. Introduction

Isonitrile-containing indole alkaloids are often present in branched, filamentous blue-green algae (cyanobacteria) belonging to the Stigonemataceae family. At present, four main classes have been identified, viz., ambiguines,[1,2] hapalindoles,[3,4] fischerindoles[5] and welwitindolinones.[6] All are indolo-terpenoids by structure. This chapter briefly outlines the isolation efforts, structural characterization, probable biosynthetic pathways and previous synthetic efforts in each class of alkaloids. Terpene isonitriles and derivatives have been isolated from marine sponges.[7]

1.2. Isolation, Structure, and Stereochemistry

1.2.1. Ambiguine Alkaloids

In a search for alkaloids with antifungal activity, Moore[2] reported the isolation of ambiguine G (**1**) from an epidaphic cyanophyte *Hapalosiphon delicatulus* W. and G. S. West (UH isolate IC-13-1). This indole alkaloid possessed a ring skeleton that is common to the ambiguine family of alkaloids isolated previously. Among the family of ambiguines, this was the only nitrile containing alkaloid. Ambiguine G was isolated from *H. delicatulus* in 0.0064% yield. Eight other known compounds belonging to the ambiguine and hapalindole family were also isolated along with ambiguine G. Ambiguine E isonitrile constituted the major component in this extract. High resolution mass spectrometry along with two-dimensional NMR experiments revealed the structure

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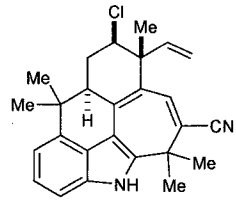
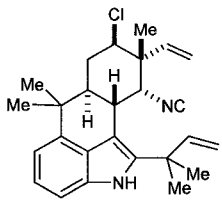
[1] Smitka, T. A.; Bonjouklian, R.; Doolin, L.; Jones, N. D.; Deeter, J. B.; Yoshida, W. Y.; Prinsep, M. R.; Moore, R. E. and Patterson, G. M. L.; *J. Org. Chem.* **1992**, *57*, 857-861.
[2] Huber, U.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1998**, *61*, 1304-1306.
[3] Moore, R. E.; Cheuk, C.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 6456.
[4] Moore, R. E.; Cheuk, C.; Yang, G. Xu-Q.; Patterson, G. M. L. J. Org. Chem. **1987**, *52*, 1036-1043.
[5] Park A.; Moore, R. E.; Patterson, G. M. L. Tetrahedron Lett. **1992**, *33*, 3257-3260.
[6] Stratmann, K.; Moore, R. E.; Bonjouklian, Deeter, J. B.; Patterson, G. M. L., Shaffer, S.; Smith, C. D.; Smitka, T. A. J. Am. Chem. soc. **1994**, *116*, 9935-9942.
[7] Mitome, H.; Shirato, N.; Miyaoka, H.; Yamada, Y.; van Soest, R. W. M. *J. Nat. Prod.* **2004**, *67*, 833.

of ambiguine G nitrile. The relative stereochemistry was elucidated based on the ^{1}H-^{1}H coupling constant data and difference NOE studies. So far, there is no experimental evidence establishing the absolute stereochemistry of ambiguine G nitrile.

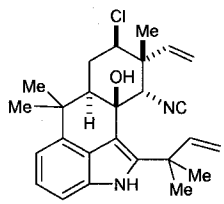


(+)-ambiguine G nitrile (**1**)

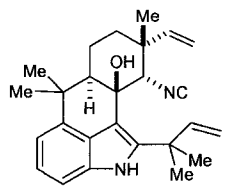
Ambiguine isonitriles A-F were first isolated from three genera of blue-green algae belonging to the Stigonemataceae family (Chart 1).[1] The extracts of these terrestrial cyanophytes, *viz. Fischerella Ambigua* (Nageli) Gomont (UTEX 1903), *Hapalosiphon hibernicus* W. and G. S. West (UH isolate Bz-3-1) and *Westiellopsis prolific* Janet (UH isolate EN-3-1) were found to inhibit the growth of five test fungi: *Aspergillus oryzae*, *Candida albicans*, *Penicillum notatum*, *Saccharomyces cerevisiae*, and *Trichophyton mentagrophytes* in a soft agar disc-diffusion assay (250 μg, 10-22-mm zones of inhibition). Ambiguine isonitriles A-F were structurally characterized using 1D and 2D-NMR, and mass spectrometric measurements. Ambiguine D isonitrile was characterized also by X-ray crystallography.



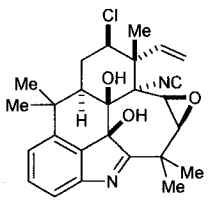
ambiguine A isonitrile (**2**)



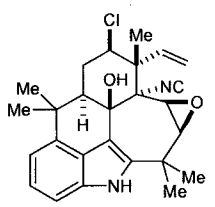
ambiguine B isonitrile (**3**)



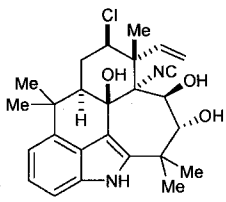
ambiguine C isonitrile (**4**)



ambiguine D isonitrile (**5**)



ambiguine E isonitrile (**6**)



ambiguine F isonitrile (**7**)

Chart 1. Ambiguine isonitriles A-F (2-7)

The ambiguines and hapalindoles have in common the indolo-terpenoid tetracyclic skeleton. However, an isoprene unit is attached to the C-2 of the indole position in the reverse prenylated fashion. While the isoprene unit is free at one end for ambiguines A-C, it is cyclized to form a 7-membered ring in ambiguines D-G. All the ambiguines isolated to-date are chlorinated at the neo-pentyl carbon of the 6-membered ring with one exception: ambiguine C isonitrile. The relative stereochemical assignments made using spectroscopic methods were further confirmed by an X-ray crystal structure for the indolenine containing ambiguine D isonitrile (Figure 1, **5**). However, the X-ray crystallographic study did not lead to the absolute stereochemistry of ambiguine D isonitrile. The CD spectra of ambiguine isonitriles A, B, C, E, and F and hapalindole G are roughly similar in shape (all six spectra show a negative minimum at 220-225 nm), suggesting that the absolute stereochemistry of the ambiguines and the hapalindoles is likely the same. Since the absolute stereochemistry of hapalindole G is known, the ambiguines are assigned the absolute configurations that are represented in Chart 1.

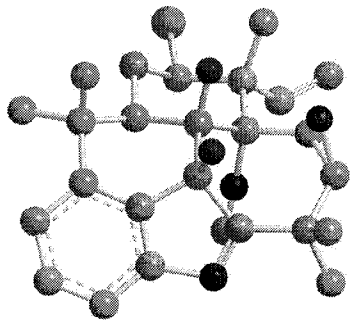
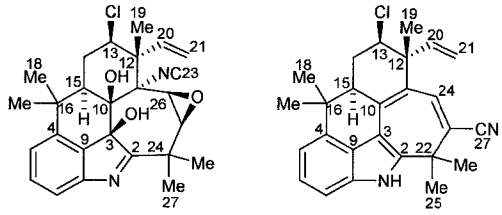


Figure 1. Chem3-D representation of the X-ray structure of indolenine containing ambiguine-D (5)

Figure 2 compares the structures of ambiguine D isonitrile (**5**) and ambiguine G nitrile (**1**). The X-ray structure shows the chloride atom on C-13 is equatorial and *cis* to the axial methyl group on the adjacent C-12 quaternary center. Based on ^{1}H NMR coupling constant data and NOE difference studies, the relative stereochemistry of the chlorine atom on C-13 in ambiguine G nitrile is also equatorial and *cis* to the adjacent C-12 methyl group. Thus the relative stereochemistry for ambiguine G nitrile is assigned to be 12*R*, 13*R*, 15*S*. Molecular models of the lowest energy conformer of ambiguine G nitrile reveal the following conformational features. (a) Of the two methyl groups on C-16, one is coplanar with the indole ring while the other is essentially perpendicular; (b)

Of the two methyl groups on C-22, one is coplanar with the indole ring while the other is essentially perpendicular; (c) the δ-cyanodienylindole is non-planar. However the distortion away from planarity is not so severe that an electronic excitation is prevented as indicated by the UV absorption profile (390 nm, ε 6750).

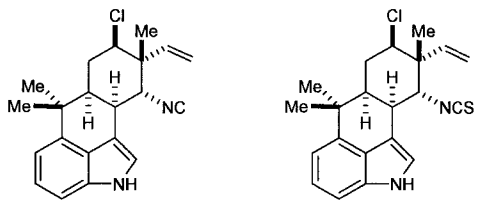


ambiguine D isonitrile (**5**) ambiguine G nitrile (**1**)

Figure 2. Atom numbered structures of ambiguine D isonitrile (5) and ambiguine G nitrile (1).

1.2.2. Hapalindole Alkaloids

In 1984, Moore and coworkers reported the isolation of a new family of alkaloids named hapalindole from the soil samples collected in the Marshall Islands.[3] *Hapalosiphon fontinalis*, the species responsible for producing hapalindoles possessed antialgal activity against *A. Oscillarioides*. Hapalindole A (**8**) and its corresponding isothiocyanate (hapalindole B, **9**) were structurally characterized using NMR and mass spectrometric techniques. They were found to possess a novel tetracyclic framework shown in Figure 3.



hapalindole A isonitrile (**8**) hapalindole B isothiocyanate (**9**)

Figure 3. Structure of hapalindole A isonitrile (8) and hapalindole B isothiocyanate (9)

Hapalindoles A and B constituted the major portions of the cyanophyte extracts, however, there were 18 other minor alkaloids that were isolated from the same cyanophyte.[4] These were labeled as hapalindole C-Q and T-V (Chart 2, **10-27**). The gross structures and relative stereochemistry was determined by spectral methods. The relative stereochemistry of hapalindole A (**8**), D (**11**) and K (**18**) were confirmed and the absolute

configuration of hapalindole K was established as 11*R*, 12*R*, 13*R* by X-ray crystallography.

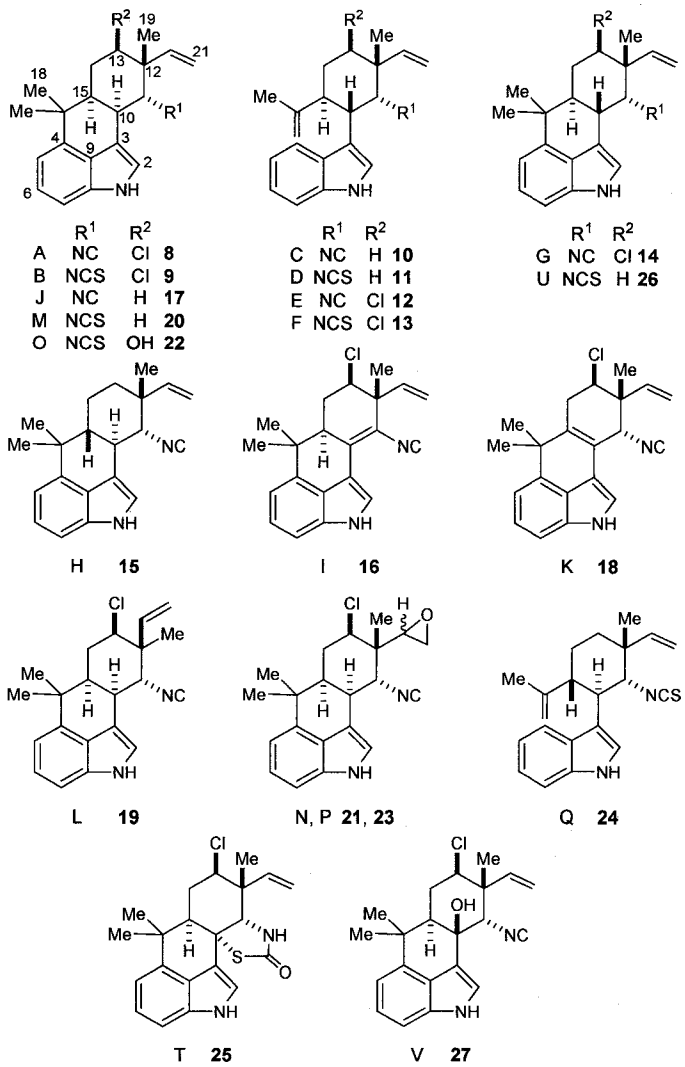
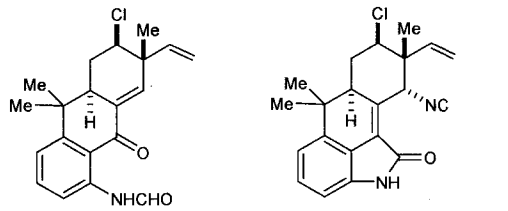


Chart 2. Structures of hapalindoles A-V (8-27)

The only members among this class for which an X-ray crystal structure could be obtained was hapalindole K (**18**) and G (**14**). Interestingly, indirect evidence for the confirmation of the absolute stereochemistry of hapalindole A was gathered from singlet oxidation studies. Hapalindole K was produced upon subjecting hapalindole A to singlet oxygen. This hapalindole K also possessed the same optical rotation as hapalindole A. This observation indirectly confirmed the absolute stereochemistry in hapalindole A to be 11*R*, 12*R*, 13*R*. Assuming that all of the alkaloids have the same absolute stereochemistry

as K, all of the hapalindoles isolated to-date are 11*R* and all of the chlorinated congeners are 13*R*. With the exception of hapalindole L, all of the hapalindoles are 12*R*. Hapalindoles A and B, the major alkaloids in the blue-green algae, and several of the minor hapalindoles are 10*R*, 15*S*. Three of the alkaloids (C-G and U) are 10*S*, 15*S* and two (H and Q) are 10*R*, 15*R*. Most of the hapalindoles are tetracyclic except hapalindole C-F and Q which are tricyclic. Hapalindole T contains an unusual thiocarbamate unit. Hapalindole V is a 10-hydroxy derivative of hapalindole G.

In 1987, Moore and coworkers reported the isolation of two new alkaloids from a cultured strain of the terrestrial blue-green algae Hapalosiphon fontinalis.[8] Fontonamide (**28**) and anhydrohapalindolinone A (**29**) appeared to be singlet oxygen oxidation products of hapalindole A, the major alkaloid in this cyanophyte (Figure 4).

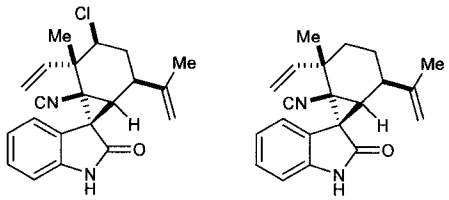


fontonamide (**28**) anhydrohapalindolinone A (**29**)

Figure 4. Structures of oxidized hapalindoles fontonamide (28) and anhydrohapalindolinone A (29)

In 1987, toward an effort to find inhibitors of arginine vasopressin binding, Schwartz and coworkers isolated two structurally unusual indolinones from the cells of a cultured cyanobacterium belonging to the genus Fischerella (ATCC 53558).[9] Hapalindolinones A and B (Figure 5, **30** and **31**) were structurally characterized by NMR, IR and mass spectral analysis. Absolute configuration of hapalindolinone A was established by single crystal X-ray diffraction. These indolinones were unusual by virtue of a spiro-fused cyclopropane ring system, yet resembled the hapalindoles bearing an isonitrile group and the basic terpene unit.

[8] Moore, R. E.; Cheuk, C.; Yang, G. Xu-Q.; Patterson, G. M. L. J. Org. Chem. **1987**, *52*, 3773-3777.
[9] Schawrtz, R. E.; Hirsch, C. F.; Springer, J. P.; Pettibone, D. J.; Zink, D. L. *J. Org. Chem.* **1987**, *52*, 3704-3706.

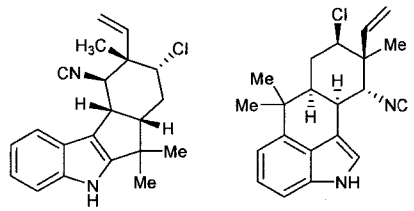


hapalindolinone A (**30**) hapalindolinone B (**31**)

Figure 5. Structures of cyclopropane containing oxindoles – hapalindolinone A (30) and B (31)

1.2.3. Fischerindole Alkaloids

In 1992, Moore and coworkers reported the isolation of fischerindole L (**32**) (Figure 6), a novel octahydroindeno [2,1,-b] indole isonitrile from the terrestrial cyanophyte *Fischerella muscicola* that possesses the same relative stereochemistry as hapalindole L (**19**).[5] This observation leads to the speculation about the biogenetic pathways shared by the organisms producing these structurally diverse natural products.

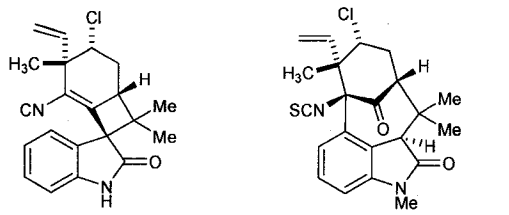


fischerindole L (**32**) hapalindole L (**19**)

Figure 6. Structures of fischerindole L (32) and hapalindole L (19)

1.2.4. Welwitindolinone Alkaloids

A search of the lipophilic extracts of *Hapalosiphon welwitschii* W. and G. S. West (UH strain IC-52-3, Stigonemataceae) resulted in identification of seven oxindole-containing natural products along with other fischerindoles and hapalindoles by Moore and coworkers in 1994.[6] Figure 7 shows the assigned structures of two of the most biologically active oxindoles isolated from this cyanophyte.

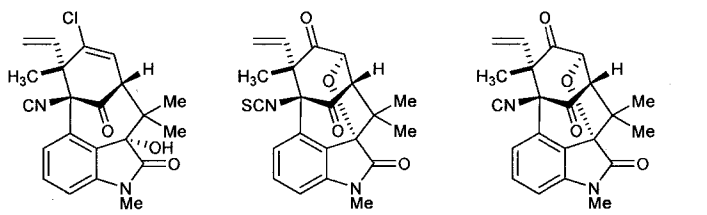


welwitindolinone A isonitrile (**33**) *N*-methyl welwitindolinone C isothiocyanate (**34**)

Figure 7. Structures of welwitindolinone A isonitrile (**33**) and *N*-methyl welwitindolinone C isothiocyanate (**34**)

Welwitindolinone A isonitrile (**33**) was found to possess antifungal properties and its structure was elucidated using spectral data. *N*-Methyl welwitindolinone C isothiocyanate (**34**) showed P-glycoprotein-mediated multiple-drug-resistance (MDR) reversing activity at doses as low as 0.1 μM in a vinblastine resistant subline. *N*-Methyl welwitindolinone C isothiocyanate was also isolated from *Westiella intricata* Borzi UH HT-29-1 and was responsible for most of the insecticidal properties of this cyanophyte. *N*-Methyl welwitindolinone C isothiocyanate was structurally characterized using spectral data and its absolute configuration was determined by X-ray crystallography.

In 1999, Moore and coworkers reported the isolation of three new alkaloids from *Fischerella muscicola* (Thuret) Gomont (HG-39-5) and *Fischerella major* Gomont (HX-7-4) that possess a 3-hydroxy welwitindolinone framework (Figure 8, **35-37**).[10] These products are believed to result from singlet oxidation of welwitindolinones isolated previously. Significantly, among the eight alkaloids isolated from this extract, one of them was 12-*epi*-fischerindole I suggesting there could be a common biogenesis for these indole alkaloids in the cyanobacteria.



3-hydroxy-*N*-methyl welwitindolinone C isonitrile (**35**) 3-hydroxy-*N*-methyl welwitindolinone C isothiocyanate (**36**) *N*-methyl welwitindolinone D isonitrile (**37**)

Figure 8. Structures of oxidized welwitindolinones 35, 36 and 37

[10] Jimenez, J. I.; Huber, U.; Moore, R. E.; Patterson, G. M. L.; *J. Nat. Prod.* **1999**, *62*, 569-572.

1.3. Biological Activity of Ambiguines and Other Related Alkaloids

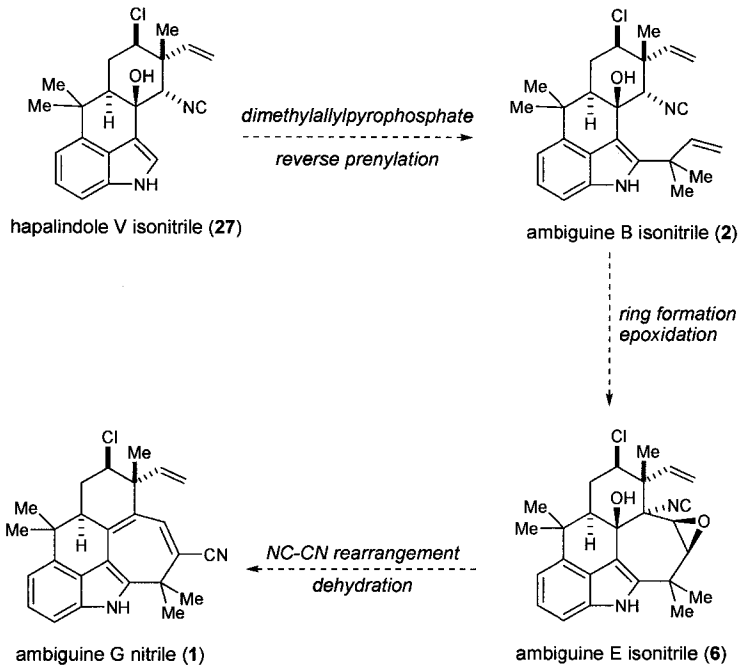
Ambiguines generally possess antifungal activity. The fungicidal activity of ambiguines A-F (**2-7**) is about 2-8 times more potent than hapalindoles G (**14**) and H (**15**). However, ambiguines are less active when compared to clinically used fungicides such as amphotericin B and tolnaftate.[1] Hapalindoles are moderately potent fungicides, and hapalindole A isonitrile (**8**) was determined to be responsible for most of the antialgal and antimycotic activity of *Hapalosiphon fontinalis*.[4] Hapalindolinone A (**30**) was found to inhibit the binding of [^{3}H] arginine vasopressin to kidney tissue with an IC_{50} of 37.5 ± 7.6 μM. This compound also inhibits kidney arginine vasopressin stimulated adenylate cyclase with an IC_{50} of 44.6 μM.[9] Fischerindole L (**32**) was isolated from extracts that possessed antifungal properties however its individual potency was not measured.[5] Welwitindolinone A isonitrile (**33**) possesses antifungal properties.[6] Welwitindolinone C isothiocyanate (**34**) however reverses P-glycoprotein-mediated multiple-drug-resistance (MDR) in a vinblastine resistant subline of a human ovarian adenocarcinoma line. Interestingly the corresponding isonitrile version (**33**) does not possess this biological activity.[6]

1.4. Biosynthesis of Ambiguines and Related Alkaloids

Owing to the structurally diverse nature of the different families of alkaloids, it would be interesting to speculate that ambiguines, hapalindoles, fischerindoles, and welwitindolinones probably share common biosynthetic pathways. The exact intermediates involved in the ambiguine G biosynthesis however are not yet known. Scheme 1 outlines the possible biogenesis of ambiguine G nitrile (**1**) from hapalindole V (**27**). Ambiguine G nitrile (**1**) can be speculated to be a rearrangement product of ambiguine E isonitrile (**6**). The exact mechanism of this rearrangement is not known. This step would also have to accompany dehydration to generate the polyolefinic system in ambiguine G. Ambiguine E isonitrile (**6**) may be biosynthesized via the corresponding

tetracyclic ambiguine B isonitrile (**2**). The tetracyclic ambiguines can be derived from hapalindole V isonitrile (**27**) through a reverse-prenylation event at C-2 of the indole ring.

Scheme 1. Probable biosynthetic pathway for ambiguine G nitrile (1)



Prenylation and reverse prenylation of indoles is a well known process. Natural products like gypsetin,[11] stephacidins,[12] and tryprostatin B[13] which contain prenylated indole rings are produced by other organisms. *In vivo*, this prenylation occurs *via* nucleophilic displacement on dimethylallylpyrophosphate (**39**) by the electron rich indole ring (**38**) (Scheme 2). Direct attack of the nucleophile in a S_N2 fashion leads to prenylated indole **40**. An S_N2' fashion leads to reverse-prenylated indole **41**. The biosynthetic pathway that produces dimethylallylpyrophosphate, the electrophile for prenylation, is known to originate from acyl-CoA *via* mevalonic acid as an intermediate.[14]

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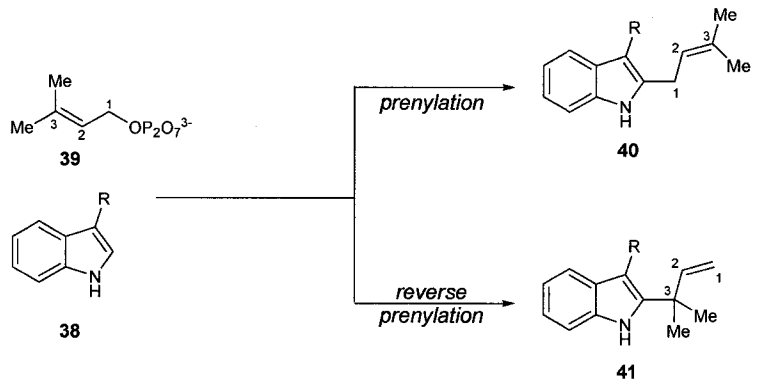
[11] Schkeryantz, J. M.; Woo, J. C. G.; Danishefsky, S. J. *J. Am. Chem. soc.* **1995**, *117*, 7025.
[12] Nussbaum, F. V. *Angew. Chem. Int. Ed.* **2003**, *42*, 3068-3071.
[13] Depew, K. M.; Danishefsky, S. J.; Rosen, N.; Sepp-Lorenzino, L. *J. Am. Chem. soc.* **1996**, *118*, 12463.
[14] John Mann in "Chemical Aspects of Biosynthesis" Oxford Science Publications; Ed. Davies, S. G. **1994**, *Ch. 4*. pp. 32-33.

Scheme 2. Biosynthesis of prenylated and reverse-prenylated indole rings



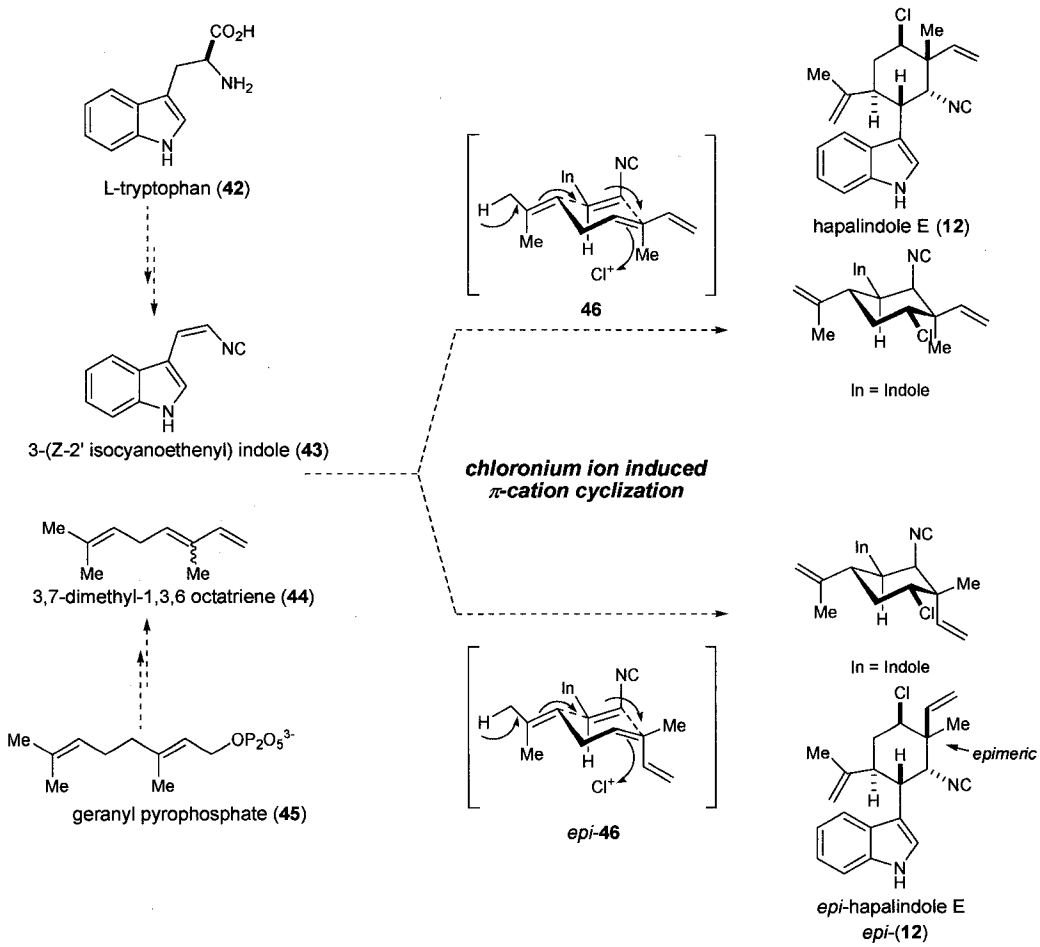
The proposed biogenetic pathway to hapalindoles involves a chloronium ion-induced enzyme-mediated π-cation cyclization that produces the six-membered ring bearing the chlorine atom, the vinyl substituted quarternary carbon, the isonitrile functionality, the indole ring and the isopropenyl group (Scheme 3).[5,6] The suitable precursors for this cyclization are believed to be 3-((Z)-2'-isocyanoethenyl) indole (**43**)[15] which is derived from L-tryptophan (**42**). 3,7-Dimethyl-1,3,6-octatriene (**44**) is known to be derived from geranyl pyrophosphate (**45**). Triene **44** in the presence of a chloronium ion is then pre-disposed to undergo a [4+2] annulation with the olefin in **43** through a 6-membered transition state **46** resulting in hapalindole E isonitrile (**12**). This pathway provides a very flexible route toward a variety of stereochemistry in the product indolo-terpenoid. For example, alternate olefin geometry in *epi*-**46** leads to 12-*epi*-hapalindole E isonitrile (*epi*-**12**). This is a powerful enzymatic way to assemble the variety of hapalindoles that are produced by Nature.

The exact biogenetic source of the isonitrile functionality has been studied intensely. Isonitriles have been identified in other fungi and marine sponges.[16] In the case of hapalindole A (**8**), it has been shown that the isonitrile group is derived from glycine and cyanide as precursors.[17] The origin of the thiocyanate group is, however, less clear,

[15] 3-((Z)-2'-isocyanoethenyl) indole (antibiotic B371) has been isolated from a *pseudomonas Sp.*" Evans, J. R.; Napier, E. J.; Yates, P. *Antibiotics*, **1976**, *19*, 850.
[16] Hagadone, M. R.; Scheurer, P. J.; Holm, A. *J. Am. Chem. Soc.* **1984**, *106*, 2447.
[17] Bornemann, V.; Patterson, G. M. L.; Moore, R. E.; *J. Am. Chem. Soc.* **1988**, *110*, 2339.

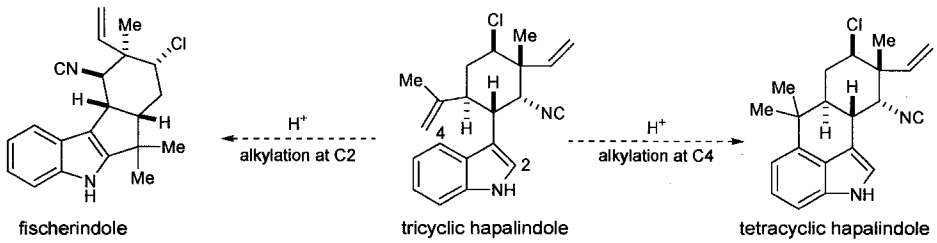
but is speculated to arise directly from inorganic thiocyanate or indirectly by introduction of a sulfur atom into an intermediate organic isonitrile.

Scheme 3. Proposed biogenetic pathway to hapalindoles through a π–cation cyclization



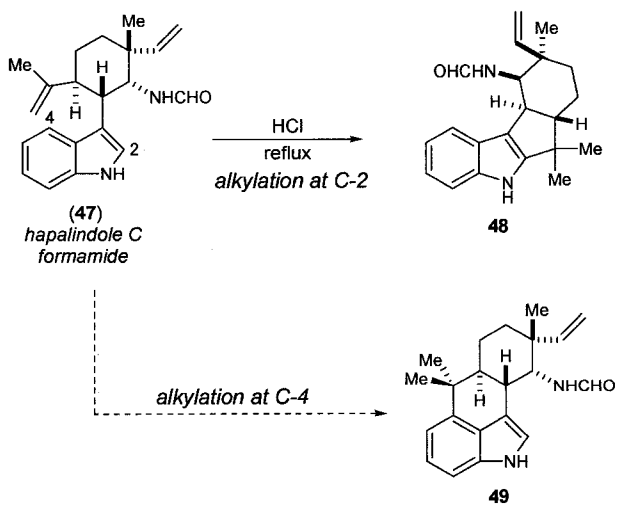
Enzyme mediated assembly of tetracyalic hapalindoles and fischerindoles from the corresponding tricyclic hapalindole framework can be envisioned to occur by simply controlling the site of alkylation of the indole ring as outlined in Scheme 4.

Scheme 4. Proposed biogenesis of fischerindoles and hapalindoles from same precursor



Speculation that an acid-mediated cyclization of tricyclic hapalindoles provides the fischerindole core was confirmed by *in vitro* experiments.[18] When the corresponding formamide of the tricyclic hapalindole C (**47**) was subjected to acid, the cyclized product **48** containing the fischerindole framework was formed (Scheme 5). This observation provides support for the hypothesis that an enzyme controlled cyclization of the isopropenyl group onto C-2 of the indole might be operative in the biogenetic pathway. Such an enzyme controlled cyclization of the isopropenyl group to C4 of the indole would lead to formation of **49** with the hapalindole framework (Scheme 5). Though biogenetically different, the similarity of the C4 alkylated tetracyclic alkaloids to those of the ergot alkaloid family is noteworthy.

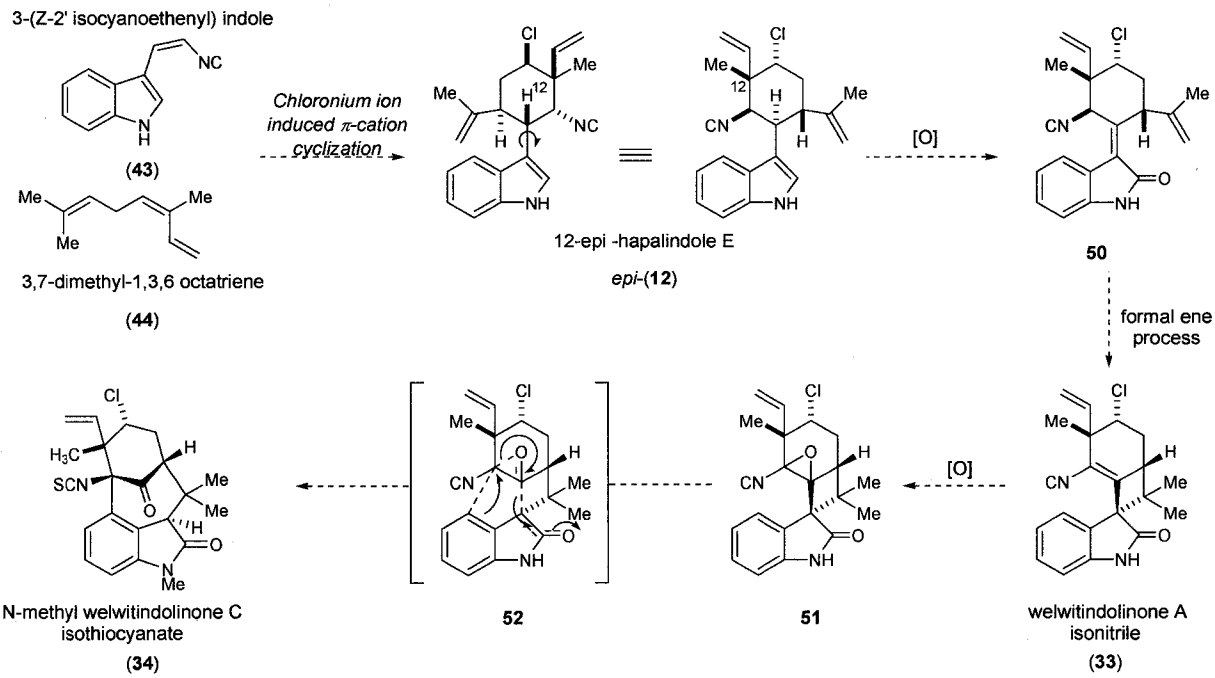
Scheme 5. Formation of fischerindole skeleton under acidic treatment of hapalindole C formamide



[18] Bonjouklian, R.; Moore, R. E. and Patterson, G. M. L. *J. Org. Chem.* **1988**, *52*, 5866-5870.

The exact biosynthetic pathway for the formation of welwitindolinone backbone is not yet clear. However, the speculated sequence of steps is shown in Scheme 6. The stereochemistry of the substituents in the six membered terpenoid-derived ring in welwitindolinones is exactly the same as in hapalindoles and ambiguines, except for the C12 quarternary center. In welwitindolinones, this center is epimerized. Thus, 12-epi-hapalindole E isonitrile (*epi*-**12**) could be envisioned as a viable biogenetic precursor to the welwitindolinones.[19]

Scheme 6. Possible biosynthetic route to welwitindolinone skeleton from hapalindole



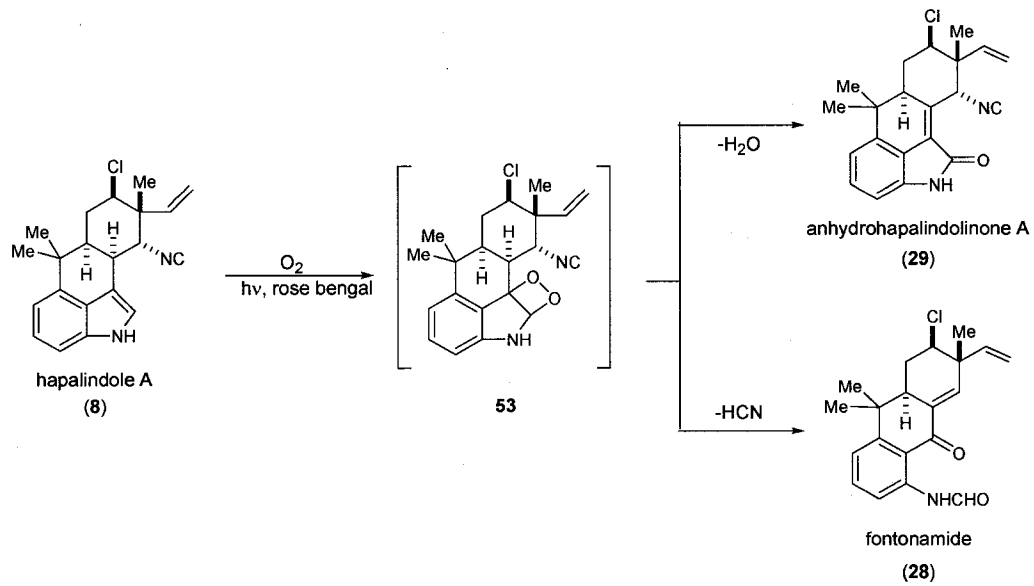
Once 12-epi-hapalindole is formed via a chloronium ion induced π-cation cyclization, the resulting indole could be oxidized to the corresponding oxindole **50**. This oxidation is a well known process in the biogenesis of oxindoles. Oxindole **50** then could undergo a formal ene reaction to give the welwitindolinone A isonitrile (**33**). It is not unreasonable to expect this molecule to be very reactive toward molecular oxygen, due to the presence

[19] In fact, 12-*epi*-hapalindole is the second most abundant alkaloid isolated from *H. welwitschii*.

of a very strained bridgehead olefin, thereby giving a transient epoxide **51**. This highly strained epoxide could undergo a ring-opening step to give the stable welwitindolinone C isonitrile, which then is converted to the corresponding isothiocyanate (**34**).

Enzyme-mediated oxidation of indoles by singlet oxygen also plays a major role toward the biosynthesis of oxindole type alkaloids such as hapalindolinones and welwitindolinones. Scheme 7 outlines the formation of oxidized hapalindoles which were isolated from *Hapalosiphon fontinalis*. The speculation of an enzyme-mediated oxidation of hapalindole to give anhydro-hapalindolinone A isonitrile (**29**) and fontonamide (**28**) was confirmed by their formation from hapalindole A isonitrile (**8**) upon its exposure to molecular oxygen, traces of rose bengal, and light. Apparently, this transformation proceeds through a 4-membered oxo-adduct **53**. The fate of this intermediate is dictated by the mode of its opening leading to either fontonamide **28** or the hapalindolinone A **29**.

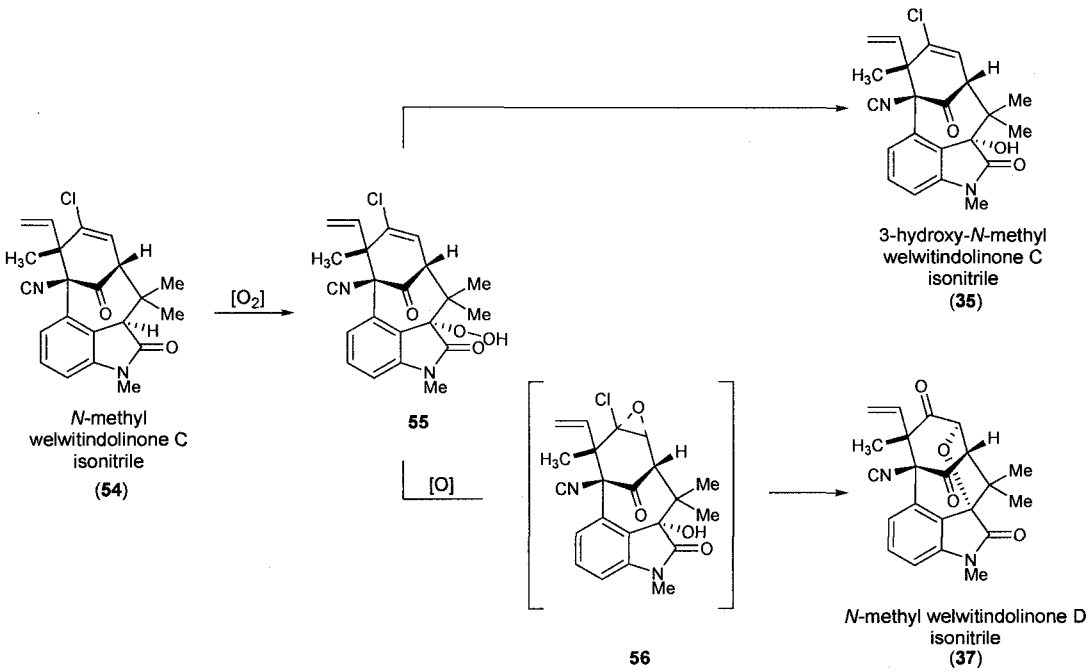
Scheme 7. Oxidation of hapalindole leading to hapalindolinone and fontonamide



Similar singlet oxygen-mediated indole oxidation is also operative in welwitindolinone alkaloids (Scheme 8). 3-Hydroxy-N-methylwelwitindolinone C isonitrile (**35**), which is isolated from *Fischerella spp.* is shown to be a product of photooxidation of N-methylwelwitindolinone C isonitrile (**54**) going through the peroxy intermediate **55**. The

same intermediate **55** could alternatively undergo further epoxidation to give **56**. This is followed by opening of the epoxide intramolecularly which can then lead to the novel cyclic ether in N-methylwelwitindolinone D isonitrile (**37**), which is also a constituent found in *Fischerella spp.*[10]

Scheme 8. Oxidation pathways in welwitindolinones

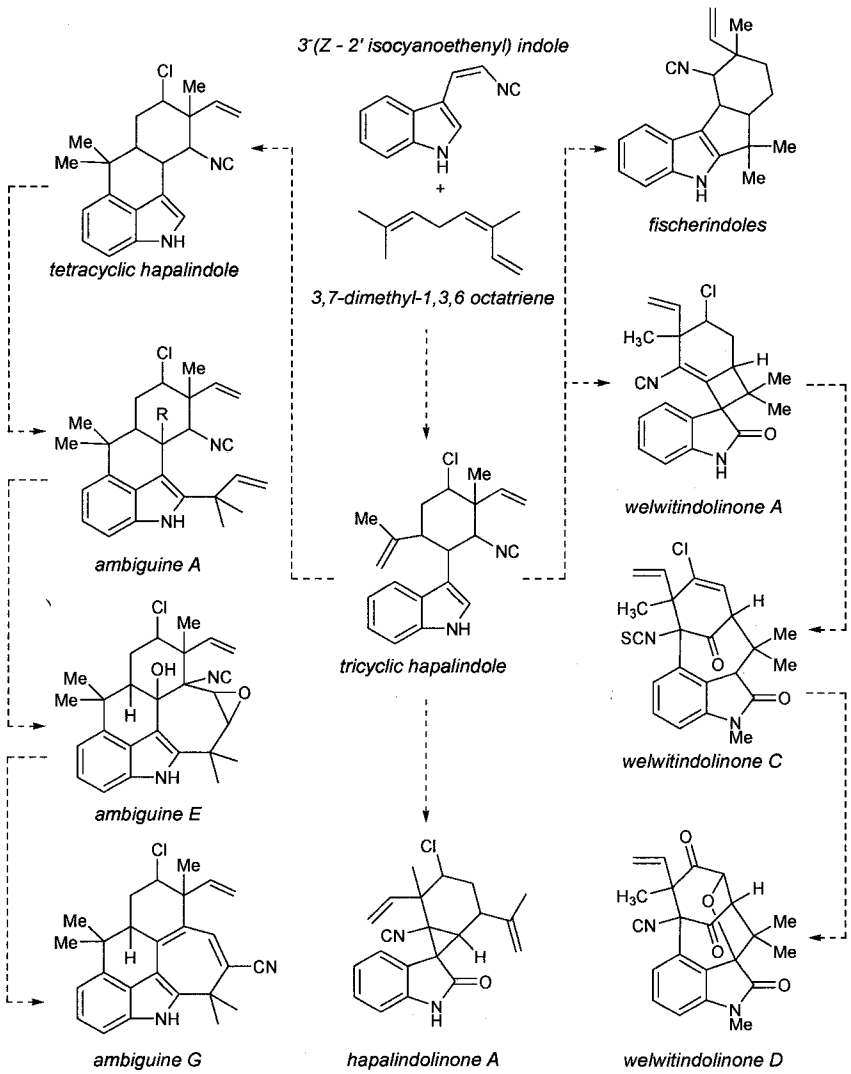


The following scheme outlines the summary of basic structural transformations beginning from easily derived starting materials that result in the bio-synthesis of hapalindoles, ambiguines, fischerindoles and welwitindolinones.[20] In summary, biogenetic relationships based on enzyme-mediated processes can relate a variety of indolo-terpenoid natural product families into a finite number of transformations, eventually giving rise to a diverse number of structures. The diversity is also increased through rearrangements and stereoselective transformations that give rise to different ring skeletons or diastereomerically related compounds within one ring skeleton. Studies on

[20] Note: Since the emphasis is on skeletal arrangements, stereochemistry is not shown in the natural product structures.

the biosynthesis of these alkaloids are not extensive and are still an active topic of research.

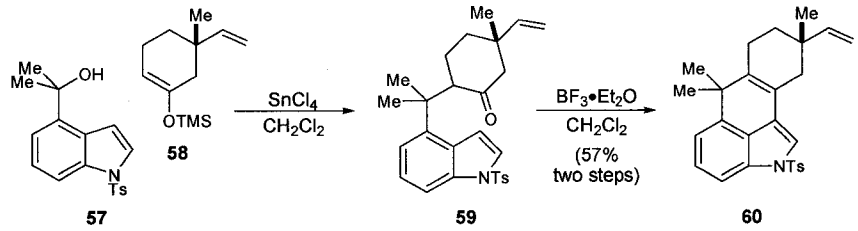
Scheme 9. Outline of skeletal transformations leading to different family of alkaloids



1.5. Previous Syntheses and Approaches toward Ambiguines and Related Alkaloids

The polycyclic structural framework and their functional group arrays render the ambiguines and welwitindolinones synthetically challenging targets. No member of the ambiguine or welwitindolinone alkaloid family has been synthesized to-date. However, initial studies and synthesis of the oxindole skeleton of welwitindolinones have been reported.[21] Several hapalindoles have been synthesized. Some of the early synthetic efforts in this field came from the laboratories of Natsume. Their concise approach was based on a two-step construction of the C-ring of the tetracyclic hapalindoles, which is outlined in Scheme 10. Tertiary alcohol **57** was readily prepared and treated with silyl-enol ether **58**[22] under tin (IV) Lewis acid condition at low temperature to afford the α-alkylated ketone **59** as the coupled product. This ketone cyclized when subjected to a stronger Lewis acid (BF_3•Et_2O) to give the olefin **60** which contains the tetracyclic framework of hapalindoles. This general strategy was elegantly utilized toward the synthesis of hapalindoles J, M, H, U and O.

Scheme 10. Natsume's general approach to the tetracyclic skeleton of hapalindoles



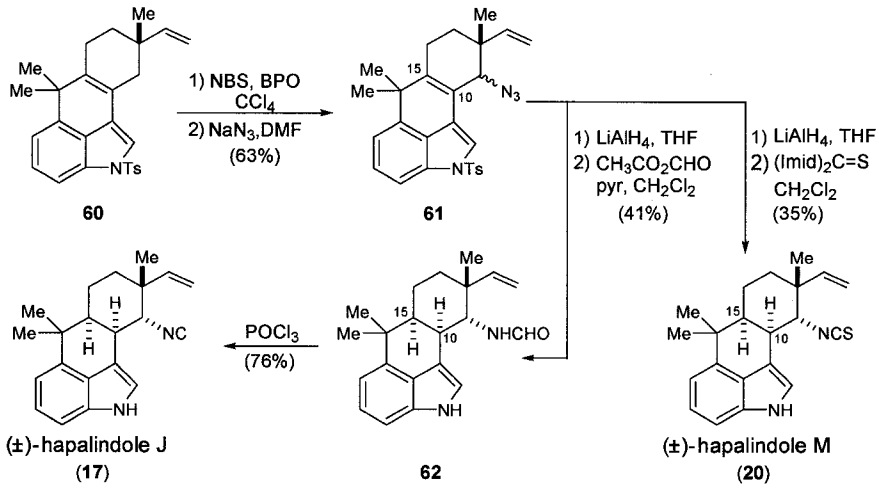
Natsume's Synthesis of (±)-hapalindole J and M

The tetracyclic indole framework in **60** built using the above mentioned strategy served as a common intermediate *en route* to hapalindole J and M (Scheme 11).[23,24] The

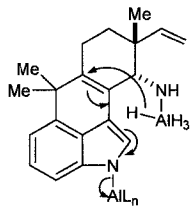
[21] Ready, J. M.; Reisman, S. E.; Hirata, M.; Weiss, M. M.; Tamaki, K.; Ovaska, T. V.; Wood J. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1270 and reference #2 therein.
[22] The silyl enol ether (**58**) was a 5:2 mixture of regioisomers. However the product derived from the minor enol ether is unreactive in the sequence, and hence ignored for this discussion.
[23] Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1989**, *30*, 1815
[24] Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6331.

necessary C11 nitrogen atom in the D-ring was introduced through radical-mediated bromination, followed by displacement of the bromide with sodium azide to give **61**.

Scheme 11. Natsume's route to hapalindole J and hapalindole M



While the α-isomer was desired, the ratio of α:β isomers at the azido carbon was 1:1. The crucial issue of *cis* stereochemistry of the hydrogens at the ring junction (C10 and C15, Scheme 11) was set in an unexpected fashion. Attempts to reduce the azido group to the amine using lithium aluminum hydride, resulted in three transformations.[25] First, the azido group underwent reduction. Second, the tosyl group was displaced. Third, there was a reduction of the tetrasubstituted olefin in a cis fashion, presumably through an *N*-indolyl aluminum species formed *in situ* (see inset). This series of changes resulted in the amine which upon formylation gave **62**. The diastereoselectivity of this remote reduction seems to be controlled by the amido species resulting from the reduction of the azido group. Overall, this multiple reduction served as a very useful transformation and led to the expedient completion of the syntheses. Dehydration of **62** using phosphoryl chloride led to (±)-hapalindole J (**17**) in an overall seven step sequence. Alternatively, isothiocyanate formation from the resulting amine directly afforded (±)-hapalindole M (**20**) in an overall six step sequence (number of steps being counted from



[25] Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6343.

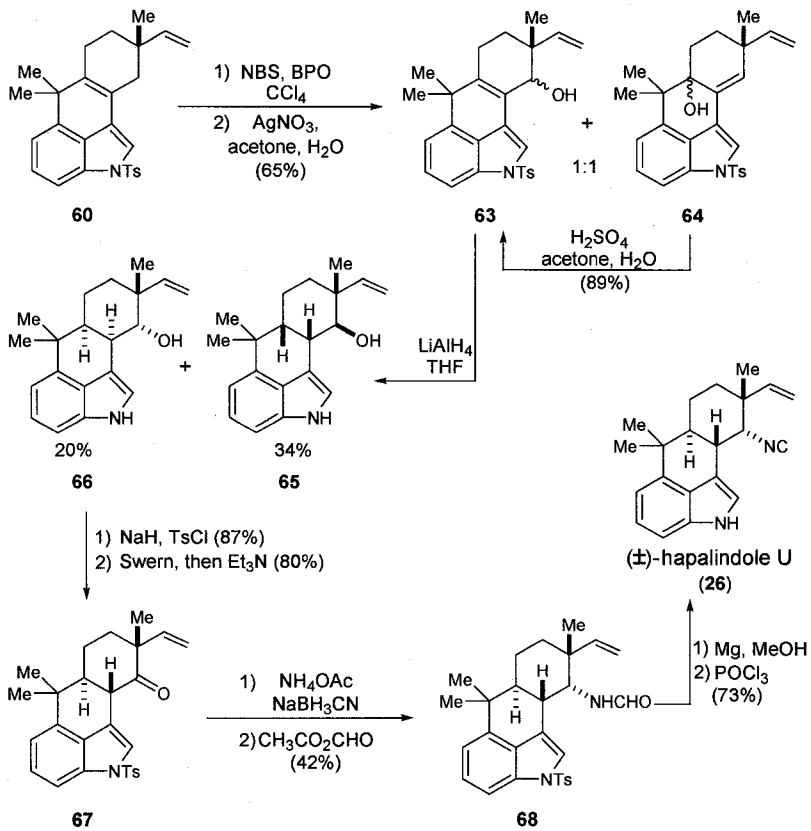
the easily accessed indole derivative **57**. The conciseness of this sequence compensates for the shortcomings of the sequence which are mainly i) nonstereoselecive azide introduction, and ii) the low yield in LAH reduction step.

Natsume's Synthesis of (±)-hapalindole H and U

Hapalindoles H (**15**) and U (**26**) differ from the J and M versions in having a C10-C15 *trans* ring junction. For hapalindole U, Natsume and co-workers undertook this challenge with their original strategy that sets the ring junction in a *cis* fashion however, chose to epimerize C10 at a later stage in order to set the *trans* stereochemistry. A ketone functionality at C11 worked out to be optimal for epimerization to the *trans* stereochemistry at C10 (Scheme 12). Application of a bromination-hydroxylation sequence to indole **60** resulted in a mixture of regioisomeric alcohols **63** and **64**. The undesired alcohol could be transformed into the desired one under acidic conditions. Reduction under the peculiar lithium aluminum hydride conditions furnished a set of *cis*-fused decalins- β isomer **65** and α isomer **66** in 34% and 20% yield respectively. Only the α isomer **66** was useful. Oxidation of the alcohols at the unprotected indole stage did not proceed well. Therefore the indole nitrogen was protected with tosyl chloride. Swern oxidation and treatment with triethylamine effectively epimerized the C10 center to give the thermodynamically more stable ketone **67** possessing the necessary *trans* C10-C15 junction. Completion of the synthesis involved a reductive amination to introduce the nitrogen at C10 followed by formylation to give **68**. Isonitrile formation resulted in (±)-hapalindole U isonitrile (**26**).[26] Overall this sequence proceeded in 11 steps from the readily accessible indole derivative **57**.

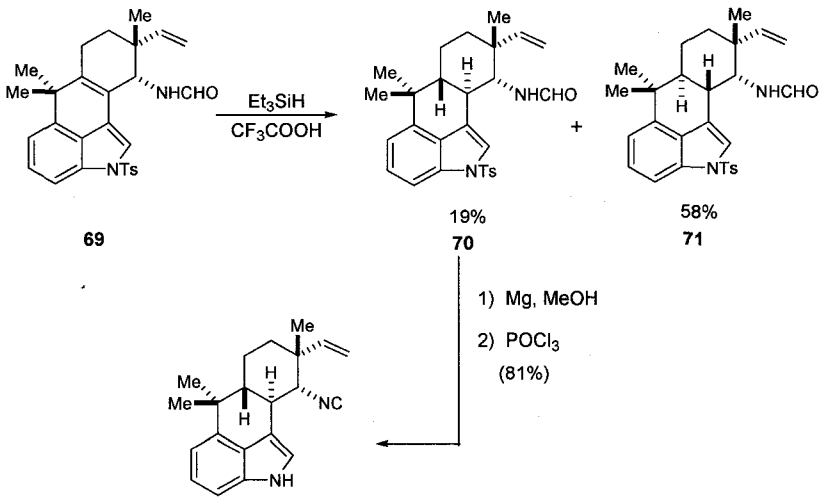
[26] Muratake, H.; Kumagami H.; Natsume, M. *Tetrahedron* **1990**, *46*, 6351.

Scheme 12. Natsume's synthesis of hapalindole U isonitrile



The *trans* ring fusion in hapalindole H isonitrile was formed using an alternative reduction step. The following scheme outlines their approach. The N-Formyl group was introduced to give the tetracyclic olefin **69**. Subjection of **69** to triethylsilane in trifluoroacetic acid resulted in a mixture of diastereomeric *trans*-fused compounds **70** and **71** in 19% an 58% yields respectively. Although, **70** was formed in lower yield, it was sufficient to complete the synthesis. Deprotection of the tosyl group and isonitrile formation resulted in (±)-hapalindole H isonitrile (**17**) in an overall 9 step sequence from readily prepared indole derivative **57**.

Scheme 13. Natsume's synthesis of hapalindole H isonitrile

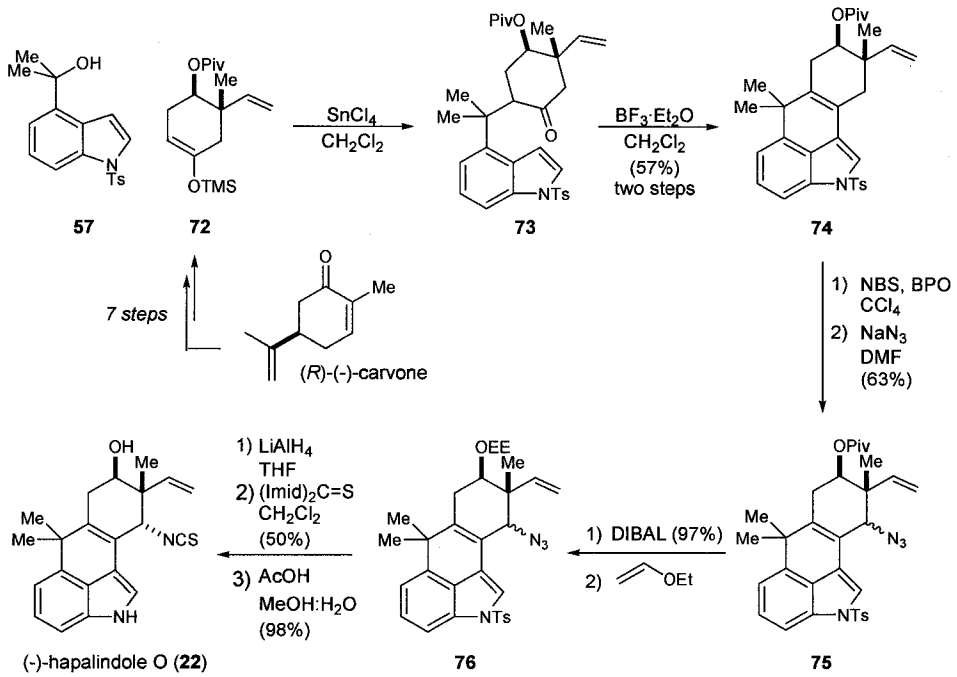


Natsume's Enantiospecific Synthesis of (–)-hapalindole O

Natsume and coworkers reported the first enantiospecific synthesis of (–)-hapalindole O by slight modification of their original strategy (Scheme 14).[27] Instead of using a racemic silylenol ether as in the previously discussed approaches, an enantioenriched silylenol ether (**72**) was used. This was prepared from the readily available (*R*)-(–)-carvone. Coupling of this silylenol ether with indole **57** proceeded in 67% yield (based on recovered starting material) to give **73**. The intramolecular cyclization of the ketone (**73**) under boron trifluoride proceeded in 66% yield to afford the enantioenriched carbon skeleton of hapalindole O in the form of **74**. Introduction of nitrogen functionality at C11 was followed by regular protecting group manipulations to complete the enantiospecific synthesis of (–)-hapalindole O in 9 steps overall from the readily available silylenol ether (**72**). To date, this is the only report of a synthesis of an C13-oxygenated hapalindole.

[27] Sakagami, M.; Muratake, H.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 1393.

Scheme 14. Natsume's enantiospecific synthesis of (–)-hapalindole-O



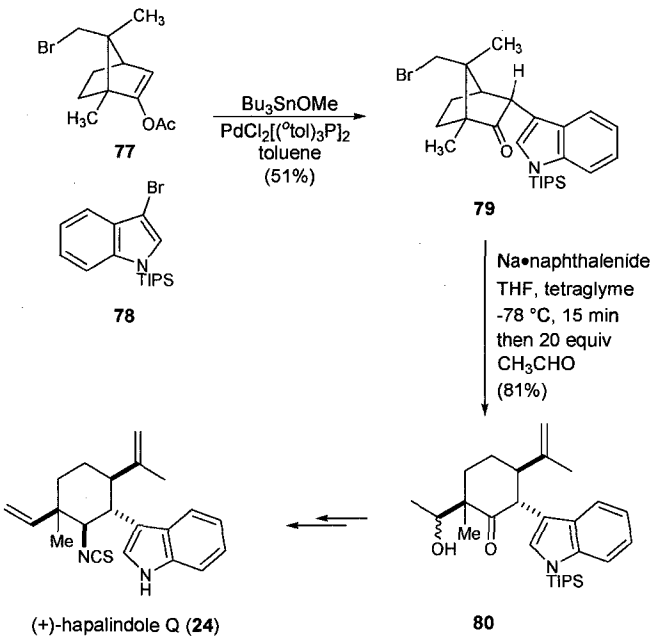
Albizati's Enantiospecific Synthesis of (+)-hapalindole Q

In 1993, Albizati and coworkers reported a very elegant and concise strategy to build the tricyclic hapalindole core from a brominated camphor derivative (Scheme 15).[28] The key bond forming reactions were i) α-arylation of bromocamphor derived enolacetate **77** with 3-bromo indole **78** under Kosugi-Migita conditions[29] to give selectively the endo diastereomer (**79**), ii) ring opening fragmentation of this bromoketone under reducing conditions to give an enolate which is trapped by acetaldehyde from the axial face to give the aldol adduct **80** in excellent yield. These two steps effectively built the carbon skeleton of hapalindole Q. Reductive amination and isothiocyanate formation gave the natural product in 8 steps overall from the camphor derivative (**77**). Since this was the first enantioenriched synthesis of any hapalindole, it

[28] Vaillancourt, V. Albizati, K. F. *J. Am. Chem. Soc.* **1993**, *115*, 3499.
[29] (a) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita.T. *J. Chem. Soc., Chem. Commun.* **1983**, 344. (b) Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita.T. *Bull. Chem. Soc. Jpn.* **1984**, 57, 242.

allowed confirmation of the absolute stereochemistry of the natural product. It was found that all reported data matched that of the synthesized material.

Scheme 15. Albizati's enantiospecific synthesis of (+)-hapalindole Q



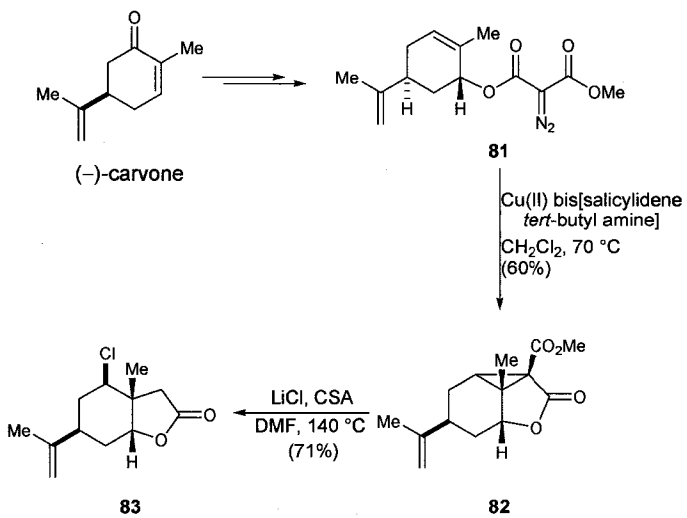
Fukuyama's Enantiospecific Synthesis of (–)-hapalindole G

Prior to 1994, there were no syntheses of chlorine atom containing hapalindoles. Fukuyama reported the first enantiospecific synthesis of chlorine containing (–)-hapalindole G.[30] Highlights of this synthetic sequence are i) the stereosepecific fashion in which the chlorine atom was installed, and ii) a novel method for indole ring construction. Scheme 16 outlines the steps leading to the stereospecific installation of the chlorine atom. Diazo compound **81** was prepared in straightforward fashion from (–)-carvone. A copper (II)-mediated intramolecular cyclopropanation led to **82**. This cyclopropane underwent regio and stereo-specific opening under lithium chloride and camphor sulphonic acid to give the chloride in **83**. A Krapcho decarboxylation of the methyl ester also occurred in the same step. The regioselectivity was dictated by the

[30] Fukuyama, T.; Chen, X. *J. Am. Chem. Soc.* **1994**, *116*, 3125.

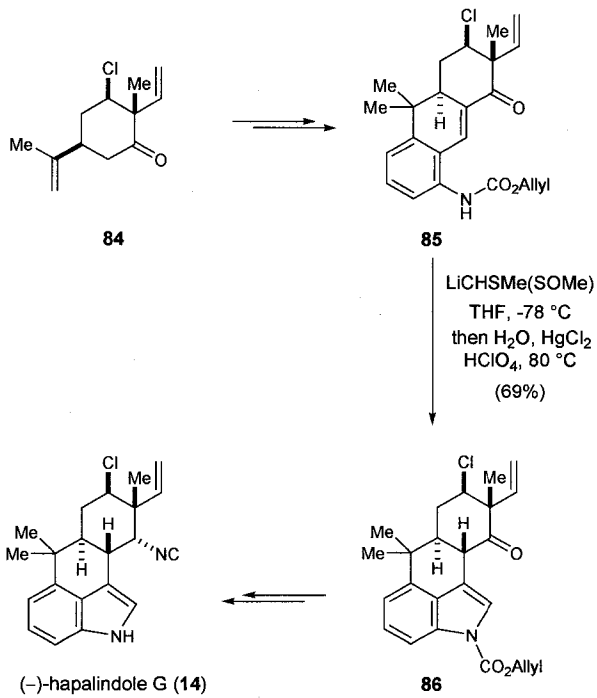
methyl group on the adjacent carbon preventing attack of the chloride anion on an otherwise susceptible carbon. The stereospecificity of chloride attack arose from the reaction conditions that favor an S_N2 mechanism.

Scheme 16. Fukuyama's enantiospecific synthesis of (–)-hapalindole G – installation of chlorine



The chlorine containing lactone **83** was converted into ketone **84** through straightforward transformations. This ketone possesses the quarternary carbon with the methyl and vinyl substituents in proper stereochemistry. This ketone was transformed into tricyclic enone **85** to set the stage for the key indole forming step (Scheme 17). Enone **85** was homologated and the adduct was treated with mercuric chloride/ perchloric acid to give indole **86** in 69% yield. This step effectively completed the carbon skeleton in (–)-hapalindole G. Reductive amination and conversion of the resulting amine into the isonitrile functionality furnished (–)-hapalindole G. The overall sequence was 19 steps from (–)-carvone. This effort is impressive for the fact that it is the only synthesis of a chlorine containing hapalindole reported to date.

Scheme 17. Fukuyama's novel indole construction strategy



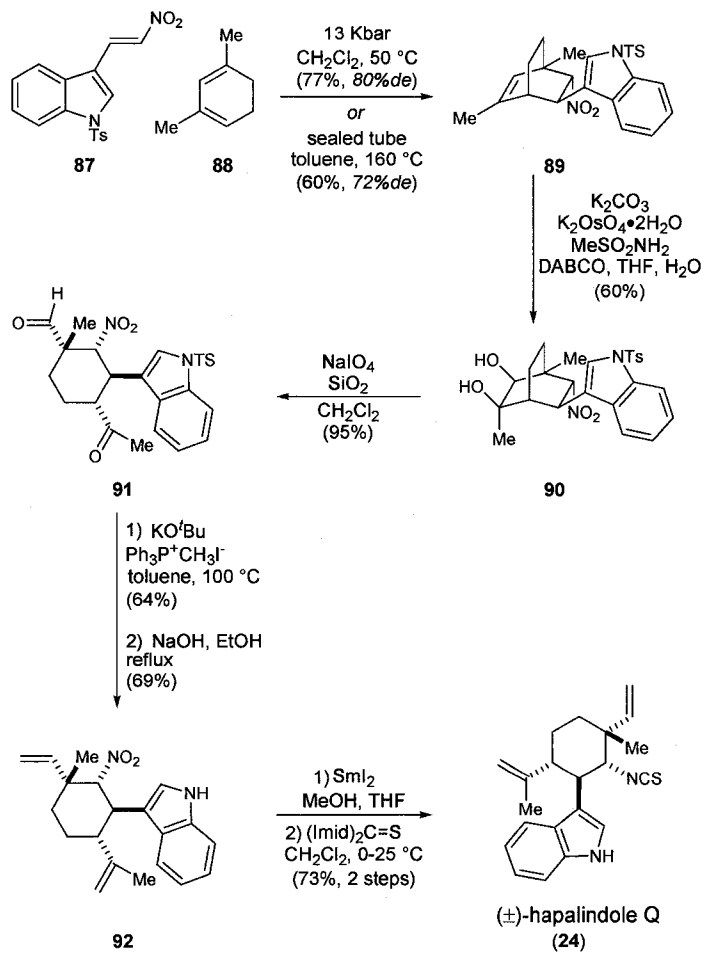
Kerr's Synthesis of (±)-hapalindole Q

Kerr and coworkers reported the racemic synthesis of hapalindole Q isothiocyanate in 2001.[31] Although it was a racemic synthesis, the sequence included a Diels-Alder reaction, which was potentially amenable to be executed enantioselectively (Scheme 18). Tosyl protected α,β-unsaturated nitroindole **87** underwent a Diels-Alder reaction with 1,3-dimethylcyclohexadiene (**88**) under high pressure or sealed tube conditions to give the endo-adduct **89** in moderate selectivity (~7:1) and good yield. Dihydroxylation under standard conditions gave **90**. This was followed by cleavage of the diol resulting in keto aldehyde **91**. This was treated with Wittig reagent followed by deprotection of the tosyl group to give nitro indole **92** which essentially contained all the carbons of hapalindole Q. Completion of the synthesis involved a samarium diiodide-mediated reduction of the nitro group to the corresponding amine which was transformed

[31] Kinsman, A. C.; Kerr, M. A. *Org. Lett.* **2001**, *3*, 3189.

into the isothiocyanate to give (±)-hapalindole Q. This sequence consisted of only seven steps starting from nitroindole **87**.

Scheme 18. Kerr's approach to (±)-hapalindole Q via a Diels-Alder reaction

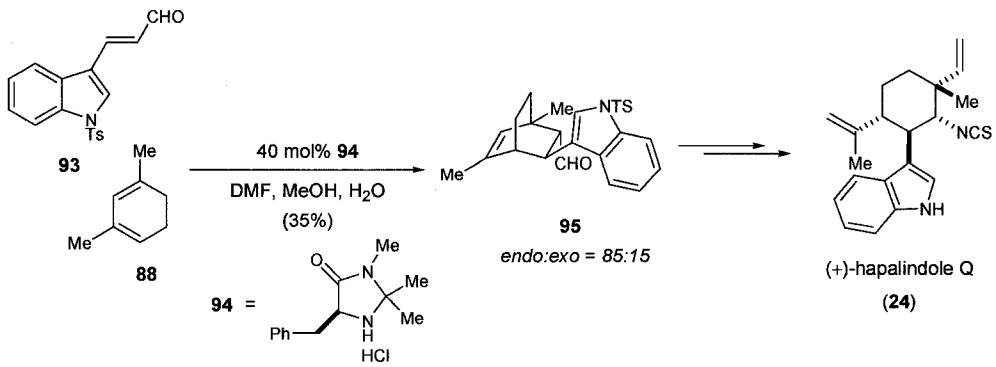


The same strategy was later applied toward an enantioselective synthesis of (+)-hapalindole Q isothiocyanate.[32] The key enantioselective Diels-Alder reaction is outlined in Scheme 19. The dienophile component was modified to aldehyde **93**. For the Diels-Alder reaction, Macmillan's organocatalytic conditions were applied using catalyst **94** which resulted in the *endo* adduct **95** through an iminium species of the aldehyde reacting with dimethyl cyclohexadiene **88**. Although the reaction proceeded with excellent enantioselectivity (*endo*, 93% ee), the diastereoselectivity (85:15 *endo*:*exo*) and yield

[32] Kinsman, A. C.; Kerr, M. A. *J. Am. Chem. Soc.* **2003**, *125*, 14120.

(35%) were only moderate. Adduct **95** was then transformed into the natural product using essentially the same pathway as in the racemic version. The overall sequence was 12 steps from 3-formylindole.

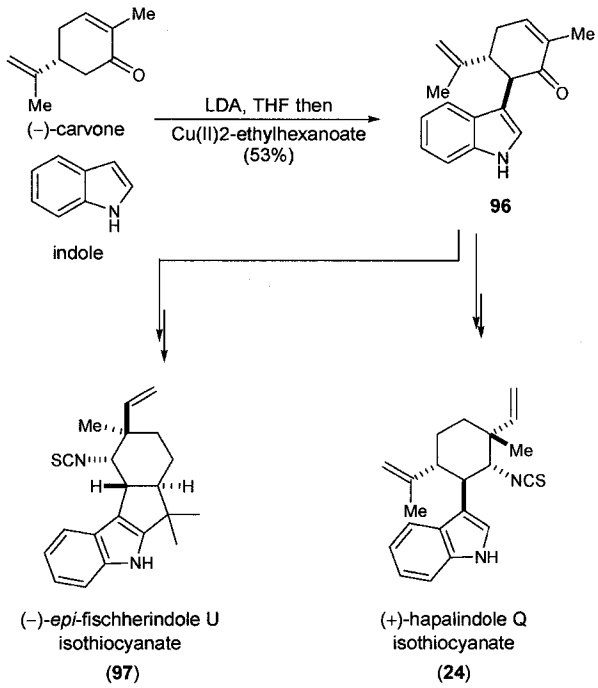
Scheme 19. Enantioselective Diels-Alder reaction toward (+)-hapalindole Q



Baran and co-workers recently reported a very direct approach to the tri-cyclic hapalindole core. This approach was successfully implemented in the enantiospecific synthesis of (+)-hapalindole Q isothiocyanate and (–)-12-epi-fischerindole U isothiocyanate.[33] The strategy relied on a key coupling reaction of indole to an enolate derived from (–)-carvone, under redox conditions as outlined in Scheme 20. Thus treatment of the enolate of (–)-carvone with indole in the presence of Cu(II) conditions results in the coupled product (**96**) in 53% yield. Straightforward manipulations of this tricyclic core led to the completion of the syntheses of the (+)-hapalindole Q isothiocyanate (**24**) and 12-*epi*-fischerindole U isothiocyanate (**97**).

[33] Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450.

Scheme 20. Baran's recent approach toward (+)-hapaindole Q and (–)-*epi*-fischerindole U



By virtue of the polycyclic framework, ambiguines, hapalindoles, fischerindoles and the welwitindolinones are challenging molecules from the standpoint of chemical synthesis. In our view, (+)-ambiguine G nitrile, the only nitrile containing halogenated indolo terpenoid, was a challenging target for a total synthesis. We decided to approach this challenge by first addressing the issue of developing conceptually new and mild approaches to synthesize indole and indoline core. The development of such a method will be the subject of the next chapter.

Chapter 2. The Development of Free Radical-Mediated Aryl Amination

2.1. Introduction

The development of methods to effect aryl-nitrogen bond formation is of broad interest and vital importance, considering the volume of medicinally valuable indole alkaloids (eq 1).[34] Most syntheses of indole or indoline-containing natural products utilize aniline-based starting compounds.[35] The widely utilized Fischer indole synthesis is an example of this approach.

(1)

However, there are only a few mild methods for effecting an aryl-nitrogen bond formation. This limits the options available for effecting an indole synthesis from non-aniline precursors. Although recent advances in transition metal-mediated aryl amination have revolutionized this field,[36] the need for milder methods suitable for synthesis of complex natural products still exists. Aryl amination under radical cyclization conditions was envisioned as a way to achieve mild, chemoselective aryl-nitrogen bond formation. Toward this goal, a conceptually unique approach of carbon radical addition to the nitrogen terminus of an azomethine was investigated.

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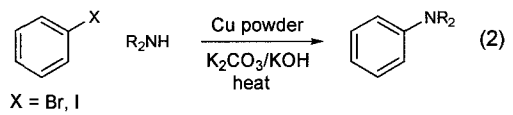
[34] *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: San Diego, CA 1998; Vol. 50.
[35] Wagaw, S.; Yang, H. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251.
[36] Hartwig, J. F. in *Handbook of Organopalladium Chemistry for Organic Synthesis* Negishi, E., Ed.; Wiley-Interscience: New York, 2002; p 1051.

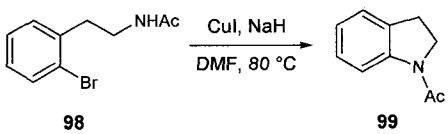
2.2. Transition Metal-Mediated Aryl Amination

Traditionally, most of the amination methods are electrophilic[37] or nucleophilic[38] aromatic substitutions, with a few exceptions which are aryne-based.[39] Although these may be the initial method of choice to effect aryl amination, most suffer problems with functional group tolerance. These concerns laid the platform for the development of transition metal-based methods. Ullmann[40] developed a procedure involving aryl bromides or iodides with amines in the presence of copper(0) under thermal conditions (usually ~130 °C) (eq 2).



(2)

Subsequent improvements by Lindley[41] made the amination process milder while increasing its generality. Kametami demonstrated an intramolecular aryl amination of **98** utilizing Ullmann conditions (copper iodide and sodium hydride), for the synthesis of *N*-acetyl indoline **99** (eq 3).[42]



98 **99** (3)

Recently, various activated aryl halide surrogates such as aryl boronic acids (eq 4),[43] aryllead triacetates (eq 5),[44] triaryl bismuthanes (eq 6),[45] and aryl siloxanes (eq 7)[46]

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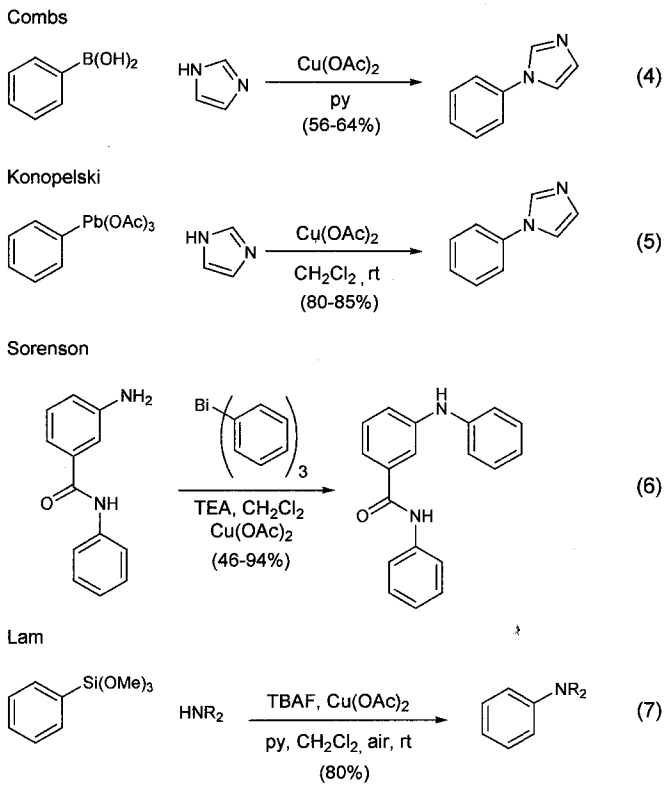
[37] Mitchell, H.; LeBlanc, Y. *J. Org. Chem.* **1994,** *59*, 682.
[38] (a) Semmelhack, M. F.; Hakjune, R. *Tetrahedron Lett.* **1993**, *34*, 1395. (b) Hattori, T.; Sakamoto, J.; Hayshizaka, N.; Miyano, S. *Synthesis* **1994**, 199. (c) Hoeve, W.; Kruse, C. G.; Lutenyn, J. M.; Thiecke, J. R. G.; Wynberg, H. *J. Org. Chem.* **1993**, *58*, 5101.
[39] Razzuk, A.; Biehl, E. R. *J. Org. Chem.***1987,** *52*, 2619.
[40] Ullmann, F.; Ochsner, P. *Annalen* **1911**, *1*, 381.
[41] Lindley, J. *Tetrahedron*, **1984**, *40*, 1433.
[42] Kametami, T.; Oshasawa, T.; Ihara, M. *Heterocycles*, **1980**, *14*, 277.
[43] Combs, P. A.; Saubern, S.; Rafalski, M.; Lam, P.Y.S. *Tetrahedron Lett.* **1999**, *40*, 1623.
[44] Konopelski, J. P.; Elliott, G. I. *Org. Lett.* **2000**, *2*, 3055.
[45] Sorenson, R. J. *J. Org. Chem.* **2000**, *65*, 7747.

have been used, affording amination products under milder conditions (Scheme 21). Although these processes are efficient in producing anilines, generality was not achieved with aliphatic amines that would result in reduced heterocycles.

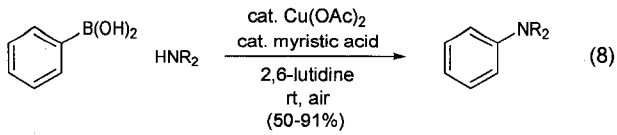
Scheme 21. Recent advances in transition metal-mediated aryl amination



Collman[47] and Buchwald[48] have developed copper (II) catalyzed amination of aryl boronic acids that is fairly mild, and tolerates a variety of functional groups (eq 8). Unlike previous examples of aminations, these reactions could be carried out with alkyl amines as well.

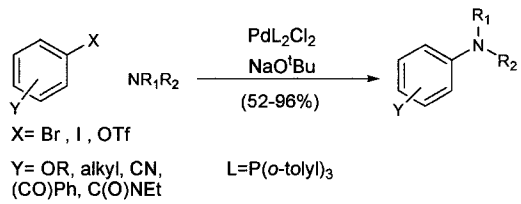
---

[46] Lam, P.Y.S.; Deudon, S. *J. Am. Chem. Soc.* **2000**, *122*, 7600.
[47] Collman, J. P.; Zhong, M. *Org Lett.* **2000**, *2*, 1233-1236.
[48] Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077-2079.



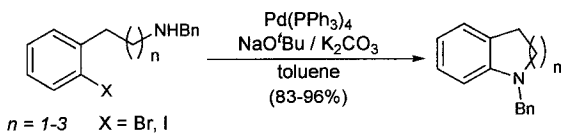
(8)

The use of palladium catalysts in C-C bond forming reactions is well developed and applied extensively in total synthesis.[49] Palladium-catalyzed C-N bond formation, on the other hand, is relatively young. Following the report by Kosugi,[50] Buchwald and Hartwig have developed several catalytic systems for the palladium-catalyzed aryl amination of aryl halides and triflates (eq 9).[51]

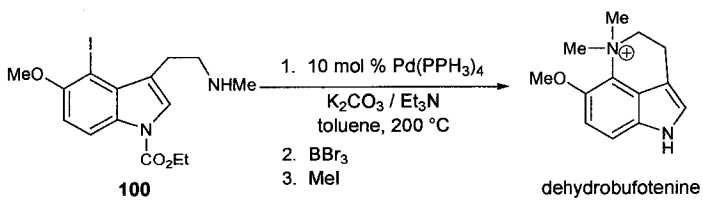


(9)

These methods are fairly general, and can be carried out both inter and intra-molecularly with high yields. A general protocol was established for the synthesis of a range of heterocyclic rings (eq 10). Such a palladium-catalyzed intramolecular amination was applied to the cyclization of iodo-amine **100** toward the total synthesis of the tetrahydropyrroloquinoline toad poison, dehydrobufotenine **101** (eq 11).[52]



(10)



(11)

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[49] Hegedus, L.S. *Transition Metals in the Synthesis of Complex Organic Molecules*, Univ. Science Books, Mill valley, CA, **1994**, pp 65-115.
[50] Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, 927.
[51] (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. F. *Acc. Chem. Res.* **1998**, *31*, 805 (b) Hartwig, J. F. *Pure Appl. Chem.* **1999**, *71*, 1417.
[52] Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 1028.

Palladium-mediated aryl amination conditions are slightly milder than those of the Ullmann reaction. However, the need for a base additive in both conditions restricts their use with base-labile moieties such as substituted indolines that are prone to elimination or aromatization to the corresponding indole.

2.3. Radical-Mediated Aryl Amination[53]

Free radical-mediated methods offer many advantages over ionic conditions. Radical reactions involve neutral intermediates and therefore are compatible with both acid- and base-sensitive functional groups. Although typically carried out at elevated temperatures, alternative methods at low temperatures are known.[54] Additionally, tandem cyclizations leading to complex molecular frameworks in a single step are possible.[55] Most importantly, the non-ionic nature of intermediates involved in radical reactions opens up possibilities for non-conventional additions (Figure 9).

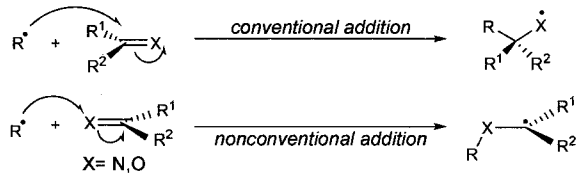
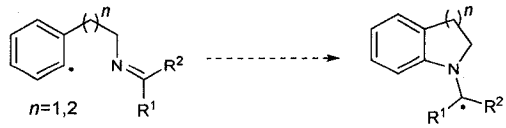


Figure 9. Concept of conventional and nonconventional radical addition modes

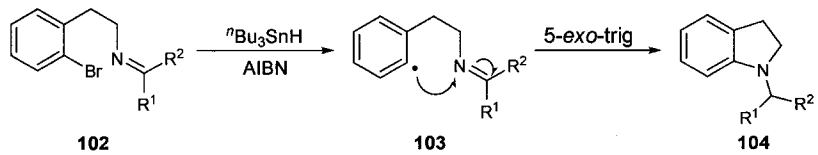
Complementary to the transition metal based amination chemistry is the concept of aryl radical addition to the nitrogen of an imine to generate the aryl-nitrogen bond (eq 12).



(12)

[53] (a) Johnston, J. N.; Plotkin, M. A.; Viswanathan, R.; Prabhakaran, E. N. *Org. Lett.* **2001**, *3*, 1009–1011; (b) Viswanathan, R.; Prabhakaran, E. N.; Plotkin, M. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 163.
[54] Haney, B. P.; Curran, D. P. *J. Org. Chem.* **2000**, *65*, 2007.
[55] For general reading: *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1 and 2. Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1996; Vol. 48, Chapter 2.

Oximes and hydrazones have been used extensively as radical acceptors, typically undergoing radical attack on the carbon atom (conventional mode).[56] Relative to oximes and hydrazones, imines (azomethines) are relatively more sensitive to hydrolysis and have been used sporadically in radical reactions. An azomethine functional group has the potential to undergo a radical addition at the nitrogen (nonconventional addition) to give an α-aminyl radical stabilized by the nitrogen lone pair forming a 3 electron 3-center bond.[57] Formation of an aryl-nitrogen bond results in further stabilization through resonance of the nitrogen lone pair with the phenyl ring. Considering these as driving forces, a nonconventional amination process was designed which consisted of a radical cyclization onto the nitrogen terminus of a pendant imine to yield the indoline product (eq 13). Precursor to an aryl radical in the form of **102** could be subjected to standard radical conditions to generate **103**. A 5-*exo*-trig cyclization would then follow resulting in indolines of the type **104**.



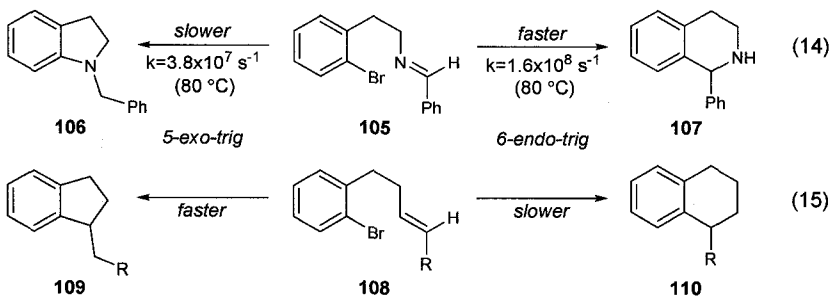
(13)

Warkentin attempted cyclizations on aldimine substrates that exhibited competitive *6-endo*-trig and *5-exo*-trig pathways (Scheme 22, eq 14).[58] Some interesting trends were observed in this study. First, imine **108** gives a 4:1 ratio favoring the *6-endo*-trig cyclization product **107** over **106**. Rate constants for the *5-exo* and *6-endo* closures reflected this trend where *5-exo* cyclization was at least four times slower than the *6-endo*-trig pathway (Scheme 22, eq 14). Products from direct reduction (ArBr ⟶ ArH) of aryl radical were consistenly produced in higher yield than the *5-exo*-trig cyclization product. This regioselectivity for the *6-endo* pathway is reversed when compared to

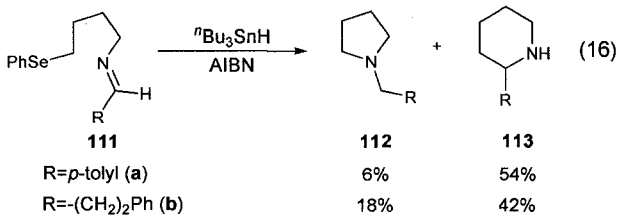
[56] (a) Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461. (b) Fallis, A. G.; Brinza, I. M. *Tetrahedron*, **1997**, *52*, 17543.
[57] Burkey, T. J.; Castelhano, A. L.; Griller, D.; Lossing, F. P. *J. Am. Chem. Soc.* **1983**, *105*, 4701.
[58] Tomaszewski, M. J.; Warkentin, J. *Tetrahedron Lett.* **1992**, *33*, 2123.

alkenes where subjection of **108** to similar radical conditions results in preferential formation of **109** over **110** (Scheme 22, eq 15).

Scheme 22. Kinetics of radical additions in olefins and azomethines



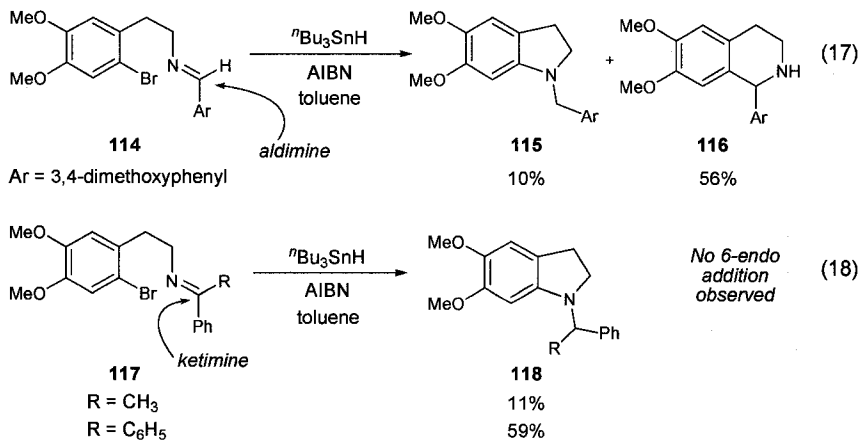
In an attempt to study the factors governing the regioselectivity of radical additions onto imines, Bowman performed competition experiments with alkyl radicals generated from selenides **111a** and **111b** (eq 16).[59] Both aldimines gave 6-*endo* addition products **113a** and **113b** preferentially.



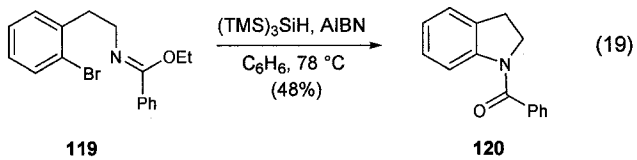
Takano observed that aldimine **114** underwent preferential formation of 6-*endo* product **116** over a 5-*exo* pathway (Scheme 23, eq 17).[60] Later they found that this regioselective mode of aryl radical addition can be reversed by increasing the steric bulk on the carbon center of the imine (Scheme 23, eq 18).[61] Thus **117** led to preferential 5-*exo* addition product **118**. Although the indoline product was formed preferentially in the ketimine case, direct reduction of the radical resulted in low yields of cyclized product.

[59] Bowman, W. R.; Stephenson, P. T.; Terrett, N. K.; Young, A. R.; *Tetrahedron Lett.* **1994**, *35*, 6369.
[60] Takano, S.; Suzuki, M.; Kijima, A.; Ogasawata, K. *Chem. Lett.* **1990**, 315.
[61] Takano, S.; Suzuki, M.; Ogasawara, K. *Heterocycles* **1994**, *37*, 149.

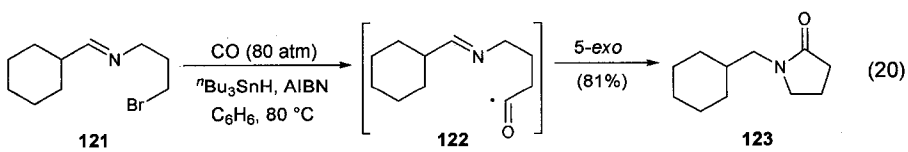
Scheme 23. Reversal of regioselectivity between aldimines and ketimines



McClure[62] reported a *5-exo*-trig radical cyclization of an arylbromide **119** with a pendant alkylimidate using tris(trimethylsilyl) silane, yielding amide **120** after cyclization followed by oxidation in 48% yield (eq 19). Conducting the reaction under stannane conditions led to a lower yield of the amide (30%), with the product of direct reduction formed in 40% yield.

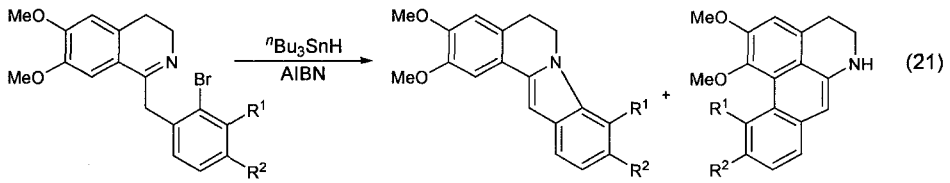


Recently, Ryu and Komatsu reported an intramolecular acyl radical addition to the nitrogen of a Schiff base giving exclusive *5-exo* addition (eq 20). The acyl radical **122** was formed *in situ* from bromide **121** with the use of carbon monoxide at high pressure eventually forming amide **123** in high yield.[63,64]



[62] McClure, C. K.; Kiessling, A. J.; Link, J. S. *Tetrahedron* **1998**, *54*, 7121.
[63] Ryu, I.; Matsu, K.; Minakata, S; Komatsu, M. *J. Am. Chem. Soc.* **1998**, *120*, 5838.
[64] Rationalization of the regioselectivity of acyl radical addition raised mechanistic questions about the possibility of charged intermediates.

Orito reported a 5-*endo*-trig cyclization, which is usually considered a disfavored process (eq 21).[65] Two possible reaction modes were identified for aryl bromides **124a** and **124b**. A 5-*endo* radical addition to the nitrogen resulting in substituted indoles **125a** and **125b**. Alternatively, a 6-*endo* radical addition formed biaryl linkage in **126b**. The 5-*endo*-trig cyclization occurred when the alternative 6-*endo* pathway was disfavored due to steric repulsion (when R^1 and R^2 are methoxy groups).



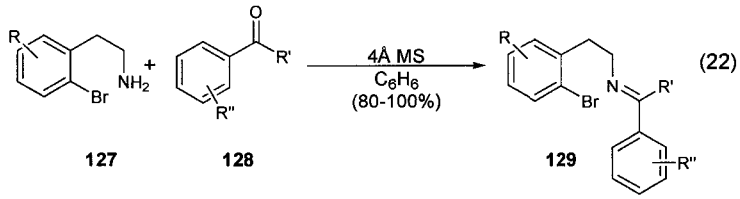
(21)

124a $R^1 = R^2 = OMe$ **125a** (68%) **126a** (0%)

124b $R^1 = R^2 = H$ **125b** (3%) **126b** (48%)

2.3.1. Synthesis of Schiff Bases

Schiff bases of the type of **129** used in this study were synthesized in excellent yields and >95% purity *via* dehydrative condensation of the amine **127** and ketone **128** using 4Å molecular sieves in benzene (eq 22).



(22)

127 **128** **129**

>95% pure by ^1H NMR

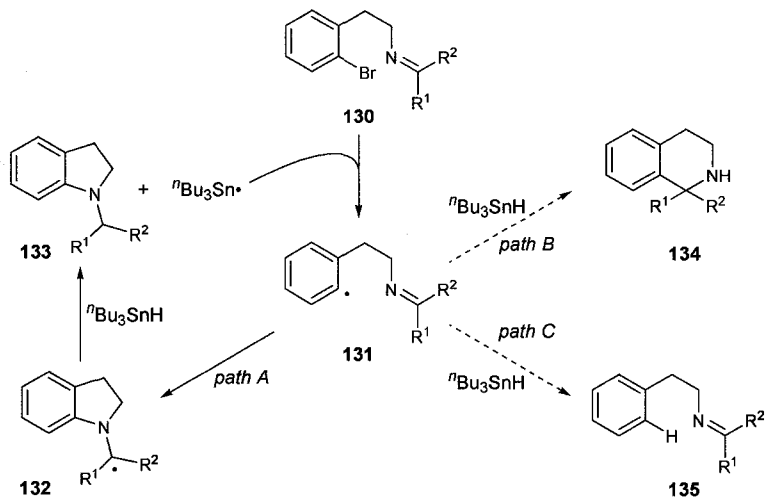
2.3.2. Reaction Design and Optimization

Possible reaction pathways from the aryl radical **131** generated from the aryl bromide **130** are shown in Scheme 24. Path A is the desired 5-*exo* cyclization followed by hydrogen atom transfer to the resulting radical **132** leading to the indoline **133**. Path B leads to the 6-*endo* addition of the aryl radical to the carbon center of the azomethine giving isoquinoline **134**. Path C leads to direct aryl radical reduction to give imine **135**.

[65] Orito, K.; Uchiito, S.; Satoh, Y.; Tatsuzawa, T.; Harada, R.; Tokuda, M. *Org. Lett.* **2000**, *2*, 307.

Reaction conditions were designed such that the desired 5-*exo* addition (path A) predominated over the undesired *6-endo* addition (path B) and the non-productive direct reduction (path C).

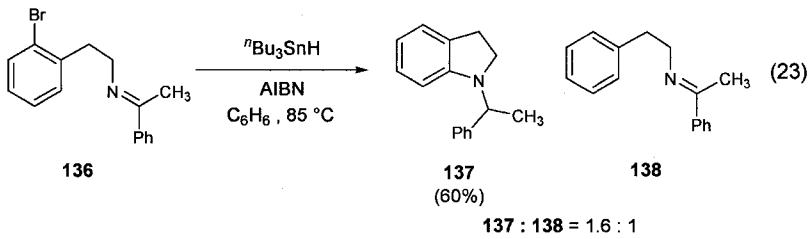
Scheme 24. Productive and nonproductive pathways involved in aryl amination



Takano[26] had shown that the usual regioselective preference in aldimines for the 6-*endo* addition reverses to give 5-*exo* addition if ketimines are used. However, the premature quenching of the aryl radical **131** (Path C) was a considerable problem in their case. Direct reduction of **131** by stannane is a bimolecular process while cyclization of **131** to **132** is a unimolecular process. Recognition of this fact identified effective tin hydride concentration as crucial in determining the ratio of **133** to **135**. However caution was exercised not to overlook the fact that radical initiation would also be affected with any change in concentration of tin hydride. Substitution both on the amine and ketone components or the alkyl chain was also recognized as an important factor determining the scope and generality of this method.

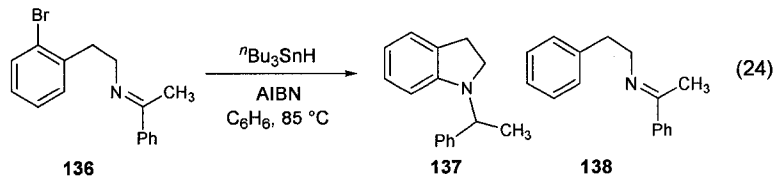
Schiff base **136** was chosen as the initial substrate for optimization of the 5-*exo* aryl amination process.[26] Thus, treatment of a refluxing 0.1 M benzene solution of the imine **136** with a benzene solution of AIBN (0.4 equiv) and $^{n}Bu_3SnH$ (1.1 equiv) over a period of 4 hours led to a mixture of two products in the ratio of 1.6:1 as determined by ^{1}H NMR spectroscopy (eq 23). Analysis of the spectral information revealed that the major product was the cyclized indoline **137** while the minor product **138** was the result

of direct reduction (ArBr ⟶ ArH). Indoline **137** was produced in 60% yield.[66] Similar to Takano's observations, no 6-*endo*-addition product could be detected by ^{1}H NMR. The identity of imine **138** was confirmed by independent synthesis from phenethylamine and acetophenone.



Since the stannane concentration could be tuned to favor path A (intramolecular) over path C (bimolecular), cyclization was conducted on a series of imine concentrations. Imine concentration was the easier factor to control than that of the stannane directly since the latter was added slowly.

Table 1. Effect of varying concentration on cyclization efficiency (eq 24)[a]



entry	**136** (M)	**137:138**[b]	**137**(%)[c]
1	0.1	2:1	60
2	0.01	5:1	82
3	0.001	4:1	75

[a] All reactions were carried out with 1.1 equiv. of ^{n}Bu$_3$SnH. [b] Ratios as determined by ^{1}H NMR. [c] Isolated Yield.

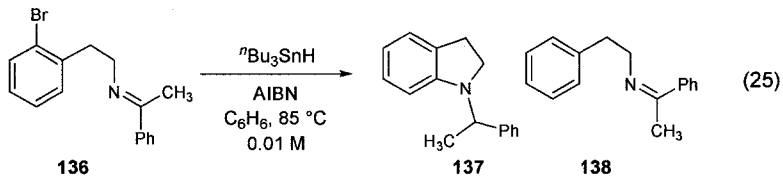
Table 1 summarizes the effects of varying concentration. Cyclization at 0.1 M of the imine solution resulted in a 60% yield and a 2:1 ratio of the cyclized product **137** (Table 1, entry 1). Diluting this imine concentration to 0.01 M led to a very efficient 5-*exo* addition giving rise to an 82% yield of the cyclized indoline **137** (5:1 ratio of the

[66] Takano reported an 11% yield for this cyclization: see ref 60.

cyclized product **137** : reduced product **138**, Table 1, entry 2). Further dilution to 0.001M slightly decreased the cyclization efficiency to give a 75% yield with a 4:1 ratio favoring the cyclized product **137** (Table 1, entry 3).

A slight improvement in the amination was achieved by slow addition of stannane using standard syringe pump technique (Table 2). Progressive increase of the tin hydride addition time from 1 hour to 4 hours (Table 2, entries 1 to 4) revealed that addition of stannane over 3 hours is optimal resulting in an 87% yield of the desired indoline **137**.

Table 2. Effect of varying stannane addition time (eq 25)[a,d]



(25)

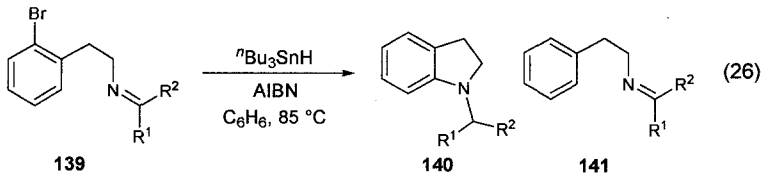
entry	$^{n}Bu_3SnH$ addition time, h	137:138[b]	137 (%)[c]
1	1	4:1	64
2	2	7:1	77
3	3	10:1	87
4	4	7:1	81

[a] All reactions were carried out with 1.1 equiv. of $^{n}Bu_3SnH$.[b] Ratios as determined by ^{1}H NMR.
[c] Isolated yield.[d] Data contributed by Michael Plotkin.

2.3.3. Scope and Generality of Radical-Mediated Aryl Amination

In order to expand the scope and generality of this amination, attempts were made to fully understand the steric and electronic factors influencing this cyclization. Toward this end, a series of aliphatic substitution at the ketimine portion was studied. Table 3 lists the results of aryl amination performed on imines **139a-c**. Under the optimized conditions, ketimines **139a** derived from acetone underwent direct reduction to the same extent as cyclization (Table 3, entry 1). This poor cyclization efficiency pointed to the lack of stabilization of the α-aminyl radical species formed prior to reduction to **140a**. However, the low yield could also have resulted due to the high volatility of the product indoline **140a**.

Table 3. Aryl amination with aliphatic ketimines (eq 26)[a]



139 140 141

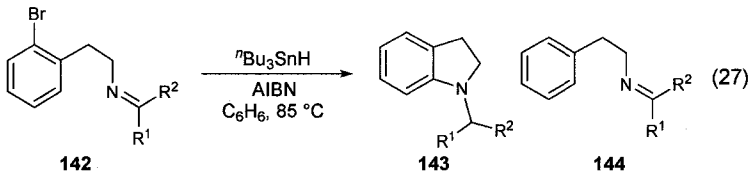
entry	R^1	R^2	**140:141**[b]	**140** (%)[c]
1 (**139a**)	CH_3	CH_3	1:1	30[d] (**140a**)
2 (**139b**)	C_2H_5	C_2H_5	nd[e]	40 (**140b**)
3 (**139c**)	CH_3	CF_3	14:1	83 (**140c**)
4 (**139d**)	Ph	CF_3	12:1	77 (**140d**)

[a] All reactions were carried out with 1.1 equiv. of ^{n}Bu$_3$SnH and 0.4 equiv of AIBN. [b] Ratios determined by ^{1}H NMR. [c] Isolated yield. [d] Volatility of the product resulted in loss of some material. [e] Not determined.

In order to eliminate this volatility factor, the corresponding 3-pentanone imine **139b** was investigated. The product indoline derived from 3-pentanone imine was found not to be volatile. However, cyclization efficiency still suffered giving only a 40% yield of the indoline **140b** (Table 3, entry 2). This clearly indicated the need for the product α-aminyl radical stabilization. In the case of ketimine **139c,** where one of the methyl groups is replaced by trifluoro methyl group, the product α-aminyl radical is sufficiently favored and results in an 83% yield of the indoline **140c** (Table 3, entry 3).[67] This confirmed that stabilization of the radical intermediate was crucial to the efficiency of the amination process. The fact that one radical stabilizing group is sufficient for an efficient amination was clear upon comparison of entries 3 and 4 in Table 3. In the case where both phenyl and triflouromethyl groups are present, no dramatic increase in amination efficiency was observed when compared to the case where only one group is present (Table 3, entry 3 and 4). It was noteworthy that even in the case of aliphatic ketimines no evidence for a 6-*endo* process was observed. Next, it was unclear whether amination conditions were tolerant of varying electronic nature of the imine. To address this issue, cyclization on an electronically diverse set of imines **142a-e** was studied (Table 4).

[67] (a) Creary, X.; Sky, A. F.; Mehrsheikh-Mohammadi, M. E. *Tetrahedron Lett.* **1988**, *52*, 6839. (b) Viehe, H. G.; Janousek, Z.; Merényi, R.; Stella, L. *Acc. Chem. Res.* **1985**, *18*, 148.

Table 4. Electronic diversity on ketone portion (eq 27)[a,d]



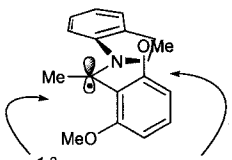
142 143 144 (27)

entry	R^1	R^2	143:144[b]	143 (%)[c]
1 (**142a**)	4-CF_3-Ph	CH_3	9:1	72 (**143a**)
2 (**142b**)	2',4',5'-trifluoro-Ph	CH_3	11:1	65 (**143b**)
3 (**142c**)	Ph	Ph	10:1	86 (**143c**)
4 (**142d**)	4-Me_2N-Ph	CH_3	9:1	90 (**143d**)
5 (**142e**)	2',6'-dimethoxy-Ph	CH_3	3:1	26 (**143e**)

[a] All reactions were carried out with 1.1 equiv. of ^{n}Bu$_3$SnH and 0.4 equiv of AIBN. [b] Ratios determined by ^{1}H NMR. [c] Isolated yield [d] With Michael Plotkin and Prabhakaran, E. N.

Imines with electron withdrawing groups on the phenyl ring (Table 4, entry 1 and 2) underwent amination efficiently. In the case of an electronically neutral phenyl substituent, the cyclization was very efficient (Table 4, entry 3). An imine bearing an electron donating *N,N*-dimethyl substituent also underwent amination very efficiently (Table 4, entry 4). Overall, the radical-mediated amination was generally efficient irrespective of the electronic nature of the ketimine.

It was interesting to note that when the ketimine exhibited dimethoxy substitution on the 2′ and 6′ positions (**142e**) the radical cyclization suffered, giving only a 26% yield of the cyclized product (Table 4, entry 5). The possibility of an electronic factor contributing to poor cyclization efficiency was discounted since electronically similar *N,N*-dimethylamino substituted imine **142d** cyclized efficiently (Table 4, entry 4). Steric factors leading to a destabilization of the α-aminyl radical in this case were suspected as the probable cause (see inset). In order for the phenyl ring to stabilize the radical generated after cyclization, there must be a good overlap of the orbital possessing the unpaired electron with its π-cloud. However, substitutions at the 2′ and 6′ positions sterically disfavor a stabilizing conformation for the α-aminyl radical formed after cyclization. This was however only a proposal to explain the low yield observed. No further experiments were carried out to substantiate this hypothesis.

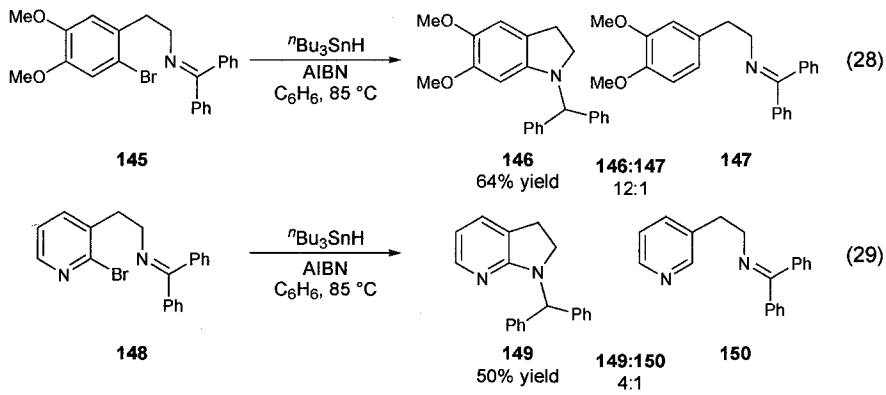


A^{1,3} strain minimized conformation disfavors overlap

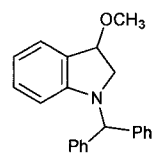
143e

In order to test if the aryl amination was sensitive to the electronic nature of the aryl halide fragment, electron rich aryl halide **145** and electron poor aryl halide **148** were synthesized and subjected to aryl amination conditions (Scheme 25). Dimethoxy substituted imine **145** (electron rich) gave a 64% yield of cyclized product **146** with a 12:1 ratio (Scheme 25, eq 28). Pyridyl imine **148** (electron deficient) gave a 50% yield of the indoline **149** with a 4:1 ratio (Scheme 25, eq 29). Since both imines underwent amination with similar efficiencies, the amination method proved rather general.

Scheme 25. Electronic diversity of aryl halide portion

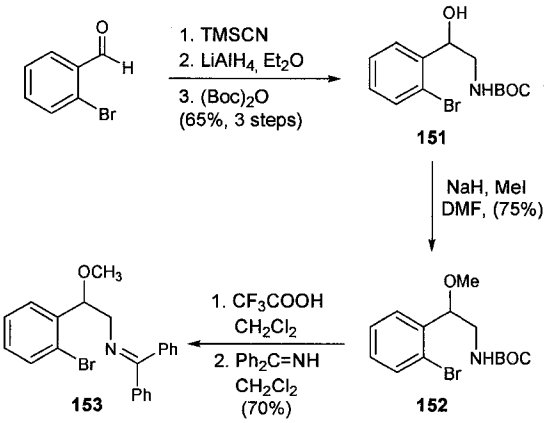


Having established the scope and generality of aryl amination for the synthesis of indolines, the mildness of the conditions was examined next. Synthesis of an indoline that would otherwise produce the indole under acid or base conditions was sought. Indoline **154** was deemed an appropriate target for this purpose (see inset). Unlike the examples discussed so far, synthesis of the Schiff base precursor to this indoline was not straightforward. Scheme 26 outlines the synthesis of imine precursor **153**.



154

Scheme 26. Synthesis of Schiff base **153**



Following the protocol developed by Evans, treatment of *o*-bromobenzaldehyde with trimethylsilylcyanide and a catalytic amount of ZnI_2 gave the silyl-protected cyanohydrin in quantitative yield.[68] Reduction of this cyanohydrin using $LiAlH_4$ led to the corresponding amino alcohol. Carbamate protection of the amino group was carried out under standard conditions to give **151** (65% yield, 3 steps).[69] Methylation of the secondary alcohol proceeded smoothly with NaH and methyl iodide to give **152** in 75% yield. Formation of imine **153** was then completed by first deprotecting the Boc group with trifluoroacetic acid[70] followed by transimination with benzophenone imine as reported by O'Donnell in 70% yield over two steps. [71]

Upon subjecting imine **153** to standard aryl amination conditions of 1.2 equivalents of AIBN and 1.1 equivalents of stannane in refluxing benzene, a smooth conversion was observed giving the cyclized product. Indoline **154** was isolated in 70% yield with no evidence of the corresponding indole **156** (^{1}H NMR) (eq 30).

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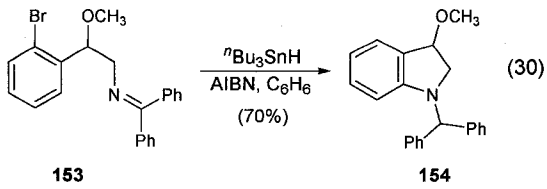
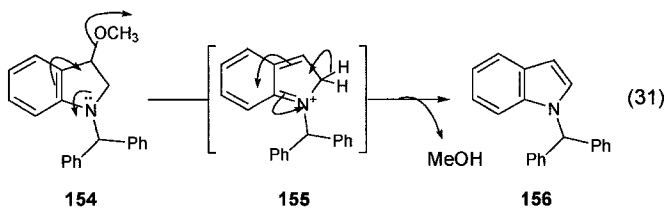
[68] Evans, D. A.; Caroll, G. L.; Truesdale, L. K. *J. Org. Chem.* **1974**, *39*, 914.
[69] Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999, pp 494-655.
[70] The deprotected amine was isolated and characterized; See Experimental section, **152a**.
[71] O'Donnell, M. J.; Polt, R. L. K. *J. Org. Chem.* **1982**, *47*, 2663.



Isolation of the indoline **154** required chromatography on neutral alumina, since it rapidly aromatized to the indole **156** upon exposure to silica gel. Infact, this aromatization occurred even upon standing at room temperature in air (eq 31). The fact that none of the indole **156** was observed during or after aryl amination supported the notion that the radical-mediated aryl amination process was indeed a very mild process. Therefore aryl amination could be conveniently used with acid or base sensitive functional groups with ease.



This initial success opened venues for possible application of this aryl amination strategy to the synthesis of complex natural products and other nitrogen containing biologically active heterocycles. As a first step towards these goals, an extension of the scope of this methodology to the synthesis of indoline α-amino acids was attempted.

2.4. Indoline α-Amino Acids

α-Amino acids play a pivotal role in diverse areas of chemistry and biology. Polymers of these chiral molecules, including enzymes, orchestrate various chemical transformations that are crucial for life. One such α-amino acid is (*S*)-indoline-2-carboxylic acid ((*S*)-**157**). From a structural perspective, it is both a constrained phenylalanine as well as a modified proline. Indoline α-amino acids have been used in many fields, a few of them are shown below.

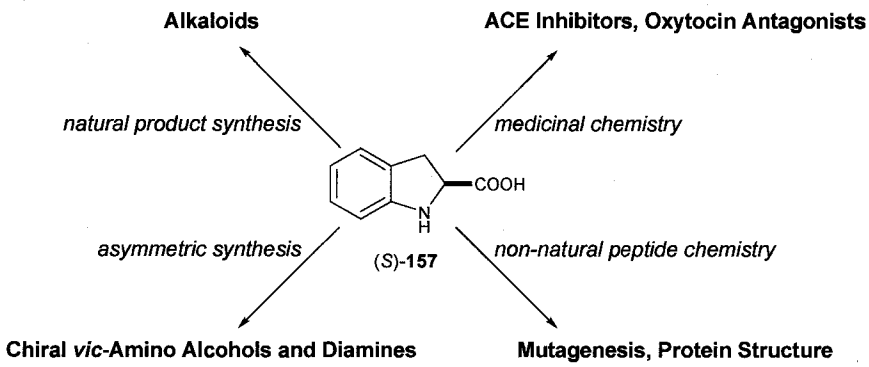
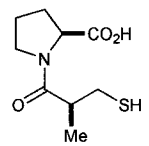


Figure 10. Applications of Indoline α-Amino Acid

2.4.1. Indoline α-Amino Acids in Medicinal Chemistry

Captopril (**158**) is an angiotensin converting enzyme (ACE) inhibitor that has been shown to be an effective anti-hypertensive agent in humans.[72] However, the drug possesses a number of side effects, rashes and alteration of taste being the most common.[73]



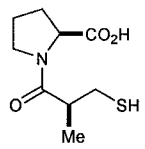
captopril (**158**)

Stanton studied a number of surrogates of captopril that would lack the thiol moiety yet retain its potency.[74] They found that the indoline amino acid derivative **160** was a potent inhibitor of ACE with an *in vitro* IC_{50} of 4.8 nM (Table 5, entry 3). Upon comparing the potency of analogous inhibitors, indoline amino acid-derived **160** was 1000 fold more effective than proline derived **159**. Another indoline amino acid based inhibitor **161** was ~200 times better binding than proline derived **159** (Table 5, entry 4 vs 2). This indicated the significance of lipophilic interactions due to the presence of a phenyl ring in **160** and **161** (Table 5, entry 3 and 4).

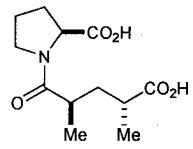
---

[72] Bravo, E.L; Tarazi, R. C. *Hypertension* **1979**, *1*, 39.
[73] Atkinson, A.B.; Robertson, J. J. S. *Lancet.* **1979**, *2*, 836.
[74] Stanton, J. L.; Norbert, G. *J. Med. Chem.* **1983**, *26*, 1277.

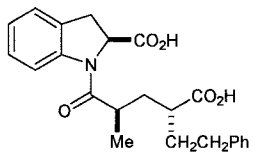
Table 5. Comparison of potency of ACE inhibition



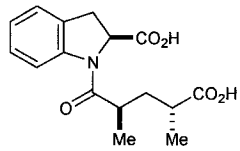
158



159



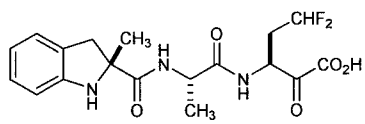
160



161

entry	Inhibitor	ACE IC_{50} nM
1	**158**	15
2	**159**	4800
3	**160**	4.8
4	**161**	28

Recently, Harper reported the design of indoline amino acid based peptidomimetic inhibitors of hepatitis C virus NS3 protease of the type **162** (Figure 11).[75] Studies on the enzyme bound crystal structure of the inhibitor highlighted the use of the indoline subunit as an *N*-terminal capping group in these dipeptide inhibitors.



162

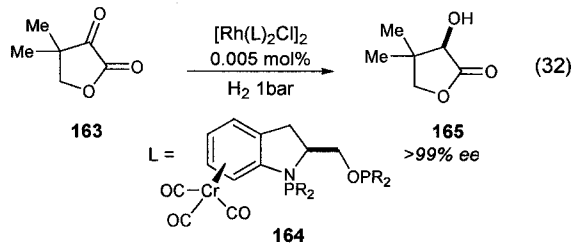
Figure 11. Indoline amino acid based peptidomimetic inhibitor **162**

2.4.2. Indoline α-Amino Acids in Asymmetric Synthesis

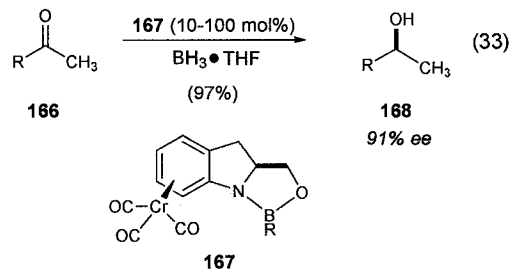
The chirality inherent in indoline α-amino acid has been exploited to generate catalysts for asymmetric synthesis by direct analogy to the use of proline derivatives. Agbossou[76] synthesized chromium arene complex with the alcohol derived from (*S*)-indoline-α-amino acid to form diphosphine ligands of the type **164**. This metal-arene

[75] Ontoria, J. M.; Marco, S. D.; Conte, I.; Francesco, M. E. D.; Gardelli, C.; Koch, U.; Matassa, V. G.; Poma, M.; Steinkühler, Volpari, C.; Harper, S. *J. Med. Chem.* **2004**, *47*, 6443.
[76] Agbossou, F.; Pasquier, C. *Organometallics*, **2000**, *19*, 5723.

complex rendered a highly face selective catalyst for the rhodium catalyzed asymmetric reduction of α-functionalized ketones of the type **163** to give the corresponding alcohol **165** with high enantioselectivities (eq 32).

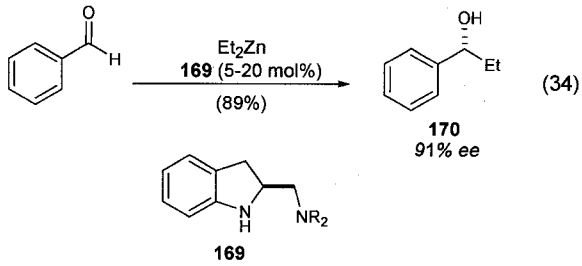


Jones has developed a modified oxazaborolidine catalyst that contains an indoline amino acid in place of a proline in the CBS system (**167**, eq 33).[77,78] They found that by coordinating chromium to one face of the arene ring, the catalyst had an excellent discriminating ability between R_L and R_S of the ketone giving rise to high enantioselectivities for reductions of ketones.



Indoline amino acid derived diamines like **169** have been used as chiral ligands for enantioselective diethylzinc addition to benzaldehyde by Asami.[79] Optically enriched alcohol **170** was obtained in high % ee and excellent yield (eq 34).

[77] Corey, E. J.; Bakshi, R. K.; Shibata, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
[78] Jones, B. G.; Heaton, S. B.; *Tetrahedron: Asymmetry* **1997**, *8*, 3625.
[79] Asami, M.; *Tetrahedron: Asymmetry* **1998**, *9*, 4165.



(34)

2.4.3. Indoline α-Amino Acids in Peptide/Protein Structure

Proline is a unique member in the class of naturally occurring amino acids. Amides *N*-terminal to proline have energetically similar *cis*- and *trans*-rotational isomers that are separated by a significant barrier for isomerization (Figure 12).[80] This is in contrast to those in nonproline peptides where the *trans* isomer is much lower in energy. Proline, by virtue of its cyclic nature, causes turns in peptide secondary structures. The structure of these turns depends on the *cis* or *trans* nature of the X-Pro amide bond. Consequently, the isomer population plays a crucial role in the structure, and hence, the function of bioactive peptides and proteins containing proline residues. For example, proline-specific peptidases require the *trans* isomer in order to hydrolyze X-Pro bonds.[81]

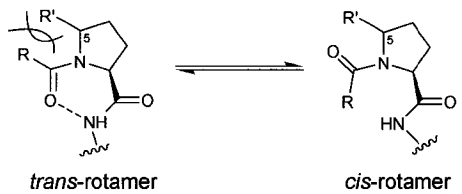


Figure 12. *cis-trans* rotational isomers around X-Pro amide bond

This equilibrium between the *cis* and *trans* isomers is significantly affected by substitution at C_5 of proline (Figure 12).[82] Indoline amino acid should therefore provide the ability to influence the *cis-trans* ratio around its *N*-terminal amide bond (Figure 13).

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[80] Larive, C. K.; Guerra, L; *J. Am. Chem. Soc.* **1992**, *114*, 7331.
[81] Lin, L. N.; Brandts, J. F. *Biochemistry* **1979**, *18*, 43.
[82] (a) Burks, H. E.; Srinivasan, J. M.; Johnston, J. N. Unpublished work. (b) Halab, L.; Lubell, W. D. *J. Org. Chem.* **1999**, *64*, 3312.

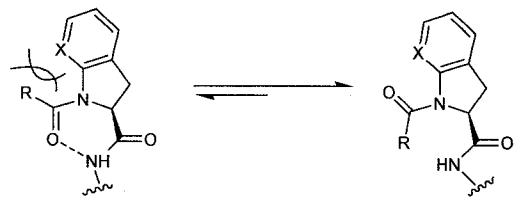
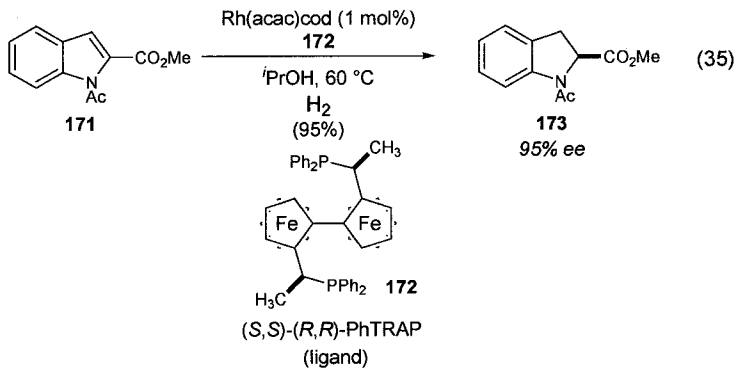


Figure 13. Population favoring *cis*-isomer in indoline α-amino acids

These applications provide a compelling basis to devise an enantioselective route to indoline α-amino acid. Many of these applications require access to either enantiomer of the indoline amino acid derivative. It is significant to note that contemporary syntheses rely on resolution *via* fractional crystallization, or in some cases, asymmetric functionalization of the indolines.

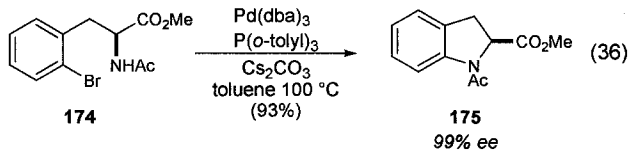
2.5. Previous Asymmetric Syntheses of Indoline α-Amino Acid

There have been two reports of enantioselective syntheses of protected indoline amino acids. Kuwano and Ito have reported the asymmetric hydrogenation of indole amino acid **171** using a rhodium based chiral catalyst derived out of ferrocenyl-phosphine ligand **172** to give enantiomerically enriched indoline amino acid derivative **173** (eq 35).[83] The method proved general and high yielding for 2-substituted indoles with high enantioselectivities. However, 3-substituted indoles suffered alcoholysis problems and were not suitable substrates under these conditions.



[83] Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7614.

Buchwald reported a palladium-mediated amination of optically enriched amide **174** leading to protected indoline amino acid **175** (eq 36).[84] The amine precursors for their methodology were obtained by asymmetric hydrogenation of the corresponding enamides through a method reported earlier by Burk.[85]



(36)

2.6. Enantioselective Synthesis of Indoline α-Amino Acid through Aryl Amination

It was envisioned that the mild and regioselective radical aryl amination method combined with an efficient enantioselective alkylation would provide a convergent assembly of a variety of indoline α-amino acids. Figure 14 outlines the effective bond disconnections leading to achiral starting compounds in order to synthesize an array of indoline α-amino acids.

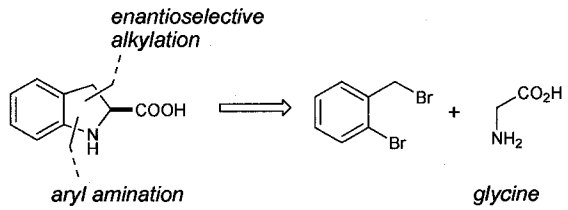


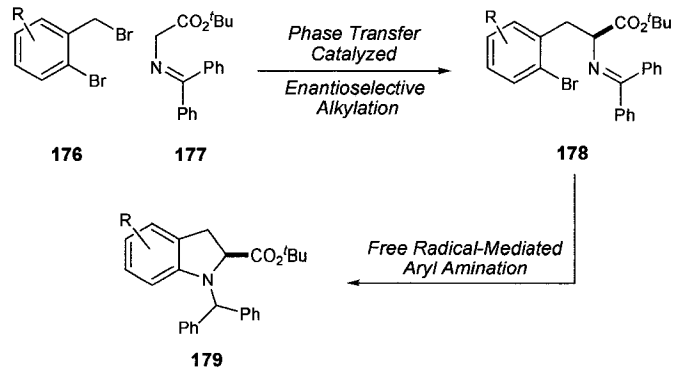
Figure 14. Retrosynthetic bond disconnections for indoline α-amino acid

Based on these disconnections, a straightforward two-step sequence was designed where the first step would be an enantioselective alkylation of glycine derived Schiff base **177** with *o*-bromobenzyl bromides **176** yielding imines **178** which are appropriate substrates for aryl amination. Use of radical-mediated amination developed previously

[84] Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451.
[85] Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1993**, *119*, 10125.

would then provide protected indoline α-amino acid **179** in a concise fashion (Scheme 27).

Scheme 27. Enantioselective synthetic plan for indoline α-amino acids



2.6.1. Phase Transfer Catalyzed Enantioselective Alkylations

The use of organic salts as phase transfer catalysts (PTC) for reactions in biphasic media is a major development in organic synthesis.[86] Stork in his early work showed that enolates derived from Schiff bases could be conveniently used as glycine anion equivalents in the synthesis of α-amino acids.[87] The use of phase transfer catalysis (PTC) for enantioselective alkylations to produce α-amino acids was developed by O'Donnell. His pioneering work with alkylations of Schiff bases of glycine *tert*-butyl ester[88] **177** led to a very convenient method for the synthesis of α-amino acids (Scheme 28).[89] This was followed by a rational improvement in the catalyst design by Corey to achieve high enantioselectivities at low temperatures.[90]

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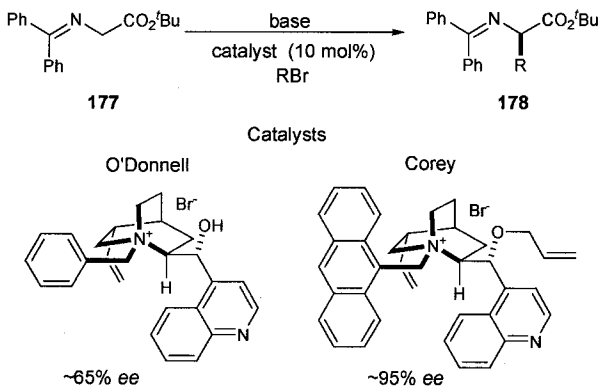
[86] *Catalytic Asymmetric Synthesis,* Ojima ,I., Ed.; VCH: New York, 1993
[87] Stork, G.; Leong, A. Y. W.; Touzin, A. M. *J. Org. Chem.* **1976**, *41*, 3491.
[88] O' Donnell, M. J.; Wu, S. Huffmann, J. C. *Tetrahedron*, **1994**, *50*, 4507.
[89] (a) O' Donnell, M. J. *Aldrichimica Acta.* **2001**, *34*, 3. (b) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518. (c) Nelson, A. *Angew. Chem. Int. Ed.* **1999**, *38*, 1583.
[90] Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.

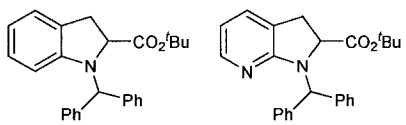
Scheme 28. Enantioselective alkylation under PTC conditions



Recently, there has been a steady increase in the use of chiral quarternary ammonium salts as catalysts in enantioselective alkylation.[91] Enantioselective versions under PTC conditions are also well developed for ketone enolate alkylation,[92] aldol reaction,[93] Michael addition,[94] Darzen reaction,[95] and enone epoxidation.[96]

2.6.2. Optimization of Racemic Synthesis of Indoline α-Amino Acids

Prior to establishing the enantioselective route, racemic protected indoline α-amino acids **179a** and **179b** were chosen as appropriate sample targets to test and optimize the aryl amination reaction.

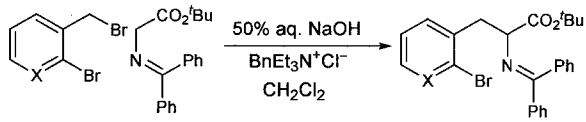


179a **179b**

[91] O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506.
[92] Corey, E. J.; Bo, Y.; Peterson, J. B. *J. Am. Chem. Soc.* **1998**, *120*, 13000.
[93] Gasparski, C. M.; Miller, M. J. *Tetrahedron* **1991**, *47*, 5367.
[94] Corey, E. J.; Zhang, F. Y. *Org. Lett.* **2000**, 2, 1097; also *Org. Lett.* **2000**, 2, 4257.
[95] Arai, S; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 2145.
[96] Corey, E. J.; Zhang, F. Y. *Org. Lett.* **1999**, *1*, 1287.

Following O'Donnell's procedure,[97] treatment of a 0.34 M solution of Schiff base **177** under phase-transfer conditions with 20 mol% of benzyl- triethylammonium chloride as catalyst and *o*-bromobenzyl bromide **176a** and the pyiridyl version **176b** proceeded smoothly to give the alkylated imines **178a** and **178b** in 85% and 73% isolated yields respectively (Table 6). Purification of these substituted phenyl alanine Schiff bases required chromatography using neutral alumina instead of silica gel in order to avoid decomposition.

Table 6. PTC racemic alkylations to produce Schiff bases **178a** and **178b** (eq 37)[a,b]



176 177 178 (37)

entry	176	time (h)	178 Yield (%)
1	CH (**176a**)	4	85
2	N (**176b**)	3	73

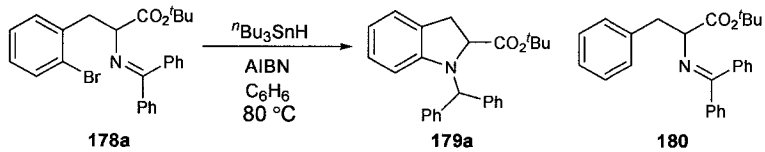
[a] Both reactions were done at room temperature and 0.34 M in **177**.
[b] Isolated yield of product purified by column chromatography on neutral alumina.

The stage was then set to test the aryl amination reaction on these imines. Treatment of imine **178a** (0.01 M in benzene) with stannane (1.1 equivalents) and AIBN (0.8 equivalents, added dropwise over 4 hours) led to an incomplete conversion giving indoline **179a** in 60% yield (Table 7, entry 1). ^{1}H NMR analysis of crude reaction mixture revealed that the reaction did not go to completion, but that the only side product formed was **180** (eq 38). There was no indication of the 6-*endo* addition product. In order to further optimize this reaction, imine **178a** was subjected to a series of aryl amination conditions with increasing equivalents of tin hydride. Treatment of imine **178a** (0.01 M in benzene) with stannane (added in 2 parts) and AIBN (0.8 equiv, added dropwise over 4 hours) led to an improvement giving indoline **179a** in 85% yield (Table 7, entry 2). Under these conditions, the ratio of cyclized product to direct reduction product was >200:1 by GC analysis. When 4.4 equivalents of stannane was used, a 75% yield of

[97] O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353.

indoline **179a** was obtained with a >20:1 ratio favoring the cyclized product (Table 7, entry 3). It was significant to note that even when using 8.8 equivalents of tin-hydride (Table 7, entry 4), cyclization predominated over direct reduction giving a 74% yield of the indoline **179a** with a 6:1 ratio. Clearly, the presence of the carboxyl group on C2 increased the rate of cyclization presumably through a Thorpe-Ingold effect. Unlike previous aryl amination substrates, in the case of imine **178a**, it was unnecessary to add the stannane dropwise. However, it was noticed that yields were slightly higher when tin hydride was added directly in parts.

Table 7. Optimization of aryl amination to synthesize indoline α-amino acid **179** (eq 38)

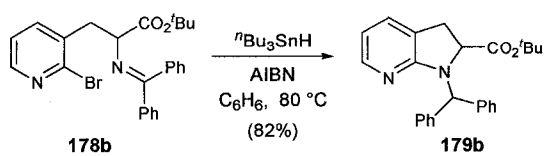


178a 179a 180 (38)

entry	$^{n}Bu_3SnH$ (equiv)	Ratio[b] **179a:180**	% yield[d]
1	1.1	-	60[e]
2	2.2	>200:1[c]	85
3	4.4	>20:1	75
4	8.8	6:1	74

[a] All reactions were performed by slow addition of AIBN (0.8 equiv) with $^{n}Bu_3SnH$ in the reaction vessel. [b] Ratio of **179a:180** as determined by ^{1}H NMR spectroscopy. [c] Determined by GC-MS. [d] Isolated yield. [e] Reaction not complete.

Similarly, imine **178b** underwent cyclization to provide the corresponding indoline in 82% yield (eq 39). Indoline **179b** was distinctly UV active as observed by the analysis of its thin layer chromatogram. In this case also the radical addition was completely regioselective to the nitrogen of the azomethine.

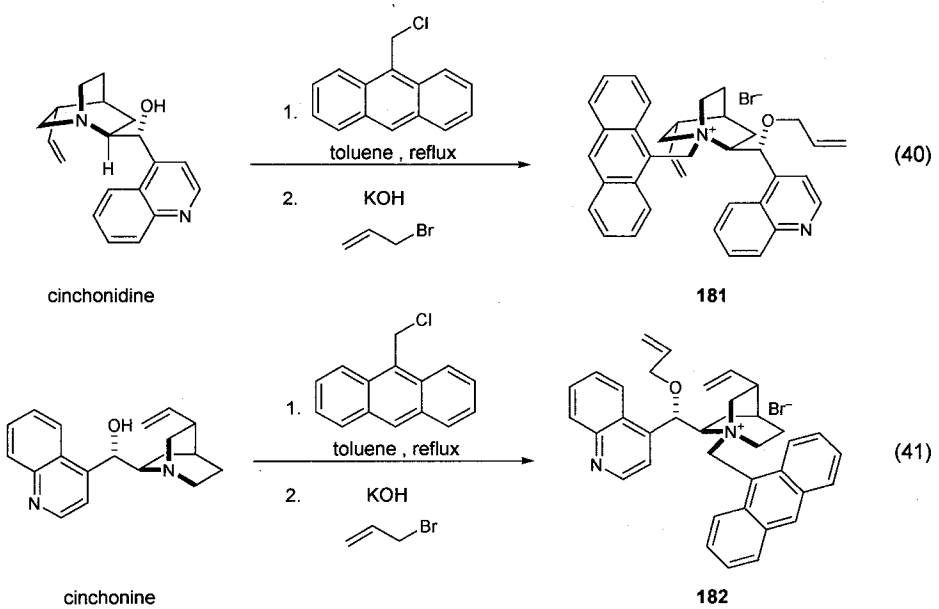


178b 179b (39)

2.6.3. Synthesis of Catalysts for Enantioselective Alkylation

Chiral catalysts **181** and **182** were synthesized as reported by Corey (Scheme 29). Cinchonidine was treated with anthracenyl methyl chloride under reflux in toluene. The product of this alkylation was easily purified by recrystallization. It was then subjected to the subsequent allylation with potassium hydroxide and allyl bromide (eq 40). Though the procedure reported by Corey called for a recrystallization of the catalyst **181**, in our hands the recrystallization failed. Therefore, we purified the catalyst using chromatography (silica gel, methanol-dichloromethane as eluent). Similarly use of cinchonine in the same sequence gave catalyst **182** (eq 41).

Scheme 29. Synthesis of cinchona alkaloid derived chiral phase transfer catalysts **181** and **182**

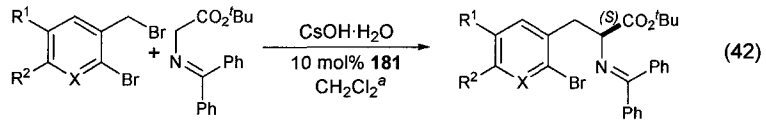


2.6.4. Enantioselective Alkylation

In the enantioselective version of the first alkylation step, glycine derived Schiff base **177** was deprotonated with solid cesium hydroxide at low temperature (typically –78 °C). With 10 mol% of chiral catalyst **181**, a series of substituted benzyl bromides **176a-e** underwent alkylation over the period of about a day.[90] Results of the alkylation are summarized in Table 8. Imine **178a**, which was originally synthesized in

racemic form, was synthesized in 96% ee and 89% yield (Table 8, entry 1). Use of the pyridyl bromide **176b**, furnished the imine **178b** in 96% ee and 77% yield (Table 8, entry 2). Monomethoxy and dimethoxy substituted bromides gave the corresponding imines **178c,d** in high % ee and yield (Table 8, entries 3 and 4). Chloro substituted bromide **176e** furnished the corresponding imine **178e** in 93% ee and 74% yield (Table 8, entry 5). Thus, an array of highly enantiomerically enriched imines (*S*)-**178a-e** were synthesized in consistently good yields.

Table 8. Enantioselective alkylation of glycinyl Schiff base using catalyst **181** (eq 42)



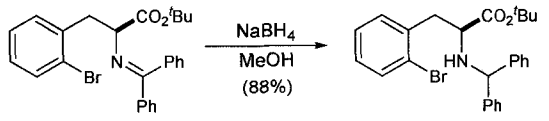
(42)

176 **177** (*S*)-**178**

entry	X	R^1	R^2	time (hr), (T)	**178**	% *ee*[b]	**178** (%)[c]
1	CH (**176a**)	H	H	20 (−78 °C)	(*S*)-**178a**	96[d]	89
2	N (**176b**)	H	H	20 (−78 °C)	(*S*)-**178b**	96	77
3	CH (**176c**)	OMe	H	2 (−10 °C)	(*S*)-**178c**	94	81
4	CH (**176d**)	OMe	OMe	16 (−65 °C)	(*S*)-**178d**	92	85
5	CH (**176e**)	Cl	H	21 (−60 °C)	(*S*)-**178e**	93	74

[a] All reactions were done at 0.34 M in **177** except entry 2 where a 0.15 M was used. [b] All % *ee* determined by chiral HPLC analysis. [c] Yield of products isolated by chromatography on neutral alumina. [d] % *ee* Determined by conversion of imine to corresponding amine using $NaBH_4$ reduction.

Inseparability of the enantiomers of imine (*S*)-**178a** by HPLC mandated its conversion to the corresponding amine (*S*)-**183a** for its % ee determination (eq 43). HPLC data revealed that this amine was produced in 96% ee thus reflecting the enantioselection in the alkylation step.

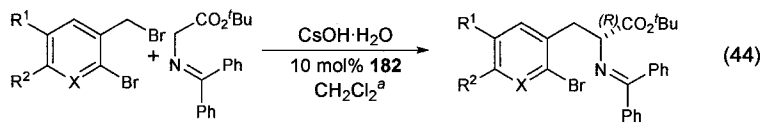


(43)

(*S*)-**178a** (*S*)-**183a** 96% *ee*

Similarly, use of the pseudo-enantiomeric catalyst **182** under identical alkylation conditions led to enantiomeric imines (*R*)-**178 a-e** with comparable % ee's and % yields (Table 9).

Table 9. Enantioselective alkylation of glycinyl Schiff base using catalyst **182** (eq 44)

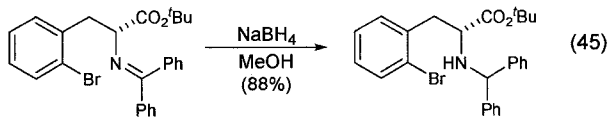


176 **177** (*R*)-**178**

entry	X	R^1	R^2	time (hr), (T)	**178**	% *ee*[b]	**178** (%)[c]
1	CH (**176a**)	H	H	20 (–78 °C)	(*R*)-**178a**	93[d]	80
2	N (**176b**)	H	H	20 (–78 °C)	(*R*)-**178b**	98	76
3	CH (**176c**)	OMe	H	2 (–10 °C)	(*R*)-**178c**	91	74
4	CH (**176d**)	OMe	OMe	16 (–65 °C)	(*R*)-**178d**	97	96
5	CH (**176e**)	Cl	H	21 (–60 °C)	(*R*)-**178e**	94	71

[a] All reactions were done at 0.34 M in **177** except entry 2 where a 0.15 M was used. [b] All % *ee* determined by chiral HPLC analysis. [c] Yield of products isolated by chromatography on neutral alumina. [d] % *ee* Determined by conversion of imine to corresponding amine using $NaBH_4$ reduction.

Imine (*R*)-**178a** had to be reduced to its corresponding amine for accurate % ee determination (eq 45). HPLC data revealed that this amine was produced in 93% ee thus reflecting the enantioselection in the alkylation step.



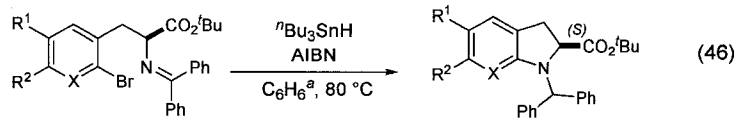
(*R*)-**178a** (*R*)-**183a** 93% *ee*

2.6.5. Aryl Amination of Enantioenriched Schiff Bases

Having gained access to imines in both enantiomeric series, radical mediated aryl amination was the next goal. Thus, the imines in the (*S*)-series were subjected to conditions similar to those used for the racemates as shown in Table 10. The optimal concentration for these cyclizations however was 0.1 M, with one exception (pyridyl imine (*S*)-**178b**, 0.01 M) (Table 10, entry 2). Imines (*S*)-**178a** and (*S*)-**178b** cyclized in good yields (Table 10, entry 1 and 2). The slight lowering in the yield of indoline product

(*S*)-**179a** (15%) when compared with the racemic case (Table 7, entry 2) was due to an increase in the concentration. This change led to a corresponding increase of the product of direct reduction. Imines (*S*)-**178c**, (*S*)-**178d**, and (*S*)-**178e** gave moderate yields, requiring higher equivalents of tin hydride than the optimal level of 2.2 equivalents (Table 10, entries 3,4,5). This was to minimize an unexpected erosion of % ee that was observed during these cyclizations. This aspect is discussed in detail in Chapter 4.

Table 10. Aryl amination of enantiomerically enriched imines (*S*-series, eq 46)

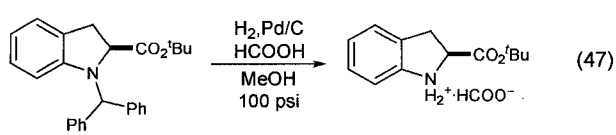


(*S*)-**178** (*S*)-**179** (46)

entry	X		R^1	R^2	$^nBu_3SnH$ (equiv)	AIBN (equiv)	**179** % *ee*[b]	yield(%)[c]
1	CH	(*S*)-**178a**	H	H	2.2	0.8	96	69
2	N	(*S*)-**178b**	H	H	2.2	0.8	90[d]	85
3	CH	(*S*)-**178c**	OMe	H	5.0	1.6	91[d]	45
4	CH	(*S*)-**178d**	OMe	OMe	5.0	1.2	82[d]	50
5	CH	(*S*)-**178e**	Cl	H	3.0	1.6	93	55

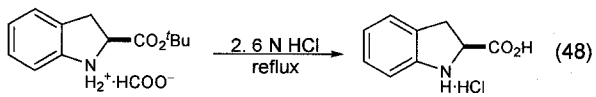
[a] All reactions were performed at 0.1 M in **178** except entry 2 where 0.01 M was used. [b] Determined by chiral HPLC analysis. [c] Isolated yield. [d] An erosion of % *ee* was observed.

Thus, an array of electronically diverse indolines was efficiently synthesized using radical-mediated aryl amination conditions. At this point, confirmation of configurational assignment of enantiomerically pure indoline α-amino acid was next goal. Hence the diphenylmethyl protecting group on the nitrogen of (*S*)-**179a** was cleaved by hydrogenolysis giving rise to the formic acid salt (*S*)-**184** (eq 47). This deprotection did not proceed without the formic acid.



(*S*)-**179a** (*S*)-**184** (47)

This was followed by deprotection of the *tert*-butyl ester using 6 N HCl at reflux to furnish the indoline amino acid (*S*)-**157** in two steps (eq 48).



(*S*)-**184** (*S*)-**157**

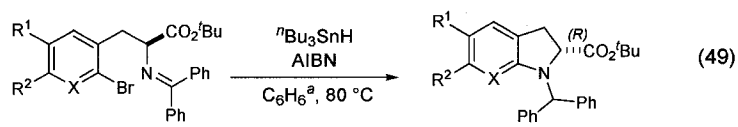
$[\alpha]_D^{21} = -60.0°$ (c 0.40, 1N HCl)

Lit $[\alpha]_D^{21} = -114°$ (c 1.0, 1N HCl)

Comparison of the sign of specific rotation of the hydrochloride salt of (*S*)-**157** with that of (*S*)-indoline α-amino acid from the literature revealed that it was indeed the assigned enantiomer. A depressed value of the specific rotation in the synthetic material was due to the residual NaCl that was present in the sample after workup that prevented accurate mass measurement.

In parallel to the synthesis of the *(S)*-series of indolines, those in the corresponding *(R)*-series were synthesized in nearly identical yields and optical purity. Results of the aryl amination of imines (*R*)-**178a-e** to their corresponding indolines are summarized in Table 11.

Table 11. Aryl amination of enantiomerically enriched imines (*R*-series, eq 49)



(*R*)-**178** (*R*)-**179**

entry	X		R^1	R^2	$^nBu_3SnH$ (equiv)	AIBN (equiv)	**179** % *ee*[b]	yield(%)[c]
1	CH	(*R*)-**178a**	H	H	2.2	0.8	93	70
2	N	(*R*)-**178b**	H	H	2.2	0.8	89	85
3	CH	(*R*)-**178c**	OMe	H	5.0	1.6	87[d]	55
4	CH	(*R*)-**178d**	OMe	OMe	5.0	1.2	82[d]	50
5	CH	(*R*)-**178e**	Cl	H	3.0	1.6	94	60

[a] All reactions were performed at 0.1 M in **178** except entry 2 where 0.005 M was used. [b] Determined by chiral HPLC analysis. [c] Isolated yield. [d] An erosion of % *ee* was observed.

Identical to their enantiomeric series, indolines (*R*)-**179a**, (*R*)-**179b** and (*R*)-**179e** were formed with no loss of configurational integrity while (*R*)- **179c** and (*R*)- **179d** underwent a slight erosion of % ee under these conditions.

In order to expand the utility of aryl amination, we then turned our attention to the synthesis of substituted indoline α-amino acids.

2.7. Stereoselective Synthesis of Substituted Indoline α-Amino Acids

Alkaloids possessing substituted indoline backbones are challenging targets both for total synthesis as well as for developing new methodologies. A few examples of alkaloids containing an indoline core are shown in Figure 15. These natural products have triggered enormous interest for target oriented synthesis.[98] Appropriately functionalized di- and tri-substituted indoline α-amino acids are attractive building blocks for the synthesis of such natural products. Therefore a short, stereoselective synthesis of this core was envisioned to be an appropriate extension of the aryl amination methodology.

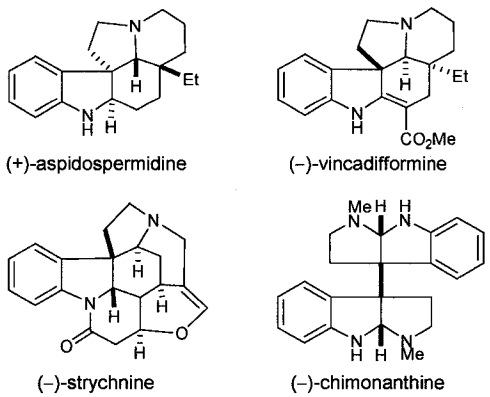


Figure 15. Examples of substituted indoline containing natural products

Retrosynthetic analysis of substituted indoline α-amino acids revealed a simple change from an alkylation to a Michael addition as the necessary modification to be adopted (Figure 16).

[98] Nicolaou, K. C.; Sorensen E. J. *Classics in Total Synthesis*; VCH publishers, Inc.: New York, NY, 1996; chapters 2, 33; Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*; Wiley-VCH: Weinheim, 2003; chapters 12, 18, 19, 20, 22.

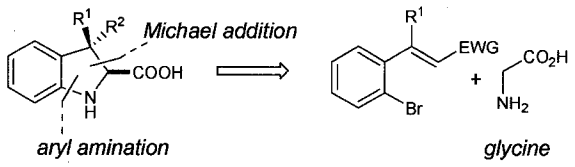
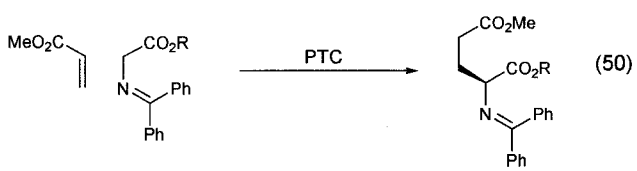


Figure 16. Retrosynthetic bond disconnections for substituted indoline α-amino acid

2.7.1. Michael Addition under PTC Conditions

There has been a renewed interest in the use of glycine Schiff base **177** in catalytic asymmetric Michael addition reactions to give protected glutamic acids (Scheme 30). Corey extended the alkylation protocol with modified cinchona alkaloid catalyst **181** to access a Michael adduct of methyl acrylate **185** in high % ee.[94,99]

Scheme 30. Recent examples of enantioselective PTC Michael addition reactions (eq 50)



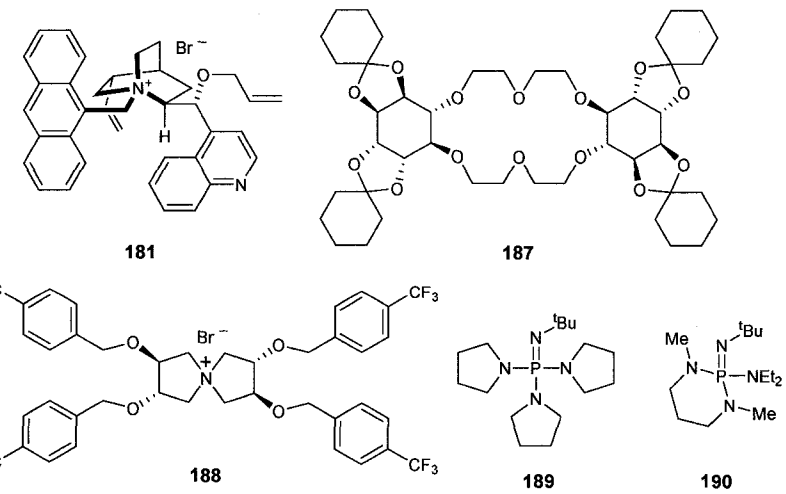
185 **177** **186**

Corey (R=^{t}Bu)	**181** (10 mol%) $CsOH•H_2O$ CH_2Cl_2 –78 °C, 4h	90% yield 95% ee
O'Donnell (R=^{t}Bu)	**181** (10 mol%) **189** or **190** CH_2Cl_2 –40 to –78 °C, 3-7h	82-93% yield 76-89% ee
Akiyama (R=Et)	**187** (20 mol%) KO^{t}Bu (cat.) CH_2Cl_2 –78 °C,15m-24h	65-80% yield 46-96% ee
Arai (R=^{t}Bu)	**188** (10 mol%) $CsOH•H_2O$ (cat.) ^{t}BuOMe –60 °C, 26h	90% yield 95% ee

O'Donnell has developed homogenous conditions for performing the same reaction using the Schwessinger bases (**189** or **190**) achieving moderate to good levels of

[99] Corey, E. J.; Noe, M. C. *Org. Synth.* **2003**, *80*, 38.

enantioselectivity. Using identical conditions, they have also developed the solid phase version of this reaction leading to unnatural peptides.[100]



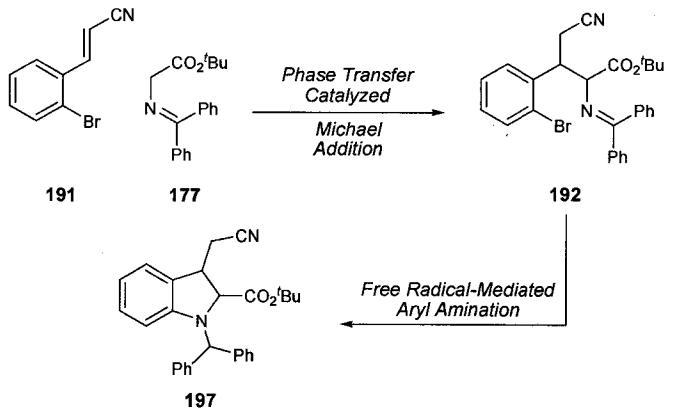
Akiyama developed inositol derived crown ether **187** as a phase transfer catalyst for the Michael addition, yielding adducts in moderate to excellent enantioselectivities.[101] A spiro ammonium salt **188** developed by Arai has also been employed efficiently in an enantioselective Michael addition reaction.[102] A diastereoselective synthesis of substituted glutamic acid derivatives under phase transfer catalysis has been developed independently by Alvarez-Ibarra and Pedregal.[103]

In the synthetic direction, our plan was to execute a phase transfer catalyzed Michael addition of glycine Schiff base **177** on a substrate like **191** as the first step. This would furnish imines like **192** which can be subjected to aryl amination to give substituted indoline amino acids like **197**. This plan is outlined in the following scheme.

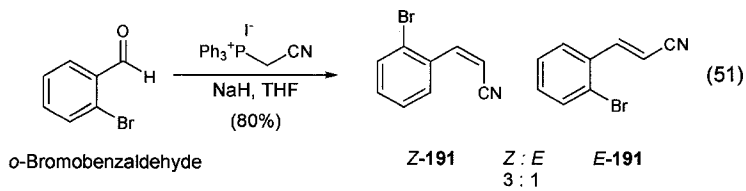
---

[100] O'Donnell, M. J.; Delgado, F.; Domíguez, E.; de Blas, J.; Scott, W. L. *Tetrahedron: Asymmetry* **2001**, *12*, 821.
[101] Akiyama, T.; Hara, M.; Fuchibe, K.; Sakamoto, S.; Yamaguchi, K. *Chem. Commun.* **2003**, 1734.
[102] Arai, S.; Tsuji, R.; Nishida, A. *Tetrahedron Lett.* **2002**, *43*, 9535.
[103] (a) Alvarez-Ibarra, C.; Csákÿ, A. G.; Maroto, M.; Quiroga, M. L. *J. Org. Chem.* **1995**, *60*, 6700. (b) Ezquerra, J.; Pedregal, C.; Merino, I.; Flórez, J.; Barluenga J.; Granda-García, S.; Llorca, M-A. *J. Org. Chem.* **1999**, *64*, 6554.

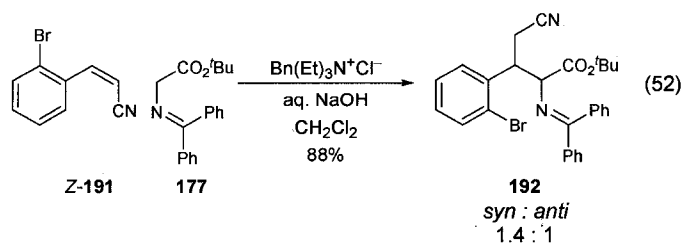
Scheme 31. Synthetic plan for substituted indoline α-amino acids



Substrate synthesis for the Michael reaction involved a Wittig olefination involving a ylide generated from ethyl cyanophosphonium iodide salt with sodium hydride and o-bromobenzaldehyde. This furnished a 3:1 (*Z*:*E*) mixture of stereoisomers in 80% overall yield of **191**. The isomers were separable by column chromatography (eq 51).

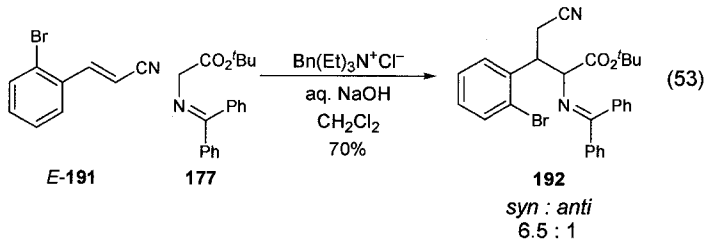


Treatment of glycine Schiff base **177** with the Z isomer of the nitrile (*Z*-**191**), under standard phase transfer conditions[97,104] resulted in a 1.4 : 1 ratio of *syn* and *anti* adducts **192** in 88% overall yield (eq 52).



[104] Use of benzyltriethyl ammonium chloride (20 mol%), 50% sodium hydroxide (20 equivalents) in dichloromethane solvent.

The Michael addition was, however, more stereoselective with the *trans* isomer of the nitrile (*E*-**191**), giving a 6.5 : 1 ratio of *syn* and *anti* diastereomers in 70% overall yield (eq 53). At this stage the *syn* and *anti* isomers were separated using flash chromatography.



E-**191** **177** **192**

syn : *anti*
6.5 : 1

2.7.2. Rationale of Stereoselectivity

The fact that Michael addition on *Z* and *E* isomers of the nitrile **191** gave significantly different diastereoselectivities was intriguing to us. In order to rationalize this stereoselectivity, we now advance a model. Here, the *E*-(O) nature of the enolate is assumed based on the model proposed by Corey to explain the enantioselectivity observed for alkylation reactions.[56] A cyclic transition state was originally proposed for Michael additions by Heathcock, however in these examples an open transition state is proposed.[105] The probable transition-states leading the *syn* and *anti* isomers of the Michael adduct are shown in Figure 17. In the case of the *E*-isomer of the Michael adduct, the transition state **193** arising from attack of the enolate on the *Re* face leads to the *anti* isomer in the product (*anti*-**192**). This conformational arrangement suffers from nonbonded interactions, both on the aryl and nitrile groups. Attack of the enolate on the *Si* face of the Michael acceptor leads to transition state **194**, eventually forming the *syn* isomer (*syn*-**192**). In this transition state, these non-bonded interactions are minimized and therefore would be lower in energy. This is reflected in the 6.5:1 ratio favoring the *syn* isomer.

[105] Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157. Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *20*, 87.

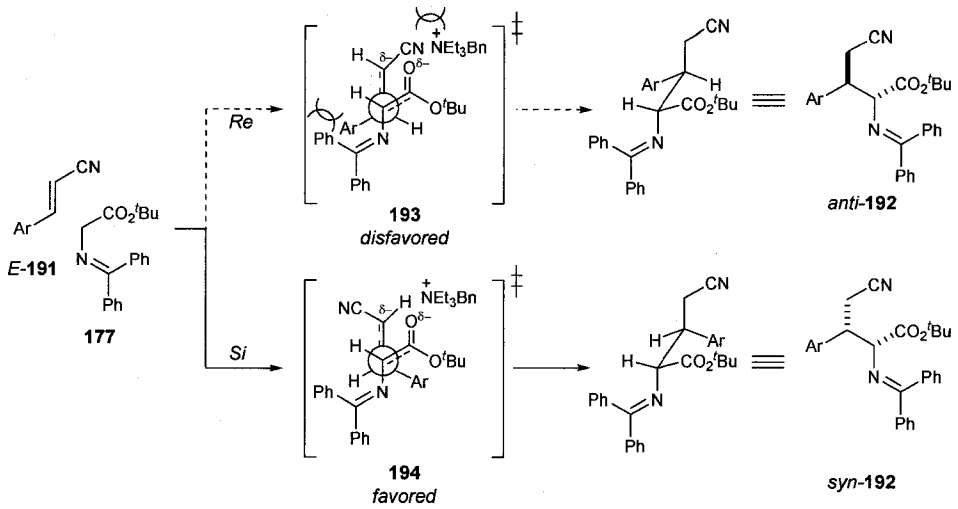


Figure 17. Proposed transition state assembly leading to *syn* and *anti* adducts for *E*-nitrile

In the case of the *Z* stereoisomer, the probable transition states are shown in Figure 18. *Re*-Face addition of the enolate leads to transition state assembly **195**. This assembly suffers from nonbonded interactions between the aryl group and the diphenylmethylene group. *Si*-Face addition of the enolate would lead to the transition state **196** in which the nonbonded interactions exist between the cyano group, enolate oxygen, and the quarternary ammonium group. Therefore, neither transition state would be preferred as they both suffer from nonbonded interactions. This is reflected in the nearly 1:1 ratio of the *syn* and *anti* adducts formed.

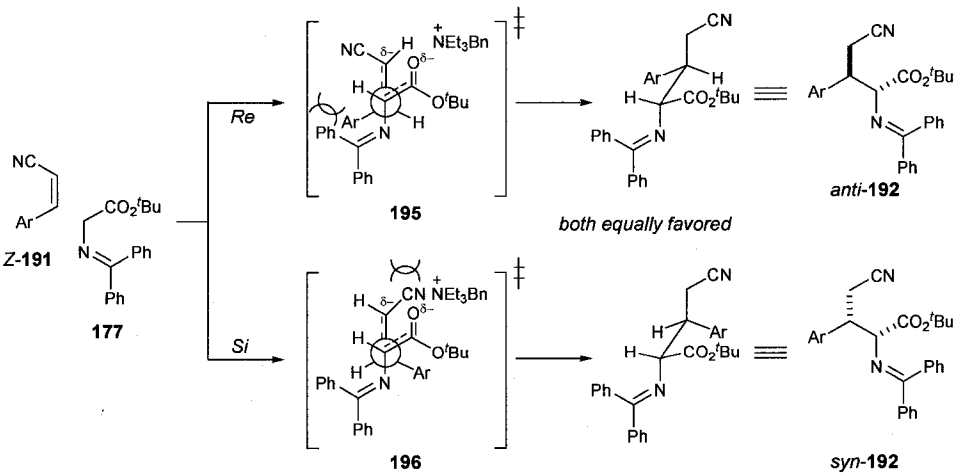
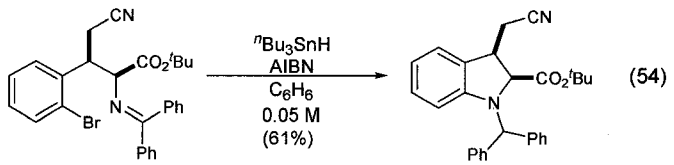


Figure 18. Proposed transition state assembly leading to *syn* and *anti* adducts for *Z*-nitrile

2.7.3. Aryl Amination of Substituted Schiff Bases

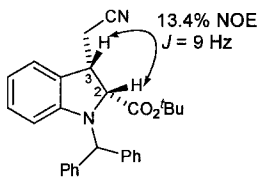
The subsequent cyclization of the *syn* diastereomer (*syn*-**192**) proceeded smoothly under standard aryl amination conditions to yield indoline *cis*-**197** in 61% yield (eq 54).[106] However, some erosion in diastereoselectivity was observed by HPLC. The mechanism to account for this erosion will be discussed in detail in Chapter 4.



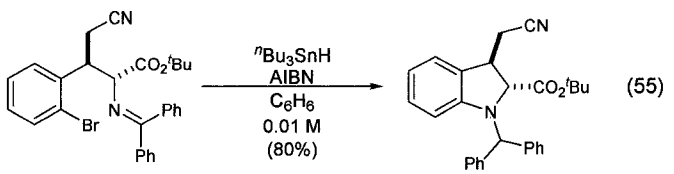
syn-**192**
dr = >200 : 1

cis-**197**
dr = 52 : 1

The relative configuration of *cis*-**197** was determined using NOE measurements and ^{1}H NMR coupling constants (see inset). In the *cis* isomer, the NOE between hydrogens on C2 and C3 was 13.4%. This was further substantiated by the *J* value of 9.0 Hz between these hydrogens, indicating a *cis* relationship between them. The *anti* diastereomer of the imine (*anti*-**192**) underwent aryl amination to furnish the corresponding indoline *trans*-**197** in 80% yield. In this case, no epimerization leading to erosion of diastereoselectivity was observed (eq 55).



cis-**197**



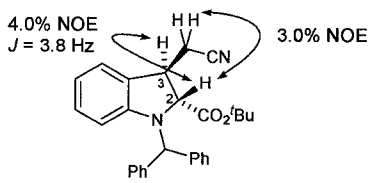
anti-**192**
dr = >200 : 1

trans-**197**
dr = >200 : 1

The relative configuration of *trans*-**197** was also determined using NOE measurements and ^{1}H NMR coupling constants (see inset). The hydrogens on C2 and C3 showed an NOE measurement of only 4.0%. The corresponding *J* value was also smaller between

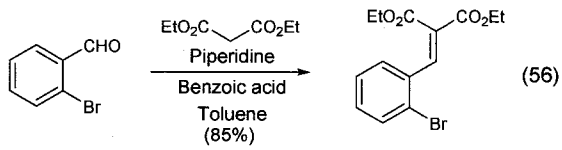
[106] Note that the terminology *syn* and *anti* refer to acyclic compounds however cyclic compounds are refered to as *cis* and *trans* isomers.

these hydrogens (3.8 Hz). This indicated a *trans* relationship between these hydrogens on the 5-membered indoline ring. Significantly, an NOE measurement of 3.0% was also seen between the hydrogen on C2 and the hydrogen on the cyanomethylene substituent on C3. This further confirmed the *trans* nature of the substituents on the indoline ring.



trans-**197**

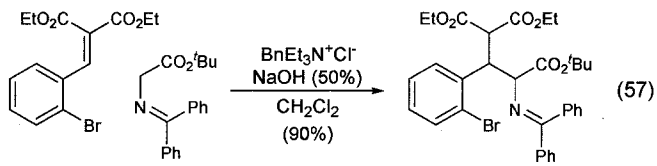
In order to diversify the scope of the Michael addition/aryl amination strategy, an alkylidene malonate substrate was designed. This substrate could be synthesized in a straightforward manner through a Knoevenagel condensation of diethyl malonate and *o*-bromobenzaldehyde (eq 56). This reaction furnished the alkylidene malonate **198** in 85% yield after distillation of the product.



(56)

o-Bromobenzaldehyde **198**

Subjecting the alkylidene malonate **198** to the standard phase transfer conditions with Schiff base **177** resulted in a very fast Michael addition reaction (eq 57). Adduct **199** was formed in 90% yield, however in a 1:1 ratio of separable *syn* and *anti* isomers.

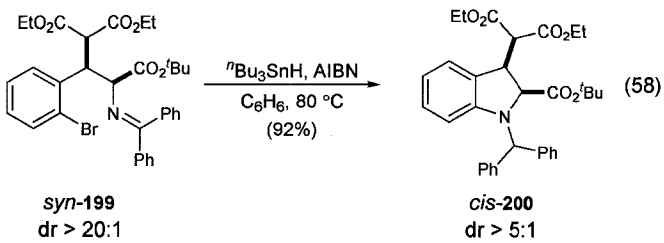


(57)

198 **177** **199**

syn : *anti* = 1 : 1

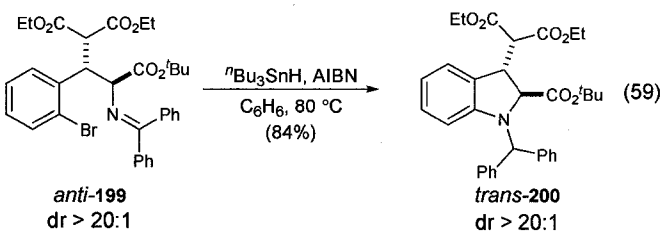
The separated diastereomeric imines were individually treated under standard aryl amination conditions. The *syn* isomer (*syn*-**199**) underwent smooth aryl amination furnishing indoline *cis*-**200** in 92% yield (eq 58). Parallel to the nitrile case discussed previously, an erosion of diastereoselectivity occurred during this reaction. The *cis* nature of the indoline ring substituents was assigned based on the ^{1}H NMR coupling constants between hydrogens on C2 and C3.



syn-**199**
dr > 20:1

cis-**200**
dr > 5:1

The *anti* isomer of imine (*anti*-**199**) was also subjected to standard aryl amination conditions. This resulted in a smooth cyclization to furnish indoline *trans*-**200** in an 84% yield (eq 59). There was no erosion of stereochemistry during the cyclization of this isomer, paralleling the observation made in the nitrile case. The *trans* nature of the indoline ring substituents was assigned based on the ^{1}H NMR coupling constants between hydrogens on C2 and C3.



anti-**199**
dr > 20:1

trans-**200**
dr > 20:1

2.8. Sequential Michael Addition/Alkylation/Aryl Amination

A one-pot protocol incorporating a sequential Michael addition-alkylation was designed in order to access highly functionalized indolines (Figure 19). The fact that the rate of the Michael addition to an alkylidene malonate is higher than that of alkylation was the key factor behind this design.

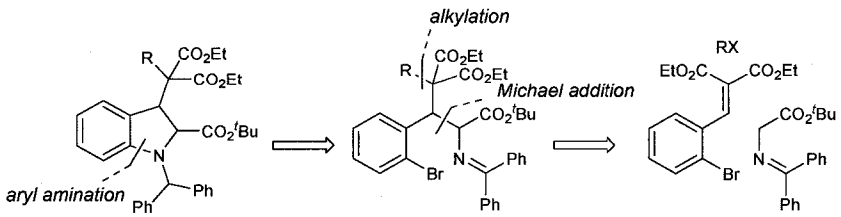
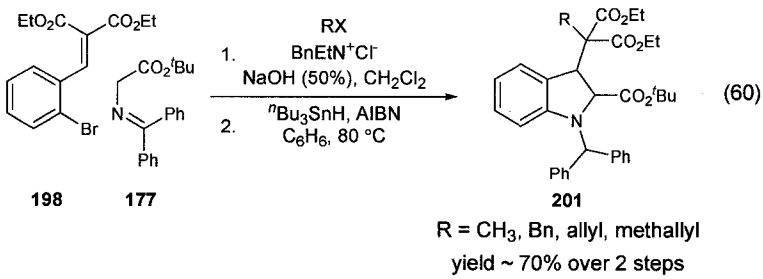


Figure 19. Retrosynthetic bond disconnections for highly substituted indoline α-amino acids

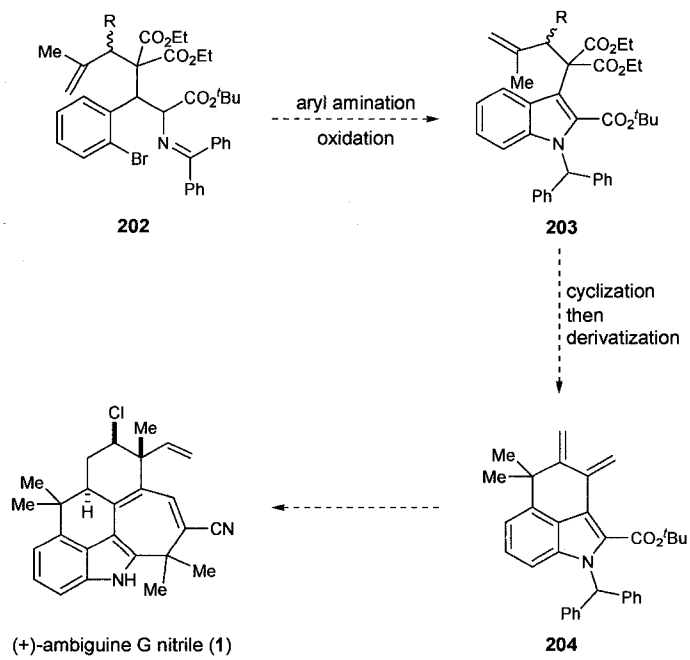
This design was executed in practice by employing a variety of alkyl, allyl, and benzyl halides.[107] Although the differential rates of Michael addition and alkylation enable addition of the alkylating agent at the beginning of the reaction, the process was fully optimized by adding the alkylating agent to the reaction mixture after the initial Michael addition was complete (after 3-4 h, eq 60).



(60)

Overall, this sequence was found to be highly efficient in building the indoline core in a concise fashion.

Scheme 32. Application of Michael addition/alkylation/amination toward (+)-ambiguine G



[107] Smith C. R.; Prabhakaran, E. N.; Viswanathan, R.; Johnston, J. N. unpublished work.

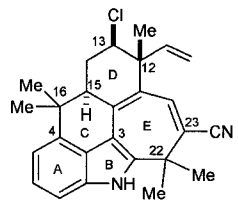
In summary, a conceptually unique aryl amination strategy was developed, and its scope and generality were explored. This method was utilized for the asymmetric synthesis of indoline α-amino acids, affording these products in high enantiomeric excess. Further expansion of this strategy led to the stereoselective synthesis of substituted indoline α-amino acids, which are functionalized building blocks toward natural product synthesis.

Currently, this protocol is being evaluated as a key strategy for accessing the ABC ring system of the indole natural product (+)-ambiguine G (Scheme 32). This will be discussed in detail in the following chapter.

Chapter 3. Synthetic Efforts Toward (+)-ambiguine G

3.1. Introduction

The structure of (+)-ambiguine G nitrile is shown in Figure 20. Among the broad family of indole alkaloids, (+)-ambiguine G nitrile possesses some unique structural features that include a neopentyl chlorine atom on C13, a C12 quaternary carbon, a nitrile group on C23, a C15 stereocenter, two geminal dimethyl groups on C16 and C22 respectively. The pentacyclic indolo-terpenoid framework (labeled as A, B, C, D and E rings in Figure 20)[108] includes a trisubstituted indole ring (C2 C3 and C4)[109] and a 1,3,5-cycloheptatriene E ring.



(+)-ambiguine G nitrile (**1**)

Figure 20. Structure of (+)-ambiguine G nitrile with ring and atom labeling

3.2. Retrosynthetic Strategies in (+)-ambiguine G

While planning the synthetic route to ambiguine G, several challenges were apparent. Introduction of the halogen atom at a sterically crowded neopentyl carbon (C13) would not likely be possible using nucleophilic substitution. Although the chlorine atom occupies an equatorial position in the energy minimized conformation of ambiguine

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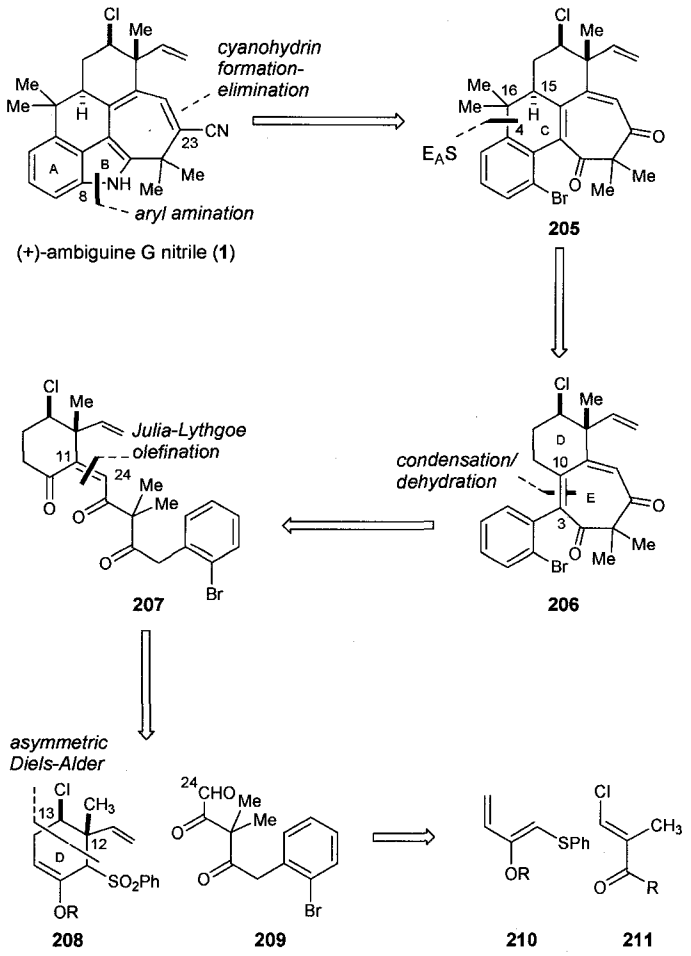
[108] Resource that describes rings and IUPAC nomenclature did not contain this entry therefore the assignment of rings is arbitrary. Numbering of the carbon skeleton follows that of the isolation report: See Chapter 1, ref 2.

[109] A similar 6-5-6-ABC indole ring system is present in *ergot* alkaloids – Rebek, J. Jr.; Tai, D. F.; Shue, Y. –K. *J. Am. Chem. Soc.* **1984**, *106*, 1813 and Martin, S. F.; Liras, S.; *J. Am. Chem. Soc.* **1993**, *115*, 10450.

G, elimination could occur through other reactive conformers under various reaction conditions. Setting the stereochemistry at the C12 quaternary carbon in a predictable fashion was anticipated to be a challenge.[110] Two significantly different disconnection approaches were envisioned to tackle these synthetic challenges. These two approaches differed in the sequence in which the rings would be assembled. The first generation approach is outlined in Scheme 33.

Scheme 33. First generation retrosynthetic approach to (+)-ambiguine G nitrile (**1**)



The mild and regioselective radical-mediated amination process developed in our laboratories will be employed to introduce the indole ring, perhaps even in the final

[110] Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363; Barriault, L.; Denissova, I. *Tetrahedron* **2003**, *59*, 10105.

stages.[111] Straightforward disconnections that include cyanohydrin formation and electrophilic aromatic substitution would then lead to the tetracyclic bisenone **206** as an advanced intermediate in the retrosynthetic direction. Construction of the seven-membered bisenone functionality in **206** was envisioned through disconnection of the C3-C10 olefinic bond using an aldol condensation/dehydration step. This would lead to triketo-olefin **207**. This key cyclization step was expected to be facile under acidic conditions considering the enolizable nature of the benzylic position on C3 and also the presence of the geminal dimethyl group on C22 assisting conformationally (Thorpe-Ingold effect). Julia-Lythgoe olefination seemed appropriate for the formation of the trisubstituted olefin in **207**. Sulfones possessing steric hindrance comparable to that of **207** have been used for olefination under Julia-Lythgoe conditions. The greater magnitude of $A^{1,3}$ strain with the quaternary center (C12) should encourage selective formation of the *Z*-olefin in **207**. Thus the precursor to the sulfone would be the corresponding sulfide **208**. This compound contains an enol-ether, two stereocenters including the neopentyl chloride. A stereoselective Diels-Alder reaction was envisioned to be the best solution for the construction of **208**. This option also opens the possibility of developing an enantioselective version using chiral Lewis acid catalysis,[112] since such catalysts have been effective for many Diels-Alder reactions.[113] Diene of the type **210** and dienophile of the type **211** were targeted as viable starting points for the synthetic route.

The alternative retrosynthetic plan that was envisioned is outlined in Scheme 34. Use of the same Diels-Alder approach toward ring D, however, as a late stage of the synthesis would lead to **212** as a viable advanced intermediate. A similar late stage Diels-Alder reaction has been executed toward the total synthesis of (–)-acanthoic acid.[114] Use of an appropriate annulation strategy and functional group transformations for the construction of the cycloheptatriene containing E-ring in **212** would then reveal tricyclic ketone **214** as a viable precursor.

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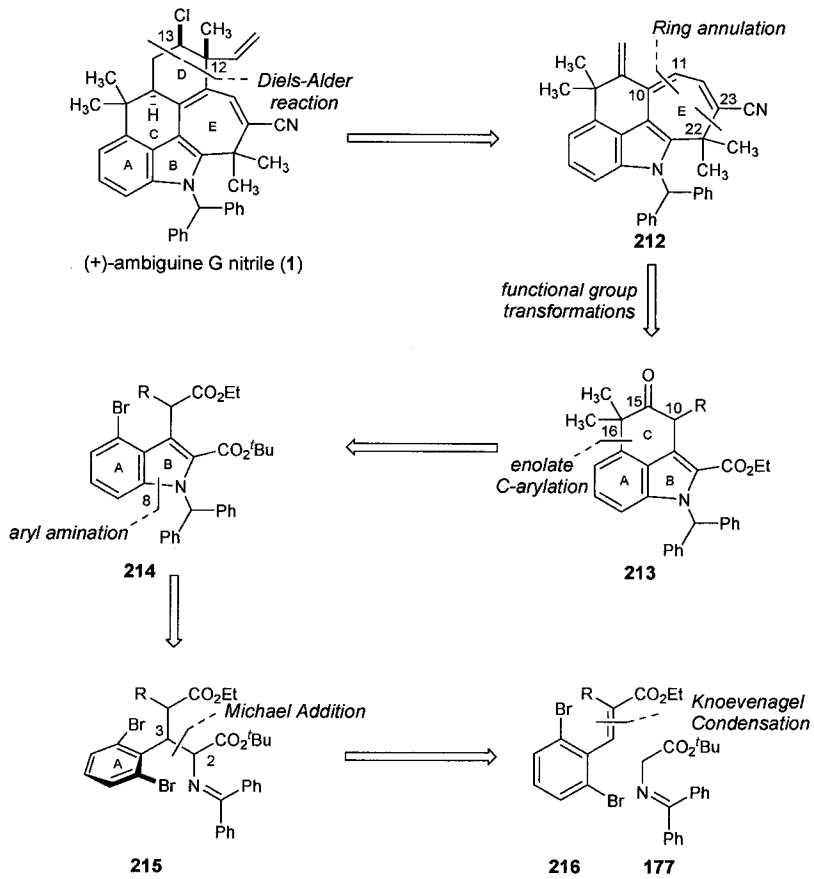
[111] Refer Chapter 2, reference 53.
[112] For Bronsted Acid Assisted Chiral Lewis Acid (BLA) Catalyst for Asymmetric Diels-Alder Reaction see: *J. Am. Chem. Soc.* **1994**, *116*, 1561.
[113] Review on Diels-Alder reactions: Evans, D. A.; Johnson, J. S. in *Comprehensive Asymmetric Catalysis* Jacobsen E. N., Pfaltz, A., Yamamoto, H. Eds.; 2004, Chapter 33, pp1178.
[114] Ling, T.; Kramer, B. A.; Palladino, M. A.; Theodorakis, E. A. *Org. Lett.* **2000**, *2*, 2074.

Scheme 34. Second generation retrosynthetic approach to (+)-ambiguine G nitrile



Disconnection of the C16-C4 bond of **213** gave rise to an enolate arylation of the indole C4 position as an appropriate strategy. Several organometallic catalysts have been developed for this bond construction step.[115] However, such a reaction has not been exploited in complex natural product synthesis. Therefore, this step was expected to be one of the challenges in the planned sequence. AB-ring containing indole **214** could arise from its corresponding indoline through an early stage aryl amination step. This regioselective 5-*exo* radical cyclization of the corresponding di-bromo precursor was expected to proceed efficiently based on prior studies done with similar substrates.[116] The imine **215** could be envisioned to be synthesized efficiently from a Michael acceptor **216** and Schiff's base **177**. This Michael addition/aryl amination sequence has been well

[115] Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.
[116] Refer to Michael addition/Aryl Amination section, chapter 2.

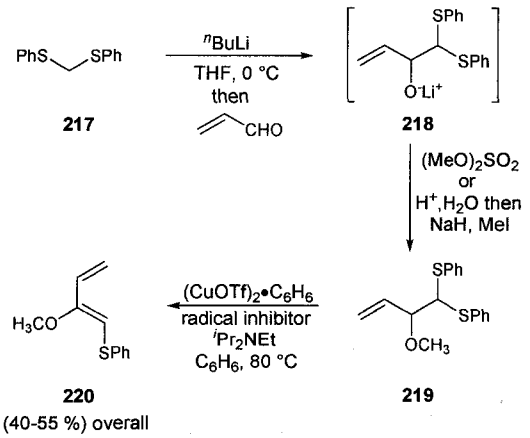
established. Cinnamate type **216** would in turn be easily synthesized from commercially available starting materials. This route offers the possibility of a late stage enantioselective variant of the Diels-Alder reaction to produce the enantiopure version of the natural product.

3.3. Efforts Along the First Generation Approach

3.3.1. Synthesis of Diene Portion

Scheme 35 outlines the synthesis of diene **220**.[117] This three step protocol involved the synthesis of bisthiophenyl methane **217** from benzenethiol and dichloromethane. This reaction proceeded smoothly at room temperature to give **217** as a white crystalline solid which could be purified by simple recrystallization. Deprotonation of **217** using butyllithium and trapping with acrolein provided the alcohol or the corresponding methyl ether **219** depending on the quenching agent. In the case where the alcohol was obtained (upon acid quench of **218**) methylation was carried out with methyl iodide and sodium hydride.

Scheme 35. Synthesis of Cohen's diene



[117] Cohen, T.; Ruffner, R. J.; Shull, D. W.; Fogel, E. R.; Falck, J. R. *Org. Syn.* **1979**, *59*, 202.

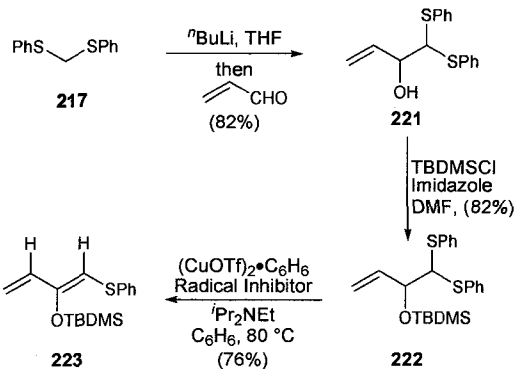
Conversion of the methylether **219** to the diene **220** involved the use of Cu(I) triflate-benzene complex. This reaction also made use of Hunig's base to quench the *in-situ* formed triflic acid. A radical inhibitor was required to prevent diene polymerization. The overall sequence typically proceeded in 40-55% yield. Such a variable yield range reflects the sensitive nature of the diene **220**.

It is known that Cohen's diene is thermal and pH sensitive, leading to olefin isomerization and/or polymerization. For example, simple stirring of the *Z*-diene in dichloromethane led to the thermodynamically more stable *E*-isomer (eq 61). Therefore, control of the diene geometry evolved as a major challenge in the development of our Diels-Alder reaction.

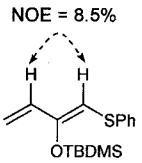
(61)

Due to the thermal instability of the methoxy substituted diene, an alternative silyloxy version of Cohen's diene **223** was envisioned as a practical alternative.[118] The parallel route for the synthesis of this diene is outlined in Scheme 36.

Scheme 36. Synthesis of siloxy version of Cohen's diene



[118] Kozikowski, A. P.; Huie, E. M. *J. Am. Chem. Soc.* **1982**, *104*, 2923.



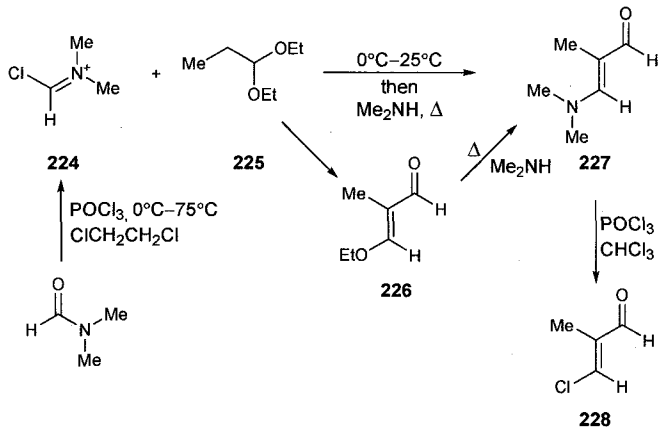
223

Cohen's protocol was employed without any alterations. TBDMS chloride replaced dimethyl sulfate in the alcohol derivatization step.[119] The diene forming step also proceeded as described in the previous case, producing the silyloxy diene **223** in 76% yield. The *Z* geometry of this diene was verified using NOE irradiation (see inset). The *Z*-nature of this diene was found to be conserved for a much longer duration when compared to the methoxy version, thus bringing the practical issues of handling the diene to a simpler level. However, doubts remained about the reactivity and synthetic utility of this diene due to its greater thermal stability.

3.3.2. Synthesis of Dienophile Portion

Synthesis of aldehyde **228** was carried out using a Vilsmeier-Haack reaction with propionaldehyde diethyl acetal, as reported by Arnold (Scheme 37).[120]

Scheme 37. Synthesis of chloro-aldehyde **228** through Vilsmeier reaction

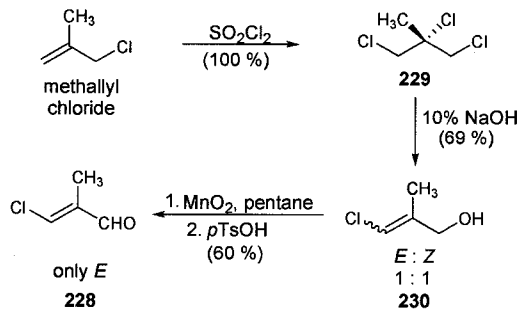


The Vilsmeier salt **224** was formed at 0 °C in dichloroethane, using phosphorous oxytrichloride and *N*,*N*-dimethyl formamide. Propionaldehyde diethyl acetal (**225**) was then added, and the mixture was heated to 75 °C to give vinylogous amide **227** after work-up. In some attempts the vinylogous amide was contaminated with vinylogous ester

[119] Corey, E. J.; Venkateswarulu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
[120] Arnold, T.; Zemlicka, J. *J. Collect. Chem. Comm.* **1959**, *24*, 2385; Barton, D. H. R.; Barrett, A. G. M.; Pfeffer, M. *J. Chem. Soc., Perkin Trans.* **1982**, *3*, 665.

226, but this was converted to the vinylogous amide under excess dimethylamine and heat. Treatment of the crude vinylogous amide **227** with phosphorous oxychloride in chloroform resulted in formation of the aldehyde **228** which could be purified by distillation. Though this sequence stereoselectively produced the *E*-isomer of aldehyde **228**, it was practically very difficult to reproduce the yields using the reported protocol. Also upon scale up there was a significant drop in the yield of vinylogous amide **227**. Therefore, an alternative method developed by Williard was attempted (Scheme 38).[121]

Scheme 38. Alternative synthesis of chloro aldehyde **228**



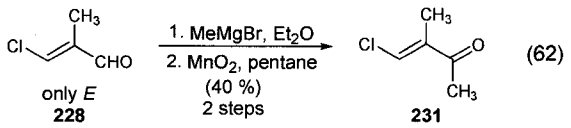
Commercially available methallyl chloride was perchlorinated using sulfuryl chloride to give the meso trichloride **229** in quantitative yield. Caution was exercised during this process as accumulation of sulfur dioxide could trigger a highly exothermic reaction. Therefore, slow addition of methallyl chloride was necessary. Straightforward base wash furnished pure chloride in quantitative yield. Hydroxide-mediated elimination and nucleophilic displacement proceeded smoothly to give chloro-allylic alcohol **230** as a 1:1 mixture of *E* and *Z* stereoisomers. Though Williard[13b] was able to separate the isomers using spinning band distillation, it proved difficult in our hands. Therefore, this 1:1 mixture was oxidized to the corresponding aldehyde using activated manganese dioxide. Without prior activation of manganese dioxide, the oxidation was very sluggish. In order to isomerize *Z*-**228** to the corresponding *E*-isomer, a catalytic amount of p-toluenesulfonic acid was added to the crude mixture before removal of the pentane

[121] Synthesis of beta chloro alpha methyl acroleins : (a) Mooridian, A.; Cloke, J. B. *J. Am. Chem. Soc.* **1946**, *68*, 785. (b) Williard, P. G.; Grab, L. A.; de Laszlo, S. E. *J. Org. Chem.* **1983**, *48*, 1123.

solvent by distillation. Thus pure *E*-**228** was produced in 60% yield. The aldehyde produced from this step was stored and purified by distillation prior to use during the Diels-Alder reactions. The aldehyde was not very stable, and long term storage even at low temperature (0 °C) resulted in decomposition.

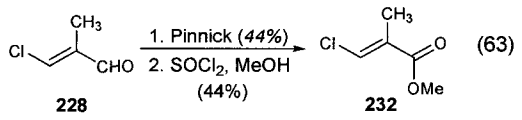
Synthesis of Methyl Ketone (231) and Methyl Ester (232) Dienophiles

Due to the unstable nature of the aldehyde **228**, synthesis of the corresponding methyl ketone and methyl ester dienophile was attempted. Aldehyde **228** was dissolved in ether and treated with methyl magnesium bromide at 0 °C to give a secondary alcohol which was subjected to manganese dioxide oxidation to give methyl ketone **231** in 40% yield over two steps (eq 62). This ketone was purified by distillation *in vacuo* to provide a liquid that could be stored for months without decomposition.



(62)

Aldehyde **228** was subjected to Pinnick oxidation[122] to give the chloro methacrylic acid in 44% yield. The resulting acid was treated with thionyl chloride in methanol to furnish the corresponding methyl ester **232** in 44% yield (eq 63). Methyl ester **232** was also stable and could be stored for long periods without decomposition.

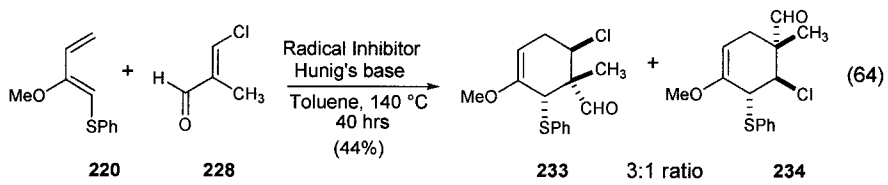


(63)

[122] Hillis, L. R.; Ronald, R. C. *J. Org. Chem.* **1985**, *50,* 470; Bal, B. S.; Childers, Jr. W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

3.3.3. Diels-Alder Reaction Under Thermal Conditions

Having synthesized both the diene (**220**) and the dienophile (aldehyde **228**) components, execution of the Diels-Alder reaction was the next goal.[123] Three major factors posed initial obstacles. First, the aldehyde was not thermally stable, and a significant amount of decomposition was observed. Second, the acid sensitivity of the diene was significant, and as a result, isomerization to the corresponding unreactive *E*-isomer was facile. Third, the diene was also prone to polymerization. Use of a base and a radical inhibitor were always necessary to overcome the latter two factors.



Diene **220** was purified using silica gel (pretreated with Et_3N) chromatography until the removal of any colored impurities (not visible by NMR) in order to minimize polymerization when heated. In order to minimize the isomerization of the *Z*-diene to the *E* isomer, the inside surfaces of the glassware was silylated by treating with methyl lithium and trimethyl chlorosilane. This procedure effectively minimized the isomerization during reaction. Dissolved residual oxygen in toluene was also a suspected cause for diene polymerization. Therefore, toluene used for thermal Diels-Alder reaction was freeze-pump-thawed prior to use. The diene solution concentration was maintained at 0.3 M. Applying these precautions resulted in a thermal reaction (sealed tube) that yielded 44% of adducts **233** and **234** as a 3:1 mixture of regio-isomers (eq 64). Only the *endo* adduct was observed (^{1}H NMR). NOE measurements confirmed the *cis* nature of the aldehyde group and the thiophenyl moiety, thus confirming the *endo* stereochemistry (Figure 21). The reaction worked on a small scale, however upon scale up the yield dropped as a result of polymerization of the diene component.

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[123] Gelmi, M. L.; Clerici, F.; Beccalli, M. E. *Tetrahedron* **1999**, *55*, 8579. Williard, P. G.; de Laszlo, S. E. *J. Org. Chem.* **1985**, *50*, 3738

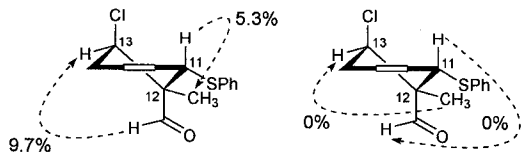
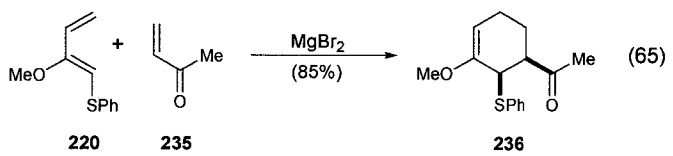


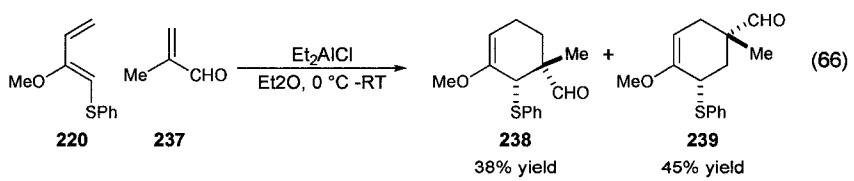
Figure 21. NOE measurements for Diels-Alder adduct **233**

3.3.4. Lewis Acid Mediated Diels-Alder Reactions

Parallel to the thermal conditions for the cycloaddition, the use of Lewis acids was also explored. Cohen had reported Diels-Alder reactions of **220** with various ketones including MVK (**235**) under thermal[124] and Lewis acid[125] conditions.[126]



Consistent with their observation, Diels-Alder adduct **236** was isolated (eq 65). Since there were no aldehydes used in the study by Cohen, we performed a test reaction by using methacrolein as the dienophile. Treatment of methacrolein **237** with diethyl aluminum chloride, provided two adducts, **238** and **239** in 38% and 45% yields, respectively. ^{1}H-^{1}H decoupling revealed the minor isomer to be the desired regioisomer (**238**). NOE enhancements confirmed the endo stereochemistry.



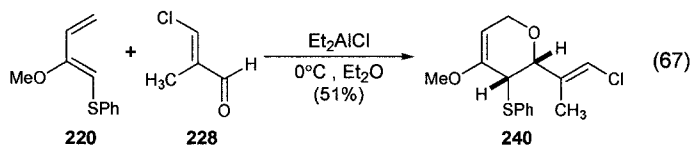
[124] Ottenbrite, R. M.; Alston, P. V. *J. Org. Chem.* **1975**, *40*, 1111; Ottenbrite, R. M.; Alston, P. V.; Cohen, T.; *J. Org. Chem.* **1978**, *43*, 1864; Cohen, T.; Ruffner, R. J.; Shull, D. W.; Daniewski, W. M.; Ottenbrite, R. M.; Alston, P. V. *J. Org. Chem.* **1978**, *43*, 4052; Alston, P. V.; Gordon, M. D.; Ottenbrite, R. M.; Cohen, T. *J. Org. Chem.* **1983**, *48*, 5051.

[125] Complete regio- and stereospecificity in the Lewis acid catalyzed Diels-Alder Reactions of Cohen's diene: Cohen. T.; Kosarych, Z. *J. Org. Chem.* **1982**, *47*, 4005.

[126] No aldehydes were used in the study.

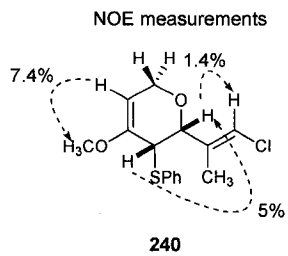
The Diels-Alder reaction between Cohen's diene **220** and chloro aldehyde dienophile **228** was screened using a series of Lewis acids consisting of BF_3•Et_2O, $MgBr_2$, $AlCl_3$, Me_3Al, Cu(I) triflate-benzene complex, lithium perchlorate-diethyl ether, and Yamamoto's[127] borane Lewis acid. Under all of these conditions there was either significant decomposition of the diene or complete isomerization of the diene and hence no identifiable product.

The reaction between diene **220** and dienophile **228** with diethylaluminum chloride[128] at 0 °C led to a 51% yield of the hetero Diels-Alder adduct **240** (eq 67). About 30% of the isomerized (*E*)-diene was also isolated from this reaction.

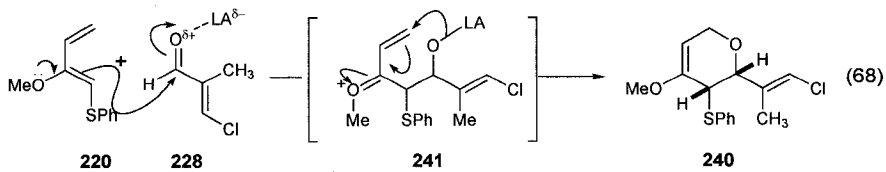


220 **228** **240**

The structural identity of adduct **240** was confirmed by ^1H-^1H decoupling study and the stereochemistry was found to be *cis* using NOE enhancements. Thus the formation of a normal Diels-Alder adduct with methacrolein and a hetero Diels-Alder product with aldehyde **228** suggested that the substitution at the β-carbon of the dienophile was crucial in dictating the course of the reaction. Mechanistically, the formation of the hetero Diels-Alder adduct also could be envisioned to occur *via* a polar non concerted pathway through **241** as depicted in eq 68.



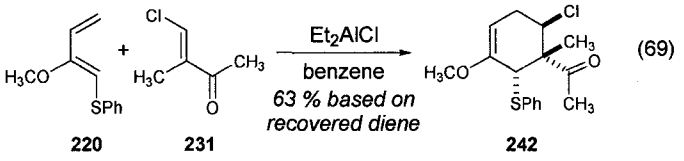
240



220 **228** **241** **240**

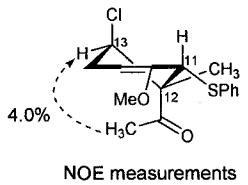
[127] Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. J. Org. Chem. **1989**, *54*, 1483.
[128] Use of Diethyl aluminum chloride as a Lewis acid catalyst for Diels-Alder reaction : Schlessinger, R. H.; Schultz, J. A. *J. Org. Chem.* **1983**, *48*, 408.

In order to circumvent this, a ketone variation was attempted under Lewis acidic conditions. Thus use of ketone **231** with Cohen's diene and diethyl aluminum chloride in benzene gave rise to a 63% yield of the adduct **242** based on recovered diene. Conditions necessitated the presence of Hunig's base in order to minimize the diene isomerization process and this factor forced the use of 2.5 equivalents of the Lewis acid.



220 231 242 (69)

The Diels-Alder adduct was found to be thermally somewhat unstable and was therefore carried through the next step immediately after isolation. The *endo* stereochemistry of the adduct was confirmed using NOE enhancements (Figure 22)

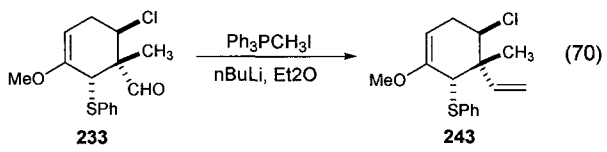


NOE measurements

Figure 22. NOE measurements for Diels-Alder adduct **242**

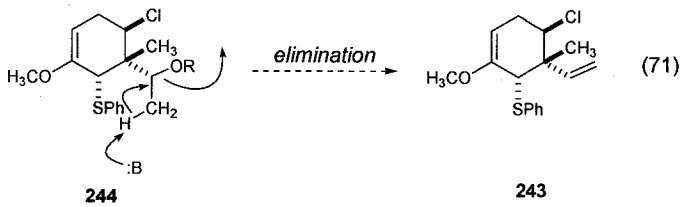
3.3.5. C20-C21 Olefination

In order to introduce the terminal C20-C21 olefin in (+)-ambiguine G, several attempts were made. The most straightforward was the conversion of the aldehyde functionality in the thermal Diels-Alder adduct (**233**) to an olefin using a Wittig reaction. Thus aldehyde (**233**) was dissolved in diethyl ether and was added to a solution of the Wittig reagent at -78 °C. This reaction proceeded smoothly to give olefin **243** in 51% yield (eq 70).



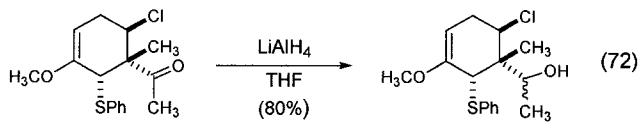
233 243 (70)

In the case of the methyl ketone derived Diels-Alder adduct, the plan was to reduce the ketone functionality to the corresponding alcohol and then convert the alcohol into a good leaving group (**244**), with final treatment with an appropriate base to create the olefin (eq 71).



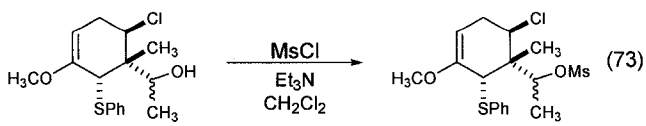
244 **243** (71)

Reduction of ketone **242** to the alcohol **245** using lithium aluminum hydride was straightforward, affording a 1:1 mixture of diastereomers in 80% yield (eq 72). Conversion of the alcohol to its mesylate was attempted with the idea that treatment of the resulting compound with base should lead to the required olefin as the elimination product.



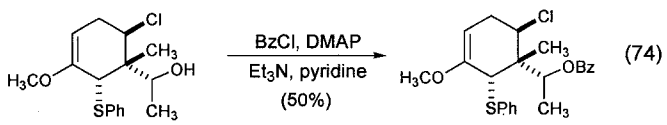
242 **245** (72)

However, the corresponding mesylate was found to readily decompose even in deuterated chloroform (eq 73). Alternative methods for the conversion of the alcohol to the terminal olefin were sought. The Burgess reagent was prepared and treated with the alcohol, without success. Next, conversion of the alcohol to the corresponding benzoate ester was considered with the idea of attempting a *syn* elimination (Chugaev).



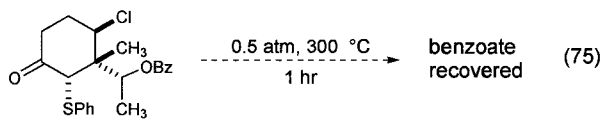
245 **246** (73)

Benzoylation was found to be a very slow process due to the sterically hindered nature of the alcohol **245**. Use of pyridine as solvent over dichloromethane had a significant rate acceleration, giving the benzoate ester **246** in 50% yield (eq 74).



245 **247** (74)

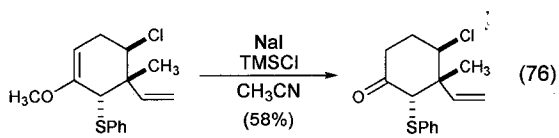
When the benzoate **247** was warmed to 300 °C under low pressure (0.5 atm), there was no change with complete recovery of starting material.



247 (75)

3.3.6. Enol Ether Deprotection

The synthetic plan required a ketone at C10. Therefore, the methyl enol ether group in **243** was deprotected using standard conditions of trimethylsilyl chloride and sodium iodide (eq 76).[129]



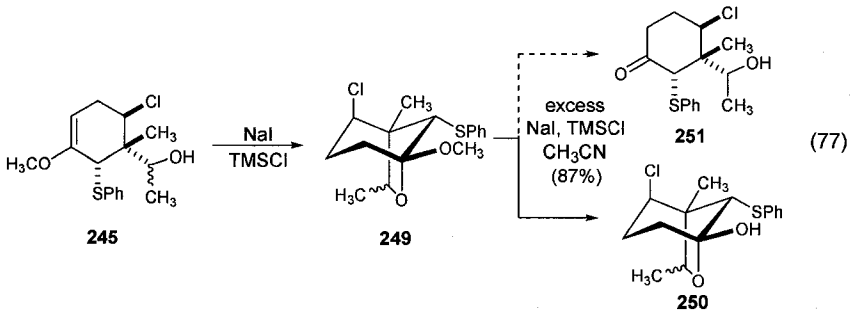
243 **248** (76)

However in the case of alcohol **245**, this deprotection step led to an unavoidable side reaction (eq 77). The alcohol group intramolecularly trapped the oxonium ion resulting in the ketal **249**.

[129] Cohen, T.; Kosarych, Z. *Tetrahedron Lett.* **1980**, *21*, 3959; Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

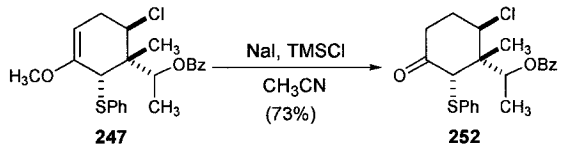
Both diastereomers of the ketal **249** were characterized. The diastereomeric ratio reflected that obtained during the previous reduction step (Scheme 39). In fact, cyclic form was so favored that an additional 10 equivalents of sodium iodide and trimethylsilyl chloride, resulted in formation of hemiketal **250**.

Scheme 39. Enol-ether deprotection leading the cyclic ketal **249**



(77)

No open form **251** was formed. In order to side step this issue of ketalization, the deprotection was attempted on the protected benzoate ester compound (**247**). Thus, when the benzoate **247** was exposed to the standard deprotection conditions, the enol ether was converted to the ketone **252** in 73% yield (eq 78).



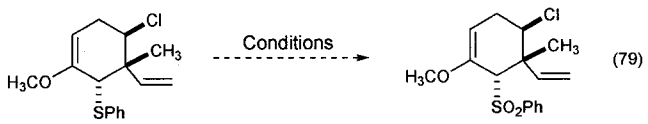
(78)

3.3.7. Oxidation of Sulfide to Sulfone

The oxidation of the sulfide group on C11 to the corresponding sulfone was the next goal. Oxidation attempts with mCPBA (with $NaHCO_3$ or pH=8.0 buffer) showed an initial reaction however, eventually resulted in decomposition of the sulfide. This probably was due to an Evans-Mislow rearrangement[130] of the initially formed allylic sulfoxide. Periodate based oxidants (sodium periodate and tetrabutyl ammonium periodate) failed to effect any reaction. Ammonium molybdate based oxidant also

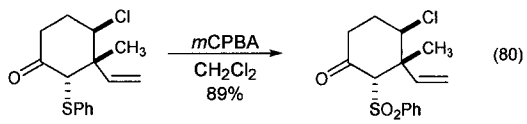
[130] Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147.

resulted in decomposition of the sulfide. DMDO also caused decomposition while oxone resulted cleavage of the enol ether.



243 253 (79)

The fairly electron rich enol-ether functionality in **243** was suspected to be interfering with the oxidation. Therefore, it was worthwhile to explore oxidation of the corresponding ketone **248**. As expected, the corresponding deprotected ketone **248** underwent smooth oxidation with mCPBA to give sulfone **254** in 89% yield (eq 80).



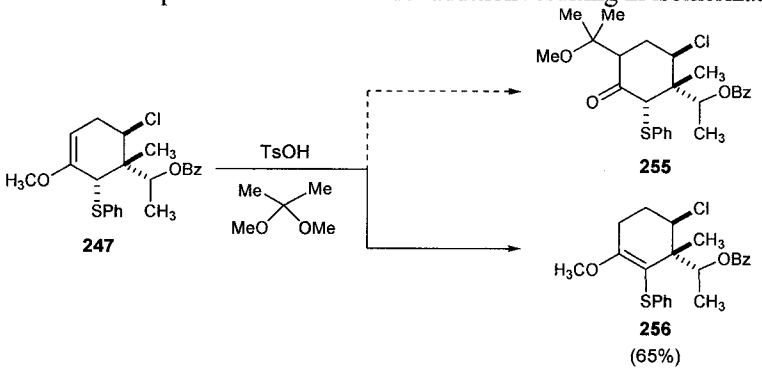
248 254 (80)

3.3.8. C16 Geminal Dimethyl Group

The enol-ether functionality in benzoate **247** may serve as a nucleophile in a Lewis acid promoted aldol type process.[131] This strategy would also circumvent deprotection of this functional group separately. Dimethoxypropane was thought to be an appropriate electrophile under acidic conditions. No reaction occurred when only a slight excess of dimethoxypropane was used. However, when dimethoxypropane was used as solvent, in the presence of p-toluenesulfonic acid, the enol ether rearranged to the isomer **256** in 65% yield (Scheme 40). No aldol product (**255**) was observed.

[131] Noyori, R.; Murata, S.; Suzuki, M. *J. Am. Chem. Soc.* **1980**, *102*, 3248.

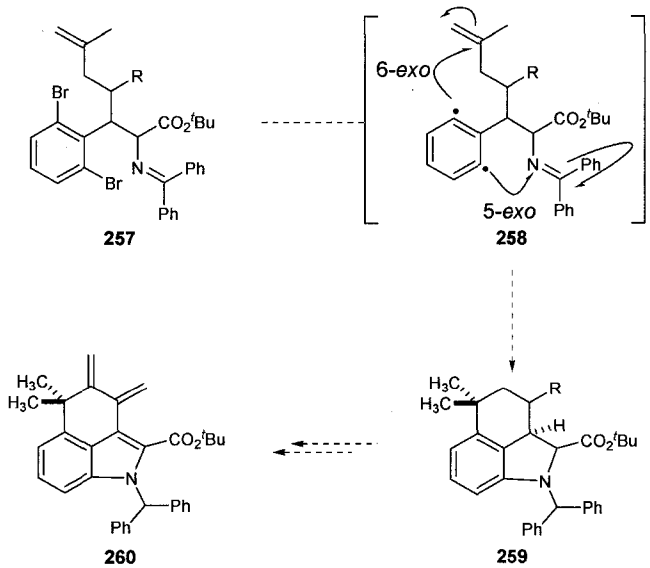
Scheme 40. Attempted acid mediated aldol addition resulting in isomerization



3.4. Efforts Along the Second Generation Approach

An alternate approach was necessary due to the problems that were faced during the scale-up of the Diels-Alder step for the construction of the D-ring of the natural product. This was further complicated due to issues of derivatization of the enol-ether moiety after the Diels-Alder step. Therefore, efforts were directed toward the construction of a diene that would already possess the ABC ring system of ambiguine (for example **260**). The initial synthetic plan toward the construction of such a diene is outlined in the following scheme.

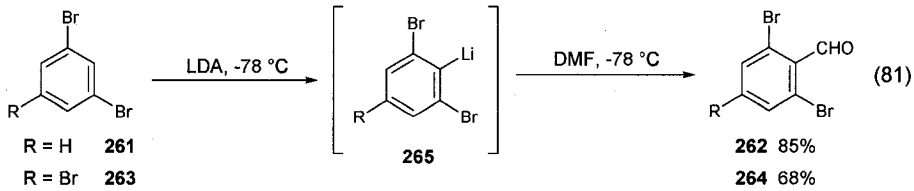
Scheme 41. Outline of the synthetic plan toward tricyclic diene **260**



Synthesis of Schiff base of the type **257** with a methallyl substituent was envisioned as a viable precursor to attempt a bis-radical cyclization to construct the ABC ring system of ambiguine in one step. This key step was expected to be possible based on the prior experience with the aryl amination protocol. A simultaneous 6-*exo*-trig cyclization was envisioned to provide the 6-membered ring. With this plan, the synthesis of an appropriate Schiff base was pursued.

3.4.1. Formylation of Di-halo Substrates

Synthesis of dibromo- and tribromo-aldehydes **262** and **264** was the first goal. Serwatowski and Lulinski have shown that *meta*-dibromo benzene can be metallated regioselectively and trapped with DMF to give formylated benzenes.[132] Accordingly, 1,3-dibromo benzene and 1,3,5-tribromo benzene were lithiated and then treated with DMF to give the corresponding formylated adducts in 85% and 68% yields respectively (eq 81). Both aldehydes were synthesized on ~15g scale and purified by recrystallization.



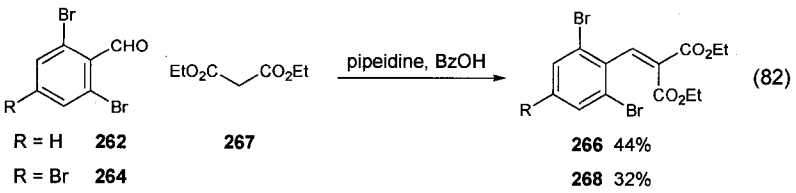
(81)

3.4.2. Knoevenagel Reaction

Aldehydes accessed by directed *ortho*-metallation/formylation were then subjected to a Knoevenagel condensation reaction according to the procedure reported by Gu and Holland.[133] The dibromo aldehyde **262** underwent condensation with diethyl malonate **267** to give the alkylidene malonate **266** in 44% yield. The tribromo aldehyde furnished the corresponding alkylidene malonate **268** in 32% yield (eq 82).

---

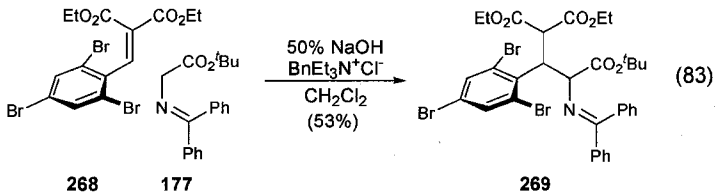
[132] For directed *ortho*-metallation reaction to give formylated product: Serwatowski, J.; Luliński, S. *J. Org. Chem.* **2003**, *68*, 5384. Review on directed *ortho*-metallation: Sneickus, V. *Chem. Rev.* **1990**, *90*, 879.
[133] For Knoevenagel condensation : Gu, J. X.; Holland, H. L. *Synth. Commun.* **1998**, *28*, 3305-3315.



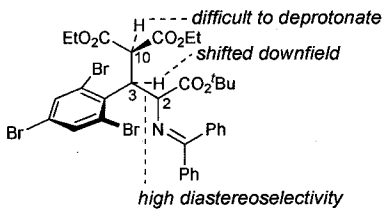
It is worth noting that both aldehydes **262** and **264** possessing disubstitution at the *ortho*-position were poor substrates for this condensation in comparison to the monobromo benzaldehyde which gave the corresponding alkylidene malonate in 85% yield.[134]

3.4.3. Michael Addition

The next step was a Michael addition of the alkylidene malonate **268** with Schiff's base **177** under phase transfer catalyzed conditions.[134] Thus, treatment of **264** and **177** with 20 equivalents of 50% sodium hydroxide and 20 mol% of benzyl triethylammonium chloride in methylene chloride gave the Michael adduct **269** in 53% yield.



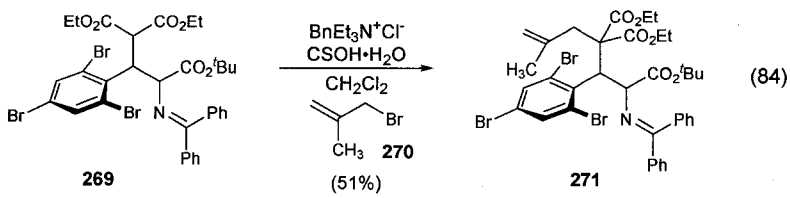
The ratio of diastereomers was >20:1 (^{1}H NMR). This ratio is significantly higher than that observed in the case of monobromo derivative **199**[134] suggesting that there is a peculiar conformational effect due to the dibromosubstitution on the *ortho*-positions of the aryl ring. The ^{1}H NMR signal of the proton on C3 of **269** was found to be significantly (~0.8 ppm) shifted downfield. Further, it was observed that the acidity of the malonate C-H was considerably lower when compared to that of the monobromo derivative. There is



269

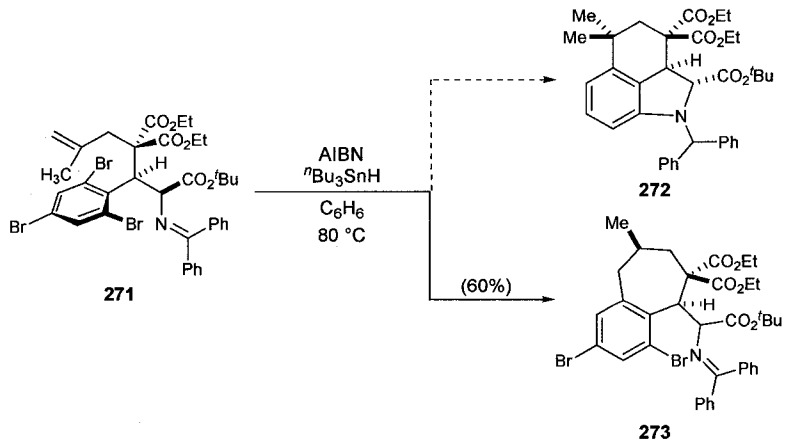
[134] Refer to section on Michael Addition/Aryl amination, Chapter 2.

presumably a unique conformational effect present here that leads to high diastereoselection during the Michael addition (see inset). The next step was the alkylation of the malonate C-H using methallyl bromide. The analogous monobromo derivatives were easier to deprotonate than this bis-*ortho*- disubstituted malonate **269**. The standard sodium hydroxide conditions failed to effect any reaction. Therefore, the more basic cesium hydroxide was used. Under these conditions, in the presence of benzyltriethylchloride catalyst and methallyl bromide, the alkylated product **271** was isolated in 51% yield as a single diastereomer (eq 84).

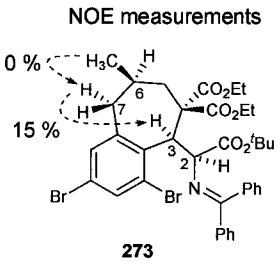


The stage was now set to examine the bis-radical cyclization reaction to form the ABC rings of ambiguine G. However, treatment of **271** with AIBN and tributyl tinhydride under standard conditions, led only to a 7-*endo* cyclization product **273**. None of the expected indoline **272** was formed.

Scheme 42. Attempted bis-radical cyclization resulting in a 7-*endo* cyclization



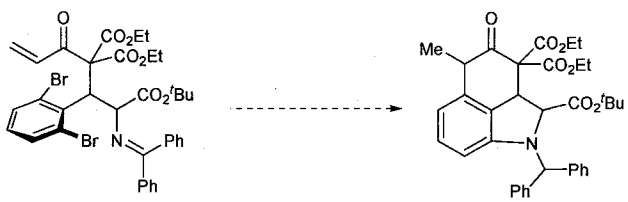
This was surprising for the following reasons: first, the radical was specifically generated at the sterically more hindered position. Second, a 7-*endo-trig* cyclization was



273

occurring predominantly over a 5-*exo-trig* cyclization onto the azomethine nitrogen. Significantly, only one diastereomer was observed by ^{1}H NMR, in 60% isolated yield (Scheme 42). The relative stereochemical assignment of the 7-membered ring was unambiguously assigned based on NOE irradiation (see inset). The protons on the two benzylic carbons C3 and C7 showed a large NOE enhancement of 15%. This pointed to a diaxial orientation of these protons. The methyl group on C6 did not show any NOE with the axial benzylic H in C7 suggesting a *trans* relationship between them. Therefore the overall substitution pattern on the 7-membered ring should be *cis* in nature. Stereochemistry at C2 could not be confirmed through NOE measurements. However, a *cis* relationship between C2 and C3 is assumed based on precedence for diastereoselection in the Michael addition step for the *syn* isomer. Although not a common process, radical-mediated 7-*endo* cyclizations have been documented in the literature.[135]

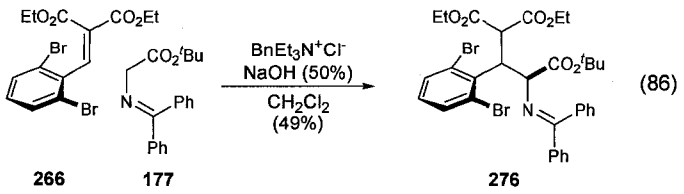
Our attention turned to redesigning the substrate by modifying the methallyl group to a less sterically hindered olefin. Therefore, enone **274** was envisioned as a viable precursor for the execution of the key bis-radical cyclization step (eq 85).



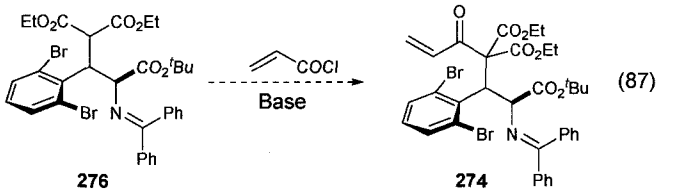
274 275 (85)

Synthesis of this substrate began with a Michael addition of alkylidine malonate **266** with the Schiff base **177**, under standard conditions. This provided adduct **276** in 49% yield (eq 86). The diastereoselectivity of this addition was ≥20:1 (^{1}H NMR). Analogous to the tribromo adduct **269**, the molecule exhibited a distinct chemical shift of the benzylic proton.

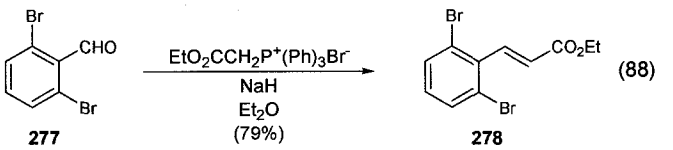
[135] 7-endo cyclization review: Yet, L. *Tetrahedron* **1999**, *55*, 9349. Nagano, H.; Hara, S. *Tetrahedron Lett.* **2004**, *45*, 4329.



The next step toward the synthesis of **276** was the acylation of the malonate carbon using acryloyl chloride (eq 87). A variety of bases including NaHMDS, LDA, NaH,[136] Mg/EtOH,[137] $MgCl_2/Et_3N$ and DBU were tried in order to effect this transformation. However, invariably all the conditions resulted in the hydrolysis of the imine portion of the molecule. None of the conditions resulted in the desired acylation of the malonate.



We then looked to an enolate which would be more reactive than the malonate anion. Toward this idea, an alternative Michael addition substrate way synthesized from the 2,6-dibromo benzaldehyde using a Wittig reaction. Thus, treatment of aldehyde **277** with a stabilized ylide led to the formation of cinnamate derivative **278** in 79% yield (eq 88). Only *E* isomer was observed by ^1H NMR.

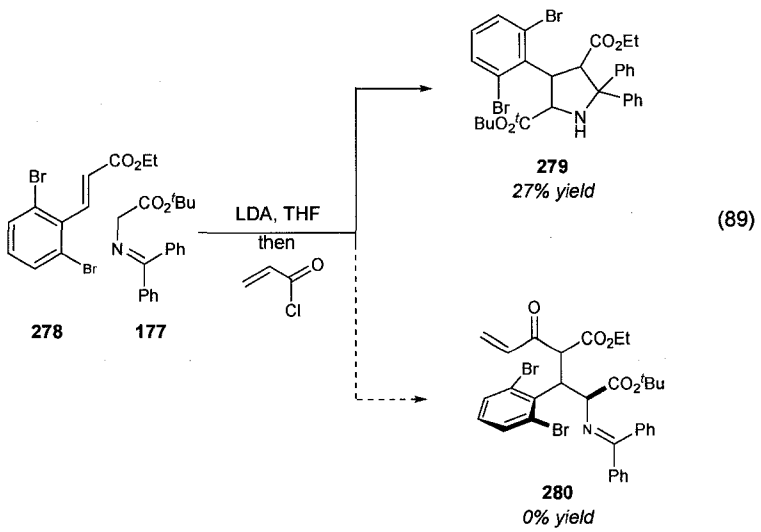


Addition of the enolate of Schiff's base **177**, to the cinnamate derivative **278**, followed by addition of acryloyl chloride resulted in the formation of the substituted pyrrolidine **279** instead of the acyl derivative **280** (eq 89). This result indicated that the

[136] Wood, J. L.; Thompson, B. D.; Yusuff, N.; Pflum, D. A.; Matthaus, M. S. P. *J. Am. Chem. Soc.* **2001**, *123*, 2097

[137] Hauser, C. R.; Reynolds, G. A. *J. Am. Chem. Soc.* **1946**, *68*, 1386.

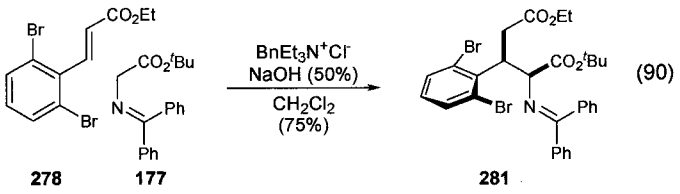
intramolecular cyclization of the enolate to the imine functionality is faster than the rate of intermolecular acylation.



(89)

3.4.4. Construction of B-ring Using Aryl Amination

Since simultaneous construction of the B and C rings of ambiguine G were proving to be too challenging, we opted to construct them sequentially. Imine **281** was chosen as the substrate for the execution of aryl amination to synthesize the B ring. α,β-unsaturated ester **278** was subjected to standard phase transfer catalyzed Michael addition conditions to furnish diester **281** in 75% yield (eq 90).



(90)

The diastereoselectivity for this Michael addition was >20:1 by ^{1}H NMR. This observation is consistent with the previously observed cases in the alkylidene malonates

derived from dibromoaldehydes. An extension of the rationale proposed to explain higher diastereoselectivity in Michael addition reactions is outlined in Figure 23.[138]

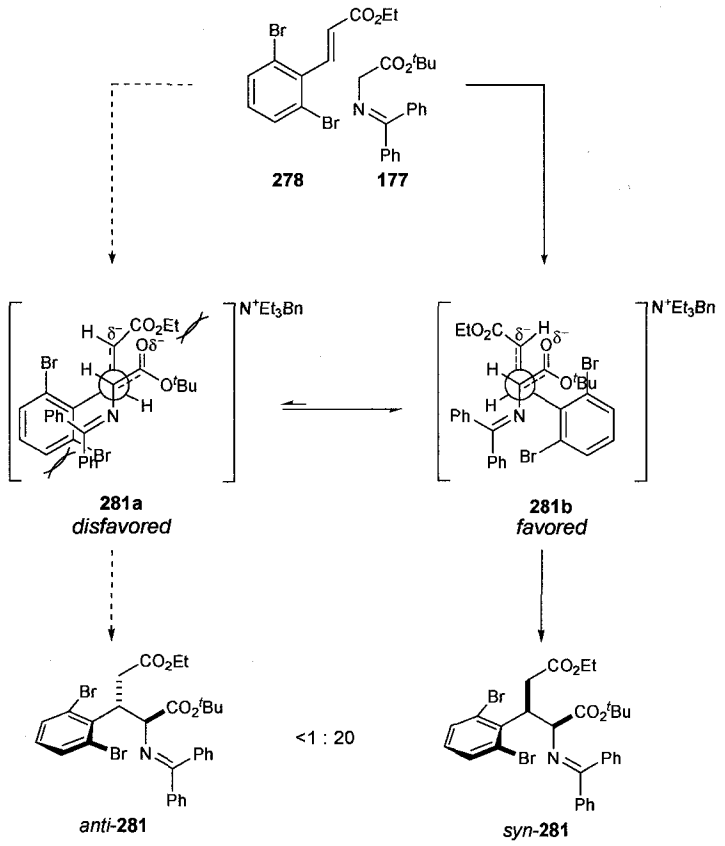


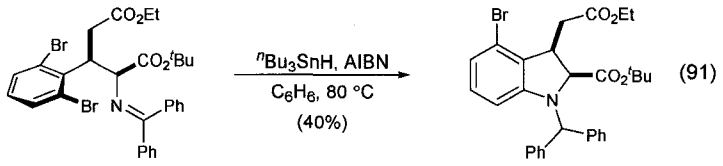
Figure 23. Transition state assembly for the Michael addition on dibromo ester **278**

The reaction conditions are assumed to have kinetic control over the product formation. However, no further experiments were performed to rigorously prove that this is true. The two possible transition states **281a** and **281b** for the Michael addition into enoate **278** are depicted in Figure 23. *Re* facial attack of the enolate leads to the *syn* adduct of **281**, while *Si* facial attack leads to the *anti* adduct. Due to the severe steric strain between the diphenylimino group of the enolate and the bisbromoaryl ring of the enoate, the transitions state **281a** would be higher in energy. This strain would be higher in magnitude than in the cases where the aryl ring of the enoate would carry only one bromine atom. This strain would be minimized in the transition state **281b** as these

[138] For a proposed rationale to explain diastereoselectivity in Michael addition reactions see Chapter 2, Michael addition/aryl amination section.

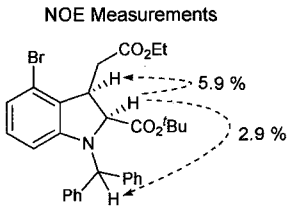
groups are away from each other. There would be further destabilization caused by steric strain in **281a** due to the ester group on the enoate and the tetra alkylammonium cation. However, the magnitude of this strain is expected to be lesser as these groups are a few bonds away from the reacting centers.

The B-ring of ambiguine was attempted to be formed using aryl amination, a process well studied in our laboratories.[134] Treatment of imine **281** with AIBN and tributyltin hydride furnished cyclized indoline **282** in 40% yield (eq 91).



281 **282** (91)

A single diastereomer was obtained from this cyclization reaction. Optimization studies revealed that even slightly higher amounts of tin hydride would result in dehalogenation of the aryl bromide of the indoline. Therefore, a 40% yield reflects a balance between maximum efficiency of the radical cyclization without over reduction. Relative stereochemistry was determined by NOE enhancement measurements of the indolinic hydrogens (see inset). The NOE enhancements were consistent with a *cis* relationship between the C2 and C3 hydrogens. This was further confirmed by the coupling constant values between these hydrogens. A $^{3}J_{HH}$ value of 8.8 Hz was reflective of a *cis* relationship based on comparisons with similar substituted indolines synthesized earlier.

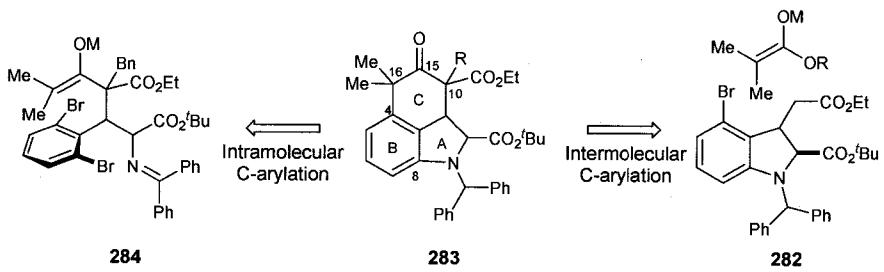


282

3.4.5. C-Ring Construction through Enolate C-Arylation Attempts

Tricyclic indoline **283** was envisioned to be built using a transition metal-mediated enolate C-arylation. This approach could in principle be executed in two ways (Figure 24). The first approach uses substrate **284** for an intramolecular cyclization of the enolate at C16 to C4 of the indoline. Alternatively, an intermolecular enolate arylation

using substrate **282** with an appropriate ester enolate would provide the tricyclic core of ambiguine G.

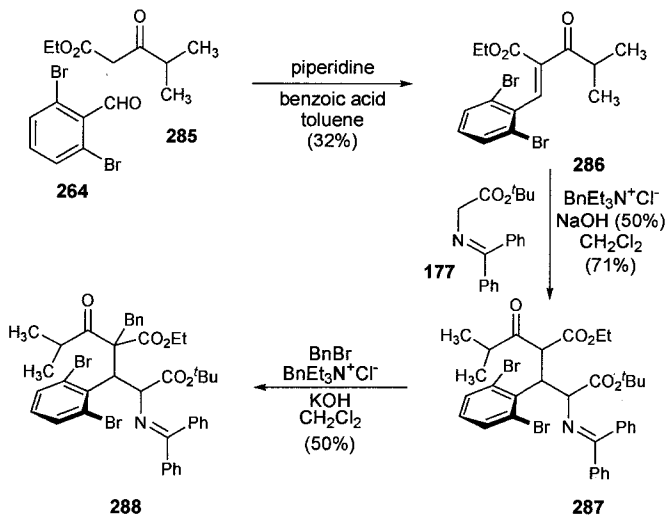


284 **283** **282**

Figure 24. Retrosynthetic disconnections for tricyclic keto-ester **283**

The intramolecular enolate arylation involved isopropyl containing ketone **288** and the use of palladium based catalysts.[139] An aryl amination event would then follow this arylation step, leading to tricyclic ketone **283**.

Scheme 43. Synthesis of keto-imine **288**

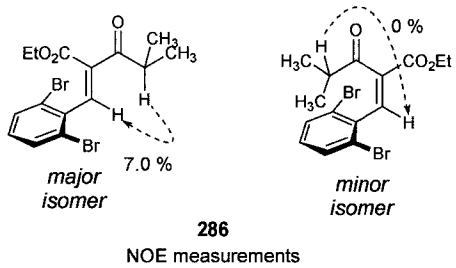


264 **285** **286** **177** **287** **288**

Synthesis of **288** was pursued using the previously established protocol of Knoevenagel condensation/Michael addition/alkylation sequence. Scheme 43 outlines the synthesis of **288**. Treatment of 2,6-dibromo benzaldehyde **264** under standard

[139] Ciufolini, M. A.; Qi, Hong-Bo; Browne, M. E. *J. Org. Chem.* **1988**, *53*, 4151; Piers, E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11; Piers, E.; Marias P. C. *J. Org. Chem.* **1990**, *55*, 3454; Solé, D.; Peidró, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225.

Knoevenagel condensation conditions with ethylisopropyl acetoacetate **285** gave the ketomalonate **286** in 32% yield as a 3:1 mixture of geometrical isomers. NOE measurements determined that the major product was *Z*-stereoisomer and the minor product was the *E* isomer (Figure 25).



286
NOE measurements

Figure 25. NOE measurements confirming geometry for isomers of **286**

This Michael acceptor **286** was subjected to standard phase transfer conditions with Schiff's base **177**, yielding adduct **287** in 71% yield. Benzylation of the malonate C-H was carried out with solid potassium hydroxide, benzyl bromide and similar phase transfer catalyzed conditions. This resulted in the formation of the target compound (**288**) in 50% yield as a 5:1 mixture of diastereomeric adducts. The final alkylation step proved difficult due the low acidity of the C-H reminiscent of the cases discussed previously. The stage was now set to investigate enolate C-arylation using palladium catalysis.

Several conditions were applied on the keto-imine **288** in order to effect an α-arylation reaction to give the an arylation product. Hartwig's protocol involving $Pd(dba)_2$ as the source of Pd(0) was applied using a variety of modifications.[140] However, no reaction was observed even under heating (eq 92). Upto a stochiometric amount of palladium source was used albeit no change. Alternatively, instead of a phosphine ligand, a *N*-heterocyclic carbene ligand was used under conditions reported by Nolan.[141] Under LHMDS and NaO^{t}Bu as base, no change was observed. Two Pd(II) catalysts that are known to promote similar intramolecular arylation of aldehydes were also attempted.[142]

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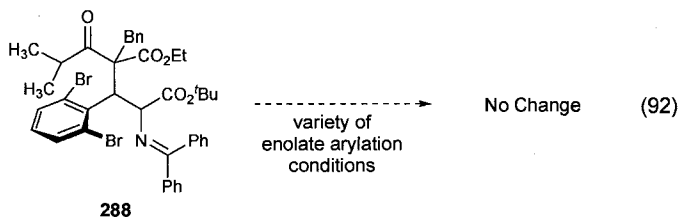
[140] Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382; Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410; Jørgensen, M.; Lee, S.; Liu, X.; Wolkowski, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 12557; Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108; Scolastico, C.; Poli, G. *Chemtracts* **1999**, *12*, 498.
[141] Nolan's catalyst: Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053.
[142] Muratake, H.; Nakai, H. *Tetrahedron Lett.* **1999**, *40*, 2355; Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581.

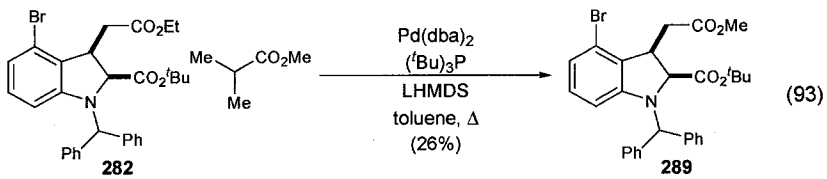
However, none of the reactions proved effective. The unreacted ketone **288** was recovered in all the cases.



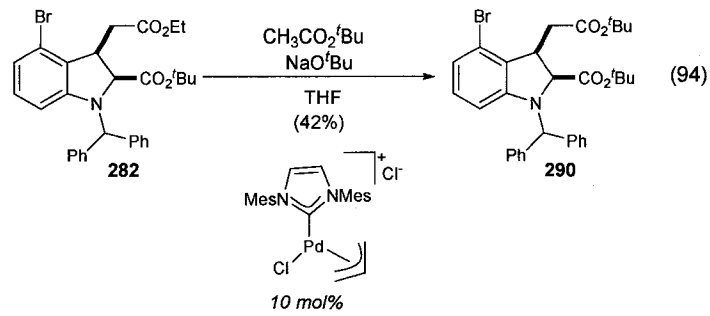
The aryl bromide is probably too sterically hindered in order to undergo a palladium insertion process. The strain involved if such a palladacycle were to form is further cause for the low reactivity. Therefore, an intermolecular version of the enolate arylation was attempted next.

3.4.6. Intermolecular Enolate C-Arylation Attempts

The indoline **282** synthesized using aryl amination was subjected to intermolecular palladium catalyzed arylation methods. Standard conditions reported by Hartwig using $Pd(dba)_2$ as the source of Pd(0) species were attempted.[140] However, the only evidence of reaction was a transesterification reaction (eq 93). The methoxide is presumably formed by elimination of methyl isobutyrate under the basic conditions.

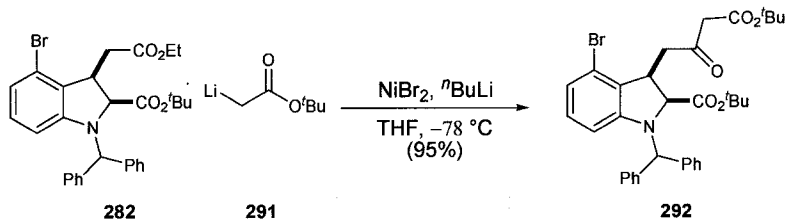


N-Heterocyclic carbene ligands were employed in an attempt to couple bromo indoline **282** with the enolate of *tert*-butyl acetate.[141] A transesterification again occurred but by the base itself, producing the corresponding *tert*-butyl ester in 42% yield (eq 94).



(94)

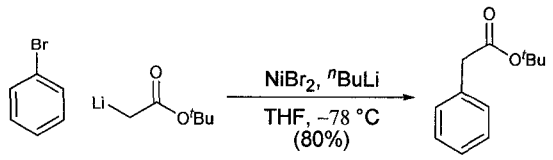
Millard and Rathke have reported a Ni(0) catalyst for the coupling of ester enolates with aryl and vinyl halides.[143] Treatment of nickel bromide with butyl lithium at –78 °C produces a putative Ni(0) catalyst that effectively couples a phenyl or a vinyl bromide with an ester enolate in moderate to good yields (41-99%). For example, iodobenzene forms *tert*-butyl phenyl acetate in 66% yield. Vinyl bromides underwent arylation with higher yields than aryl bromides. Wender and Wolanin applied this protocol in their total synthesis of quadrone and terrecyclic acid A.[144] With this precedence, a similar coupling of bromo indoline **282** was attempted. However, upon treatment of nickel bromide with butyl lithium, followed by addition of indoline **282**, and lithio-*tert*-butyl acetate **291**, an unexpected Claisen addition reaction occurred. The product β-ketoester (**292**) was isolated in 95% yield (eq 95).



(95)

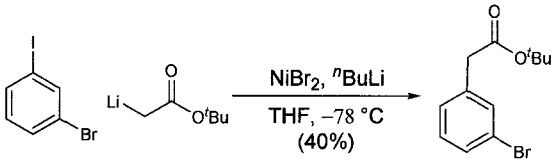
The bromine atom was intact on the aryl ring indicating that the oxidative addition of Ni(0) was not occurring under these conditions. Therefore, simpler substrates like bromo benzene and 3-iodo-1-bromobenzene were tested. Bromobenzene underwent coupling with the enolate producing *tert*-butyl phenyl acetate **293** in 80% yield (eq 96).

[143] Millard, A. A.; Rathke, M. W. *J. Am. Chem. Soc.* **1977**, *99*, 4833.
[144] Wender, P. A. Wolanin, D. J. *J. Org. Chem.* **1985**, *50*, 4418.



291 293 (96)

3-Iodo-1-bromobenzene **294** furnished the regioselectively C-arylated product **295** in 40% yield (eq 97). These experiments pointed to two probable reasons for the failure of Ni(0) to insert into the indoline-Br bond: 1) the electron rich nature of the indoline and 2) the substitution on indoline may make the C-Br bond sterically hindered.

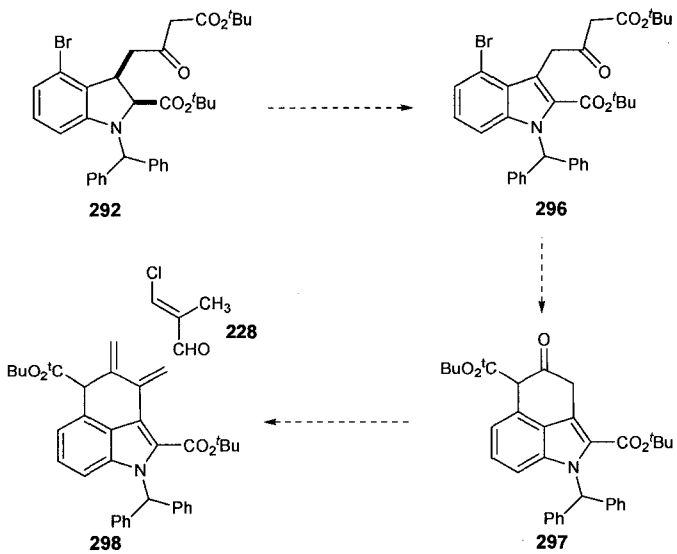


294 291 295 (97)

3.5. Future Plan

Currently, our focus to construct the C ring of ambiguine G is through the indole **296** (Scheme 44).

Scheme 44. Current plan for the construction of the C-ring of ambiguine G

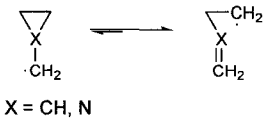


Indole **296** is thought to be a slightly better substrate for the enolate C-arylation strategy due to the less electron rich nature of the indole thereby facilitating the oxidative addition of the transition metal. The C-arylated tricycle **297** would then be converted the diene (**298**) necessary to carry out the late stage Diels-Alder reaction.

Chapter 4. Azacyclopentenyl Carbinyl Radical Isomerizations (ACCRI)

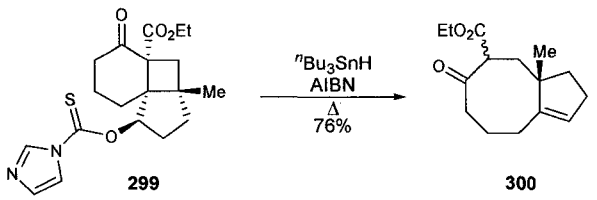
4.1. Introduction

Radical isomerizations (e.g. eq 98) have been widely used as a tool in organic synthesis, mechanistic physical organic chemistry, and biochemistry.



(98)

Radical fragmentation reactions have been used in a cascade fashion either to build structural complexity or to generate medium sized rings that are otherwise difficult to synthesize.[145] For example, Crimmins utilized a radical fragmentation reaction of **299** to construct the 8-5 fused ring system in **300** that is common to terpenoid natural products (eq 99).[146a]



(99)

A radical fragmentation of **301** was used by Lange for the construction of 5-7 fused 1,5-diene framework in **302**. Later this step was employed in the synthesis of alismol (**303**) and dictamnol (**304**).[2b]

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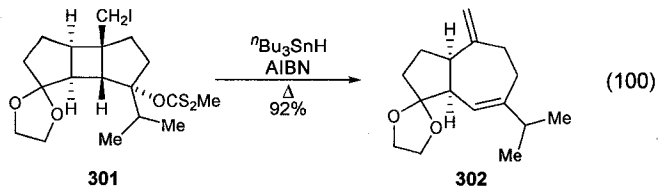
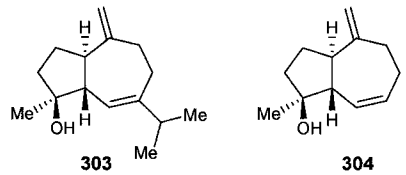
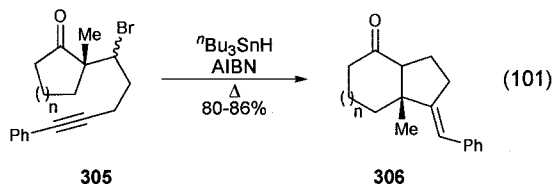
[145] Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091.

[146] (a) Crimmins, M. T.; Huang, S.; Guise-Zawacki, L. E. *Tetrahedron Lett.* **1996**, *37*, 6519; (b) Lange, G. L.; Gottardo, C.; Mercia, A. *J. Org. Chem.* **1999**, *64*, 6738.

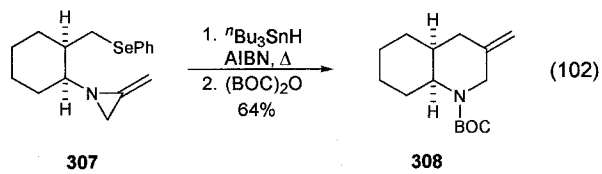




As a strategy to build fused carbocycles, Boger executed a sequence in which initial radical addition to carbonyl carbon followed by an intermediate fragmentation results in a final *5-exo-dig* cyclization (eq 101).[147]



Similarly, an ingenious design by Shipman incorporated a vinyl aziridine in **307** to undergo a radical addition/fragmentation sequence providing **308** and thereby access to 6-6 *cis*-fused alkaloids (eq 102).[148]

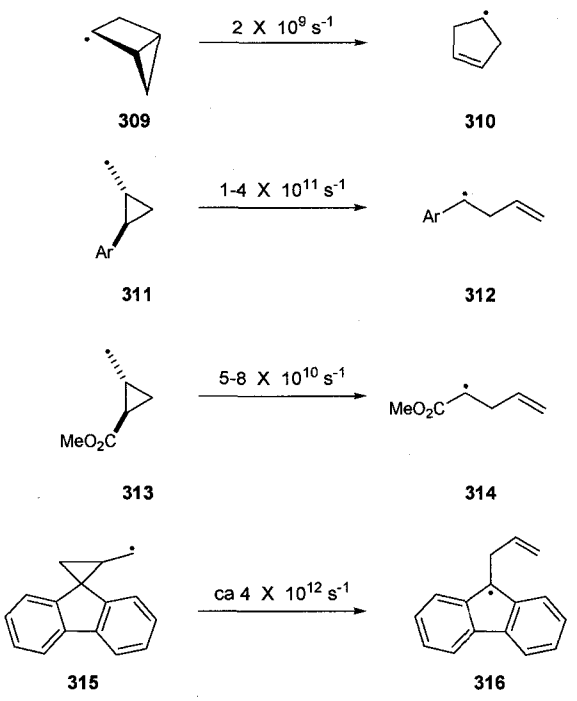


Isomerizations involving ring-chain tautomerization are particularly prominent and include the "radical clocks" for which absolute rate constants have been measured.[149] Cyclopropyl carbinyl radical fragmentations have been used as a kinetic tool in

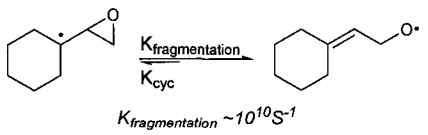
[147] Boger, D. L.; Mathvink *J. Org. Chem.* **1990**, *55*, 5442.
[148] Prévost, N.; Shipman, M. *Org. Lett.* **2001**, *3*, 2383.
[149] (a) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317. (b) Newcomb, M. *Tetrahedron*, **1993**, *49*, 1151.

enzymology.[150] Scheme below illustrates a few of the examples of ultrafast radical rearrangements used as probes. These cyclopropylcarbinyl radical isomerizations are very fast and their rate constants measured at ambient temperature are listed below.

Scheme 45. Some ultrafast rearrangements used as radical clocks



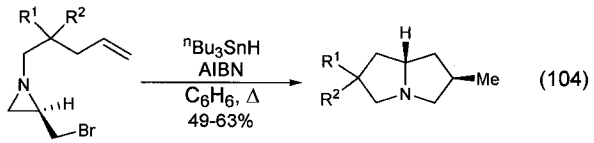
Isomerizations in which a heteroatom plays a direct role include oxiranyl carbinyl radical fragmentations (eq 103). These are among the fastest reactions known. Using cyclohexyl based epoxide as a probe Rawal approximated the absolute rate constant for this fragmentation to be 10^{10} s^{-1} (eq 103).[151]



(103)

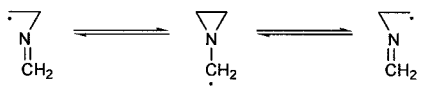
[150] Newcomb, M.; Toy, P. T. *Acc. Chem. Res.* **2000**, *33*, 449.
[151] Krishnamurthy, V.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 1572.

The aziridinyl carbinyl radical fragmentation (**317** to **318**) though, a slower process than the corresponding oxy version, have been utilized to access the pyrrolizidine alkaloid skeleton (eq 104).[152]



317 **318** (104)

An alternative arrangement of the atoms involved in an aziridinyl carbinyl radical isomerization leads to open chain radicals rearranging *via* an aziridine intermediate (eq 105).



(105)

Indeed, this type of radical isomerization has been implicated as the mechanism operative in enzymes such as lysine 2,3-aminomutase[153] and those responsible in the formation of unusual sugars.[154] A different version of such a rearrangement is also found in the coenzyme B_{12} dependent enzyme that carries out the glutamate-methyl aspartate carbon skeleton rearrangement.[155]

4.2. Lysine Amino Mutases (LAM)

The interconversion of L-lysine and β-lysine is catalyzed by lysine 2,3-aminomutase (2,3-LAM) in *Clostridia* (eq 106). The K value for the enzyme catalyzed reaction is 7 at pH=8.

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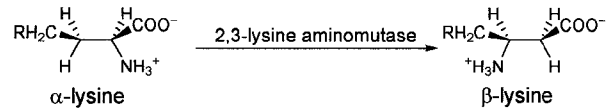
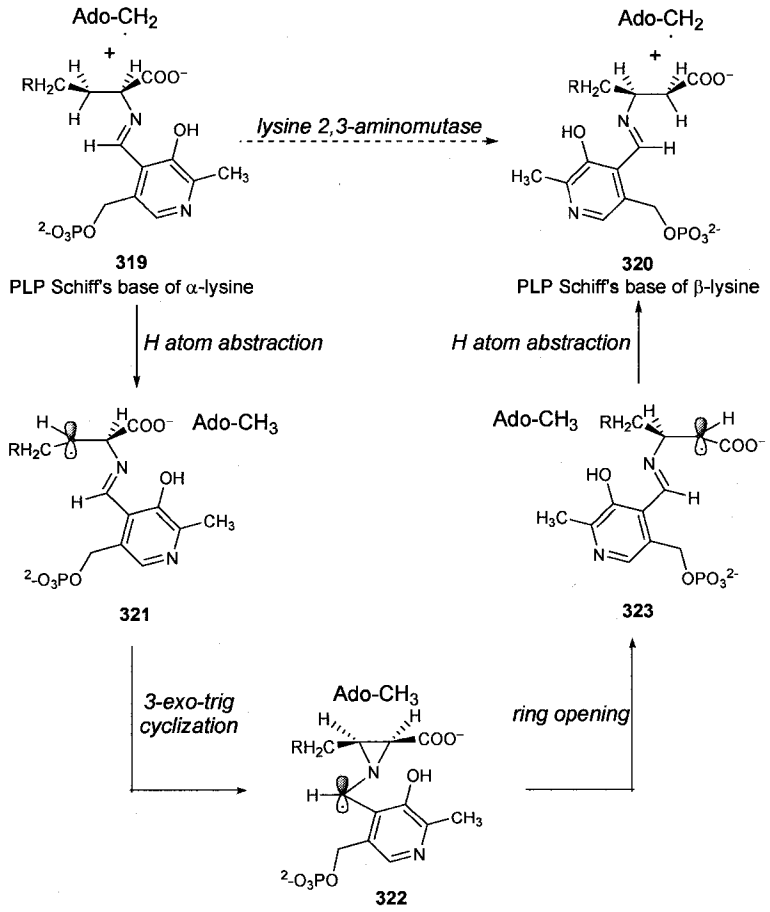
[152] DeSmaele, D.; Bogaert, P.; Dekimpe, N. *Tetrahedron Lett.* **1998**, *39*, 9797.
[153] Frey, P. A.; Reed, G. H. *Arch. Biochem. Biophys.* **2000**, *382*, 6.
[154] He, X.; Liu, H. *Annu. Rev. Biochem.* **2002**, *71*, 701.
[155] Choi, S. –C.; Dowd, P. *J. Am. Chem. Soc.* **1989**, *111*, 2313.



(106)

2,3-LAM a PLP (pyridoxal 5'-phosphate) dependent, adenosylcobalamine independent enzyme which uses *S*-adenosyl methionine (SAM) along with an FeS cluster to initiate radical generation. Using EPR techniques, Frey[156] has verified the proposed mechanism of action of 2,3-LAM, proceeding through an azacyclopropyl carbinyl radical rearrangement step (Scheme 46). Initial hydrogen atom abstraction from the β-position of α-lysine leads to a carbon centered radical **321** which undergoes a 3-*exo*-trig cyclization onto the nitrogen atom to form the aziridinyl carbinyl radical species **322**.

Scheme 46. Mechanism of 2,3-Lysine Amino Mutase

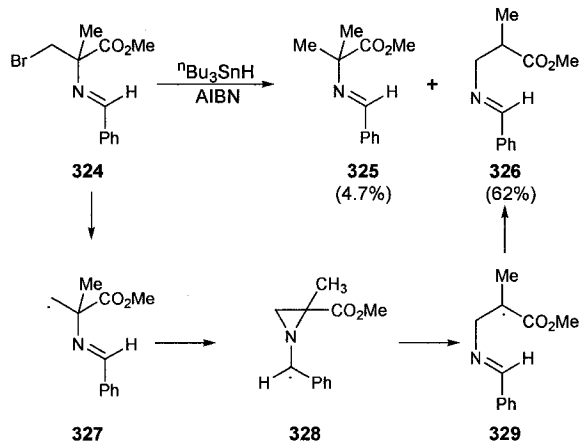


[156] Frey, P.A.; Booker, S. in *Advances in Free Radical Chemistry.* Zard, S. Z., Ed.; JAI: Greenwich, 1999, vol. 2, pp-1-43.

The strain of this 3-membered ring causes it to favor the open form leading to a radical on the α-carbon giving **323**. Hydrogen atom abstraction then completes transfer of the imino group to the β position of lysine (**320**). Radom has since used *ab initio* calculations to underscore the importance of PLP in these rearrangements.[157]

A chemical model developed by Frey that mimics this proposed enzymatic pathway is outlined in Scheme 47.[158] When **324** was treated with AIBN and tributyltin hydride, Frey observed the formation of **325** and **326** in a 13:1 ratio favoring **326**. Aldimine **325** is the product of direct reduction of radical **327**, a second order process dependent on effective tin hydride concentration. Isomerized **326** is the product arising out of a rearrangement of **327** to **329** through an azacyclopropyl radical **328**.

Scheme 47. Frey's chemical model for mechanism of 2,3-LAM



The formation of the rearranged product reflected a mechanism proceeding through a 3-*exo* radical addition to the *N*-terminus of the imine leading to azacyclopropyl radical **328**. This was followed by a selective ring opening event to give the more stable radical **329**. Imine **326** was formed upon hydrogen atom transfer. This sequence is analogous to the mechanism in 2,3-LAM, thus adding further evidence for an azacyclopropyl carbinyl radical rearrangement in 2,3-LAM. In order to gain further insight into this rearrangement, Handa studied the corresponding salicylaldehyde imines **330a-c** (eq 107).[159]

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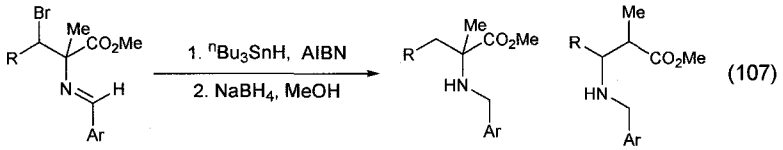
[157] Wetmore, S. D.; Smith, D. M.; Radom, L. *J. Am. Chem. Soc.* **2001**, *123*, 8678.
[158] Han, O.; Frey, P.A. *J. Am. Chem. Soc.* **1990**, *112*, 8292.
[159] Handa, S.; Rose, C. J. *Tetrahedron Lett.* **2004**, *45*, 8643.

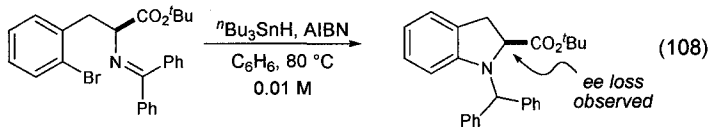


330	331	332
R = H (a)	22%	25%
R = CH_3 (b)	0%	58%
R = Ph (c)	64%	0%

Three salicylaldehyde imines **330a,b,c** were subjected to standard radical conditions. In general, salicylaldehyde derived imines underwent poorer migration when compared to benzaldehyde imines studied by Frey.[158] This fact was rationalized as a result of a higher barrier for the initial 3-*exo*-trig cyclization in cases with an *ortho* hydroxyl substitution on the phenyl ring.

4.3. Identification of Azacyclopentenyl Carbinyl Radical Isomerization (ACCRI)

During the course of our studies of aryl radical addition to the nitrogen of azomethines, we observed a racemization event (eq 108). When enantiomerically enriched imine (*S*)-**178** (96% ee) was subjected to our standard radical cyclization conditions, the resulting indoline (*S*)-**179** exhibited diminished enantiomeric enrichment (63% ee).

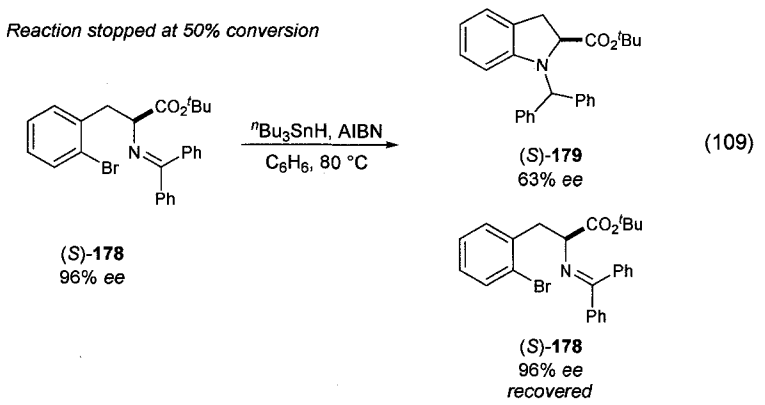


(*S*)-**178** 96% *ee*

(*S*)-**179** 63% *ee*

Control experiments were performed to discover the cause of racemization. Reagent induced racemization, though unlikely, was discounted by treating imine (*S*)-**178** and cyclized indoline (*S*)-**179** with each reagent, including the mildly Lewis acidic

tributyltin bromide.[160] In none of the cases was there any observable racemization. This confirmed that racemization was not caused by any individual reagent. We considered the possibility that either starting imine or product indoline racemized under the reaction conditions. To test this, we planned a key experiment in which identical conditions were implemented but the reaction was stopped at 50% conversion (eq 109).



(109)

In this experiment indoline (*S*)-**179** and imine (*S*)-**178** were recovered in 96% and 63% ee respectively. This result showed that neither imine (*S*)-**178** or indoline (*S*)-**179** was racemizing under the reaction conditions. Therefore isomerization must occur after aryl radical formation yet prior to chain-propagating hydrogen atom transfer from stannane.

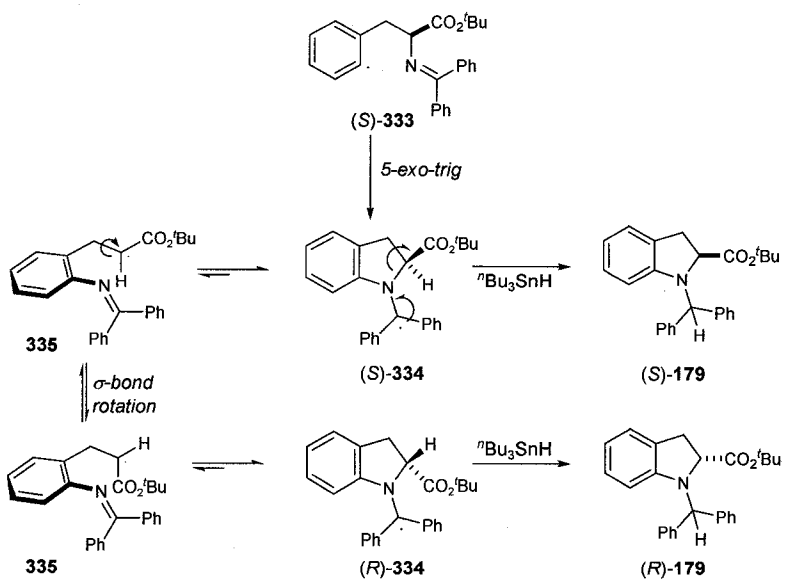
4.4. ACCRI – Hypothesis

In order to mechanistically explain the racemization event, we envisioned the pathway outlined in Scheme 48. Initial formation of the nucleophilic aryl radical (*S*)-**333** followed by a 5-*exo*-trig cyclization would form a radical (*S*)-**334** which is stabilized by phenyl group and by nitrogen. Due to this stability, the lifetime of this radical is prolonged. Under these conditions, we hypothesized that the resident strain in the 5-membered ring could cause a ring opening event resulting in a chain isomer **335** with concomitant loss of stereochemical information. A σ-bond rotation in this chain isomer

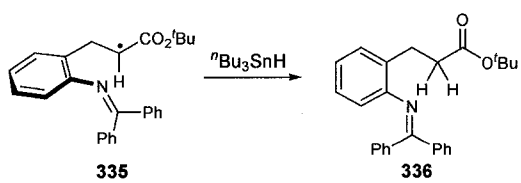
[160] Evidence of the Lewis acidity of stannyl halides is somewhat contradictory. (a) Yoder, C. H.; Otter, J. C.; Grushow, A.; Gannuis, T. F.; Enders, B. G.; Zafar, A. I.; Spencer, J. N. *J. Organomet. Chem.* **1990**, *385*, 33. (b) Sibi, M. P.; Ji, J. *J. Am. Chem. Soc.* **1996**, *118*, 3063 and references therein.

leads to a conformation that would be predisposed to cyclize to the opposite enantiomer (*R*)-**334**.

Scheme 48. AzaCyclopentenyl Carbinyl Radical Isomerization (ACCRI)



Since none of the chain isomer was detected (^{1}H NMR), the rate of ring closing (**335** to **334**) and final reduction (**334** to **179**) must be greater than the rate of ring opening (**334** to **335** then to **336**, eq 110). This observation indicated that the ring-chain isomerization was operating as a background process, while the formation of indoline remained as the main course of the reaction pathway. Racemization being partial and not complete was consistent with a competitive process, whose extent would depend on the conditions.



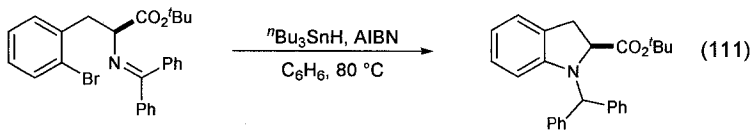
(110)

At this juncture, an azacyalopentenyl carbinyl radical isomerization was a reasonable way to account for the racemization observed. However, it awaited further experimental evidence.

4.4.1. Dependence of ACCRI on Stannane Concentration and Additives

Since the main issue that guides ACCRI process is the ability of radical **334** to persist long enough to isomerize, changing the effective stannane concentration could exert control over the isomerization. Rapid reduction of the radical **334** by increasing the effective stannane concentration, should lead to lesser % ee loss over the course of the reaction (Scheme 48). Indeed, when the effective stannane concentration was varied, a corresponding change in the % ee loss was observed (Table 12).

Table 12. Dependence of % ee loss on stannane concentration (eq 111)[a]



(111)

(*S*)-**178** (*S*)-**179**

entry	$^{n}Bu_3SnH$ (equiv)	(*S*)-**178** (M)	% ee loss[b]	% yield[c]
1	2.2	0.005	37	45
2	2.2	0.01	33	85
3	2.2	0.05	16	74
4	2.2	0.1	0	70

[a] All reactions performed with 0.8 equiv. AIBN except for entry 1 where 1.2 equiv. was used. [b] Determined by chiral HPLC analysis.[c] Isolated yield.

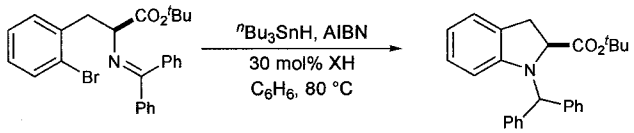
Thus with 2.2 equivalents of tributyltin hydride at 0.005 M imine concentration, a 37% ee loss was observed (Table 12, entry 1). Keeping the tin hydride stoichiometry constant, the molarity of the solution was increased progressively (from 0.005 M to 0.1 M). Correspondingly, the reaction furnished indoline product with diminishing % ee loss (Table 12, entries 2-4). At 0.1 M concentration of imine, the isomerization was completely avoided (Table 12, entry 4).

Another possible way to test this isomerization would be to reduce the radical (*S*)-**334** with a more effective hydrogen atom donor before it rearranges to (*R*)-**334**. It is known that benzene thiol[161] and PhSeH[162] are better hydrogen atom donors than tributyltin hydride. Therefore, 30 mol% of either benzenethiol or PhSeH was used as an

[161] Rychnovsky, S. D.; Buckmelter, J. A.; Kim, A. I. *J. Am. Chem. Soc.* **2000**, *122*, 9386.
[162] Crich, D.; Yao, Q. *J. Org. Chem.* **1995**, *60*, 84.

additive under standard conditions (2.5 equiv $^{n}Bu_3SnH$, 1.2 equiv AIBN, 0.01 M). Use of benzene thiol had no effect on minimizing the racemization (Table 13, entry 2), however, PhSeH minimized the racemization from 33% to 7% (Table 13, entry 3). This result added further credence to the notion that the lifetime of radical **334** directly affects % ee of the product.

Table 13. Effect of additives on % ee loss (eq 112)



(112)

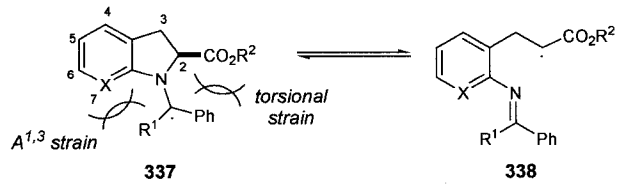
(*S*)-**178** (*S*)-**179**

entry	XH	**178** (M)	% ee loss[a]
1	none	0.01	33
2	PhSH	0.01	31
3	PhSeH	0.01	7

[a] % ee determined by chiral HPLC analysis.

4.4.2. Steric Effects in ACCRI

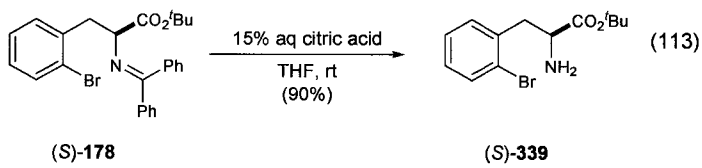
The hypothesis that an isomerization event is occurring raised questions about the effect of the steric nature of the substituents on the process. Resident strain in the southern periphery of the indoline species **337** can be attributed to $A^{1,3}$ strain between C7 and the substituent on nitrogen (diphenyl methyl in the parent indoline). A reasonable amount of torsional strain was also expected to reside between the substituent on nitrogen and the ester group (Figure 26). Attempts were made to measure the extent to which substituents on C7, nitrogen, and the ester group on C2 affect the isomerization process.



337 **338**

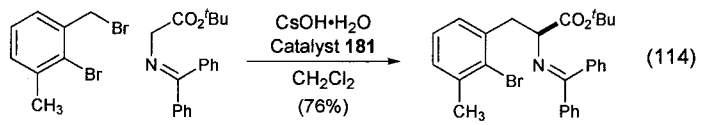
Figure 26. Steric strain causing ring opening

In order to synthesize a series of enantio-enriched substrates, imine (*S*)-**178** was hydrolyzed to the corresponding amine (*S*)-**339** using 15% citric acid in THF.



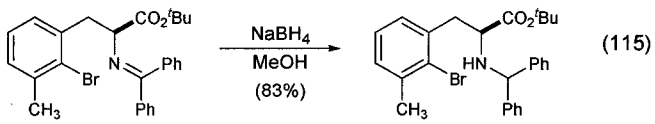
(*S*)-**178** (*S*)-**339** (113)

Enantioselective glycine Schiff base alkylation was employed for the synthesis of imine (*S*)-**341a** which was designed to be a sterically biased substrate to study the effect on ACCRI (eq 114). Upon subjecting bromide **340** and Schiff base **177** to alkylation conditions using catalyst **118**, imine (*S*)-**341a** was formed in 76% yield.



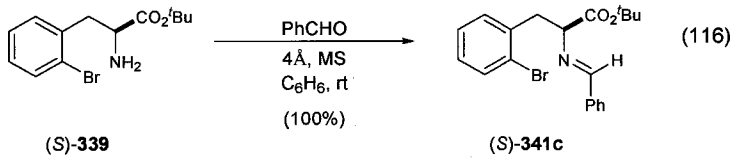
340 **177** (*S*)-**341a** (114)

This imine however required reduction to its corresponding amine for % ee determination (eq 115). This amine (*S*)-**342** revealed an 88% ee for the imine (*S*)-**341a**.



(*S*)-**341a** (*S*)-**342** (88% ee) (115)

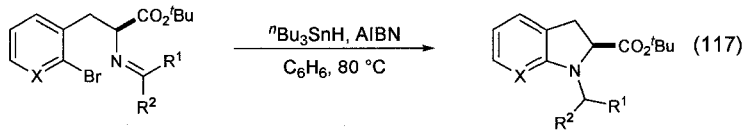
Amine (*S*)-**339** was subjected to standard dehydrative condensation conditions with benzaldehyde to give aldimine (*S*)-**341c** in quantitive yield (eq 116). This aldimine was one of the substrates for the study of steric effects on ACCRI.



(*S*)-**339** (*S*)-**341c** (116)

Table 14 outlines the effects of varying steric bulk of substituents upon the % ee loss observed during cyclization. Progressive increase of steric bulk at C7 (from N to CH to CCH_3, Table 14, entries 1 to 3) revealed a dramatic effect upon the % ee loss. While the pyridyl imine (*S*)-**178b** cyclized with no loss of % ee, the parent imine (*S*)-**178a** underwent a 33% ee loss. Even with high stannane concentration (that suppresses isomerization) imine (*S*)-**341a** with a C7 methyl substituent underwent a 100% ee loss, clearly indicating that an increase of $A^{1,3}$ strain results in increased isomerization. Cyclization yielded only 15% indoline product mainly due to direct reduction (ArBr to ArH) in this case.

Table 14. Steric effects on %ee loss (eq 117)[a]



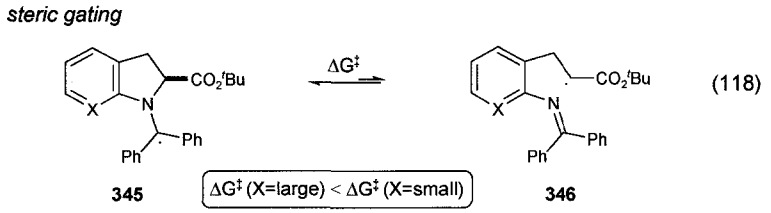
(*S*)-**178/341** (*S*)-**179/343** (117)

entry	178/341	X	R^1	R^2	% *ee*[c] 178/341	% *ee*[c] 179/343	% *ee* loss	yield[d] (%)
1	(*S*)-**178b**	N	Ph	^{t}Bu	96	96	0	50
2	(*S*)-**178a**	CH	Ph	^{t}Bu	96	63	33	85
3	(*S*)-**341a**[b]	CCH_3	Ph	^{t}Bu	88	0	100	15
4	(*S*)-**341b**	CH	CH_3	^{t}Bu	99	57[e]	42	76
5	(*S*)-**341c**	CH	H	^{t}Bu	95	81	14	6[f]
6	(*S*)-**341d**	CH	Ph	allyl	76	38	38	75

[a] All reactions were carried out with 2.2 equiv. of ^{n}Bu_3SnH, 0.8 equiv. AIBN and 0.01M in imine.[b] Imine concentration was 0.1M [c] % *ee* determined by Chiral HPLC analysis.[d] Isolated yield.
[e] ee of major diasteroemer. Diastereoselectivity = 5:1 (65% ee for minor diastereomer)-contributed by Daniel Mutnick.[f] Major product is the tetrahydroisoquinoline **344** (67%, 95%ee).

Varying substitution (R^1 group) on the imine moiety also revealed steric effects on the isomerization process. Thus when R^1 is changed from a phenyl to a methyl substituent in (*S*)-**341b**, there was an increase in the amount of isomerization taking place, resulting in a 42% ee loss (Table 14, entry 4). Replacing the phenyl group with hydrogen gave aldimine (*S*)-**341c** which underwent a 14% ee loss during the 5-*exo*-trig

cyclization (Table 14, entry 5).[163] As expected, these results indicated that the isomerization was sensitive to the steric nature of substituents on the imine group. Finally, changing the ester group on C2 from a *tert*-butyl to an allyl group did not affect the rate of racemization appreciably (Table 14, entry 6). This pointed to the greater importance of $A^{1,3}$ strain between C7 and the nitrogen substituent than the torsional strain between the ester and nitrogen substituents.



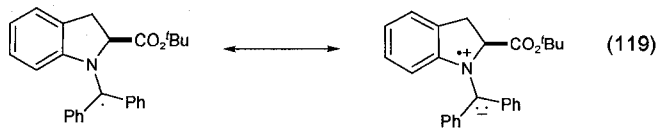
(118)

The steric effect of substituents on the isomerization process is summarized in eq 118. The larger the substituent, the lower the barrier to isomerization due to increased $A^{1,3}$ strain. This ground state destabilization causes **345** to ring open to the isomeric chain form **346** reflecting in product indoline with diminished % ee.

4.4.3. Electronic Effects in ACCRI

In addition to the steric effects, there exists an electronic effect for the isomerization. The polar character of the radicals involved in the ring-chain isomerization is different. In the ring form, the diphenylmethyl radical **334** is nucleophilic due to the electron rich nitrogen and the aromatic rings. Hence, the charge separated resonance structure **347** is a contributor and the enabling effect of the nitrogen is apparent (eq 119).

[163] (a) Prabhakaran E. N.; Cox, A. L.; Nugent, B. M.; Nailor, K. E.; Johnston, J. N. *Org. Lett.* **2002**, *4*, 4197. (b) Takano, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. *Chem. Lett.* **1990**, 315. (c) Tomaszewski, M. J.; Warkentin, J. *Tetrahedron. Lett.* **1992**, *33*, 2123. (d) Bowman, W. R.; Stephenson, P. T.; Terrett, N. K.; Young, A. R. *Tetrahedron Lett.* **1994**, *35*, 6369. (e) Ryu, I.; Ogura, S.; Minakata, S.; Komatsu, M. *Tetrahedron Lett.* **1999**, *40*, 1515. Reviews: (f) Freistad, G.; *Tetrahedron* **2001**, *57*, 5461. (g) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543.



334 347 (119)

In the chain isomer, the radical is α to a carboxy group and therefore electrophilic in nature. Due to the influence of these polar effects, ring substituents that stabilize the resonance form **347** would promote isomerization by lowering the energy barrier (Figure 27).[164]

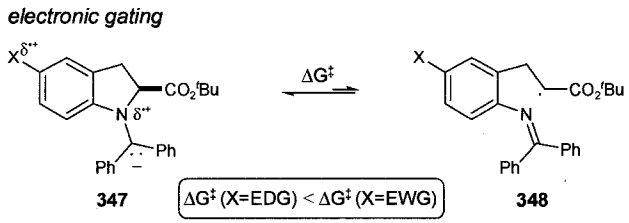
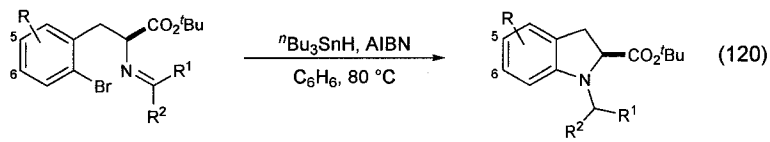


Figure 27. Remote electronic effect of ring substitution on ACCRI

Thus, electron donating substituents on the aryl ring of the indoline would be expected to lower the barrier to isomerization. Similarly, electron withdrawing groups are expected to raise the isomerization barrier. Table 15 shows the effect of increasing electron donation from the aromatic ring upon the extent of isomerization (eq 120).

Table 15. Effect of remote electronic substitution on % ee loss (eq 120)[a]



(120)

(*S*)-**178** (*S*)-**179**

entry	(*S*)-**178**	R	% *ee*[b] (*S*)-**178**	% *ee* (*S*)-**179**	% *ee* loss	yield (%)
1	(*S*)-**178a**	H	96	96	0	70
2	(*S*)-**178e**	5-Cl	94	91	3	55
3	(*S*)-**178c**	5-OMe	94	86	8	45
4	(*S*)-**178d**	5,6-OMe	97	81	16	50

[a] All reactions were carried out with 2.5-3.0 equiv. of $^{n}Bu_3SnH$, 0.8 equiv. AIBN and 0.1M in (*S*)-**178**. [b] % *ee* determined by Chiral HPLC analysis. [c] Isolated yield

[164] Polar effects in radical reactions: (a) Newcomb, M.; Horner, J. H.; Emanuel, C. J. *J. Am. Chem. Soc.* **1997**, *119*, 7147. (b) Delle, E. W.; Kostakis, C.; Smith, P. A. *Org. Lett.* **1999**, *1*, 363.

When the C5 position was substituted with chloride or methoxy groups (Table 15, entry 2 and 3) the % ee loss increased progressively when compared to the unsubstituted indoline (Table 15, entry 1). This indicated that groups with electron donation ability caused increased isomerization. In the case of disubstitution at the C5 and C6 position with methoxy groups, an apparent additive effect was observed (Table 15, entry 4). These results are in complete agreement with the presence of polar effects on the isomerization.

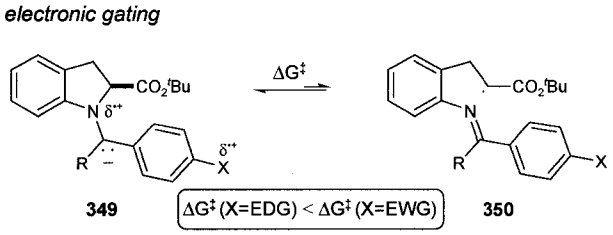


Figure 28. Direct polar effects on ACCRI due to ketimine substituents

Alternatively the electronics of the ring-chain isomerization could also be controlled by altering substitution on the ketimine portion (Figure 28). Electron donating substituents on the ketimine aryl ring would be expected to make the radical **349** more nucleophilic, and consequently increase isomerization. Conversely, electron withdrawing substituents would be expected to raise the barrier to isomerization.

In order to test this hypothesis, two additional enantio-enriched imines (*S*)-**341e** and (*S*)-**341f** were synthesized using standard dehydrative condensation conditions (Scheme 49).

Scheme 49. Synthesis of electronically diverse imines (*S*)-**341e** and (*S*)-**341f**

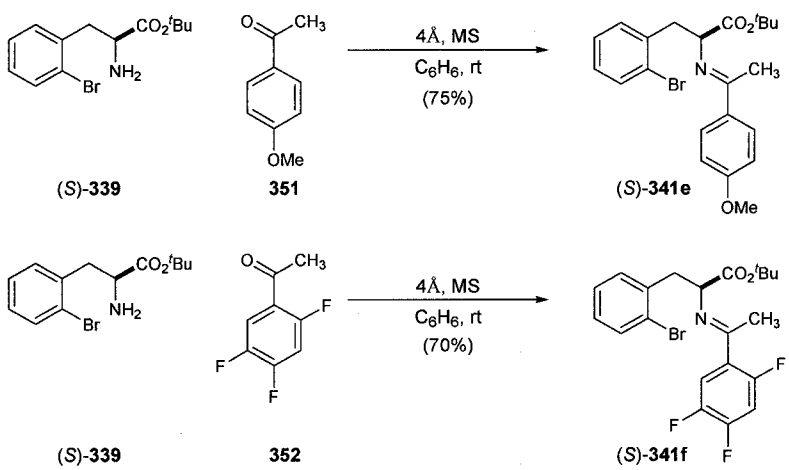
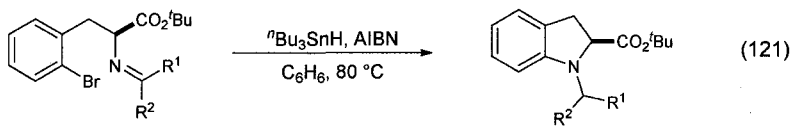


Table 16 lists the effect of ketimine electron donating and electron withdrawing groups on isomerization. When the phenyl group on the ketimine was changed to a methyl group, the % ee loss increased slightly (Table 16, entry 1 and 2).[165]

Table 16. Dependence of % ee loss on polar effects due to ketimine substituents (eq 121)[a]



(121)

(*S*)-**178/341** (*S*)-**179/343**

entry	(*S*)-**178/341**	R^1	R^2	% *ee*[b] **178/341**	% *ee*[b] **179/343**	% *ee* loss	yield (%)[c]
1	(*S*)-**178a**	C_6H_5	C_6H_5	96	63	33	85
2	(*S*)-**341b**	CH_3	C_6H_5	99	57[e]	42	76
3	(*S*)-**341e**	CH_3	4-$MeOC_6H_4$	87	20[d]	67	50
4	(*S*)-**341f**	CH_3	2,4,5-$F_3C_6H_2$	87	80[f]	7	67

[a] All reactions were carried out with 2.2 equiv. of $^nBu_3SnH$, 0.8 equiv. AIBN and 0.01M in (*S*)-**178/341**. [b] % *ee* determined by Chiral HPLC analysis. [c] Isolated yield. [d] ee of major diastereomer. Diastereoselectivity = 2.6:1. [e] ee of major diastereomer. Diastereoselectivity = 5:1 (65% ee, minor diastereomer) - contributed by Daniel Mutnick. [f] ee of major diastereomer. Diastereoselectivity = 4.9:1.

However, a more pronounced loss of % ee was observed when the *para* position of the phenyl ring was substituted with an electron donating methoxy group (Table 16, entries 2 and 3). Similarly, when the aromatic ring was substituted with three fluorine atoms on *ortho*, *meta* and *para* positions, there was a corresponding decrease in the extent of isomerization (Table 16, entries 2 and 4). These effects also fully correlated with the presence of polar effects in the isomerization.

4.5. 1,4-Imino Transfer – Proof of Concept

In all the examples studied so far, the isomerization between the ring form and the chain form of the radical has always favored the ring form. This implied that the rate of the ring closing process (5-*exo*-trig cyclization) and subsequent reduction is higher than

[165] This also could be due to a mixture of electronic and steric factors.

that for the reverse ring opening event. One possible way to slow this rate of cyclization is to increase the steric bulk at C2 such that the radical addition would be hindered (Figure 29).

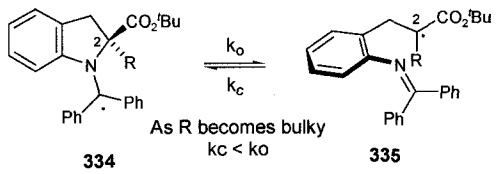
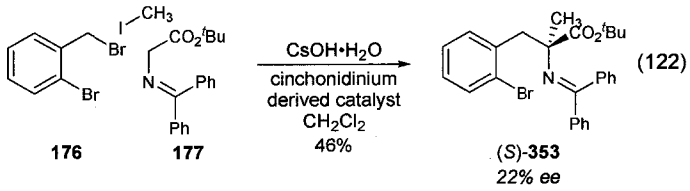


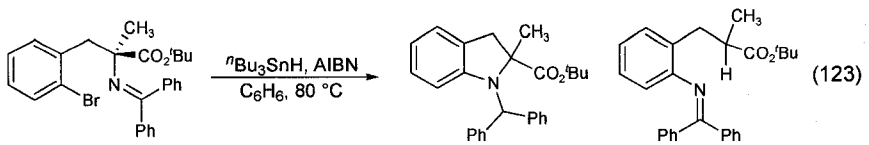
Figure 29. Steric effect of C2 substituent causing ring opening

Imine (*S*)-**353** with a methyl group at C2 was designed to test this hypothesis. Treatment of O'Donnell's glycine Schiff base **177** with methyl iodide followed by *o*-bromo benzyl bromide **176** in the presence of cesium hydroxide and cinchonidine-derived catalyst led to the doubly alkylated imine (*S*)-**353** in 46% yield and 22% ee (eq 122).[166] The low enantioselectivity observed was the result of the higher temperature needed for the deprotonation of the monoalkylated Schiff base.



As predicted, subjection of imine (*S*)-**353** to radical conditions led to isolation of two racemic products in equal yields (eq 123). Indoline **354** was formed out of cyclization followed by reduction with stannane (normal course of the reaction). However, imine **355** was the product arising from the open chain radical formed after isomerization. This constitutes a formal 1,4-imino transfer process, and confirmed our notion that an azacyclopentenyl carbinyl radical isomerization was responsible for the observed racemization. Isolation of indoline **354** in racemic form is further confirmation of the impact of torsional strain leading to ground state destabilization.

[166] For details of this alkylation reaction, refer to the section on indoline amino acids in Chapter 2.



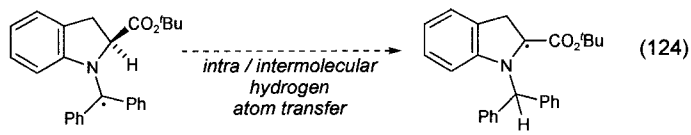
(*S*)-**353**
22% ee

354
48% yield, *0% ee*

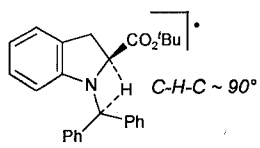
355
45% yield, *0% ee*

4.6. Alternative Mechanism

During these studies, we did not rule out the possibility that racemization might occur through a 1,3-hydrogen atom transfer (either intramolecular or intermolecular, eq 124). This process would also furnish indoline with a diminished % ee since the product radical could easily racemize.



356 **357**



358
Transition State for Intramolecular H abstraction

In general, 1,5- and 1,6-hydrogen atom transfers have been well documented.[167] However, for any intramolecular hydrogen atom transfer process, the bond angle between the atoms engaged in the transition state is optimal at 180°. The activation barrier for such a transfer increases substantially as this angle deviates from 180°. In the case of the indoline radical, a 1,3-hydrogen atom transfer would likely have a C-H-C angle close to 90° in the transition state (see inset). Based on this fact, we discounted the possibility of an intramolecular hydrogen atom transfer process causing the racemization.

However, the possibility of an intermolecular (formal) transfer of a hydrogen atom with the aid of stannyl radical remained a possibility. Imine (*S*)-**178** was therefore subjected to tributyltin deuteride under standard conditions for observing isomerization (eq 125).

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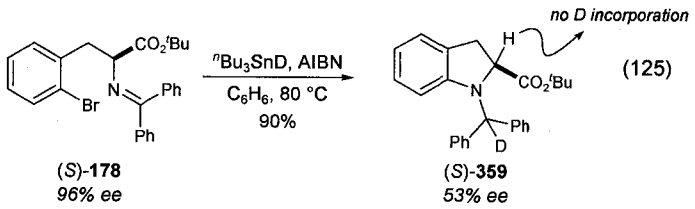
[167] (a) Visklocz, B.; Lendvay, G.; Kortvelyesi, T.; Seres, L. *J. Am. Chem. Soc.* **1996**, *118*, 3006. (b) Lomas, J. S.; Briand, S. *J. Chem. Soc., Perkin Trans. 2* **1992**, 191. (c) Lopez-Romero, J. M.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2000**, *2*, 2591.



(*S*)-**178**
96% ee

(*S*)-**359**
53% ee

There was complete deuterium incorporation on the diphenylmethyl carbon, and no deuterium incorporation on the α-carbon of the ester (suspected to be the hydrogen atom donor). (*S*)-**359** was isolated in 90% yield and fully characterized. Therefore, it was concluded that a hydrogen atom transfer process was not operative.

4.7. Conclusion

This study identified the first examples of the azacyclopentenyl carbinyl radical isomerization. Key to this discovery was the observation of partial racemization. The isomerization process could be controlled by varying the effective tinhydride concentration or by use of faster hydrogen atom donors as additives. This proved that the lifetime of the radical was crucial to the extent of isomerization.

Moreover, the ACCRI is sensitive to steric variations on C7 of the indoline ring as well as on the nitrogen. The ester protecting group did not significantly affect the isomerization. Polar effects were shown to be highly influential on the isomerization, with electron donating groups on the ketimine portion leading to increased isomerization and electron withdrawing groups leading to decreased isomerization.

A highly sterically congested imine allowed isolation of the chain isomer resulting from a 1,4-imino transfer process. Overall, this isomerization exists as a complement to the cyclopropyl carbinyl isomerization that occurs in 2,3-lysine amino mutases.

Chapter 5. Experimental Section

General Experimental Details

Flame-dried (under vacuum) glassware was used for all non-aqueous reactions. All reagents and solvents were commercial grade and purified prior to use when necessary. Diethyl ether (Et_2O), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and benzene (C_6H_6) were dried by passage through a column of activated alumina as described by Grubbs.[168] Benzene was additionally passed through a column containing activated Q-5 reactant. Solvents other than benzene were degassed using the freeze-pump-thaw method when necessary. All additional solvents were dried by distillation from calcium hydride when necessary. Magnesium sulfate was used to dry organic solutions unless otherwise noted.

Thin layer chromatography (TLC) was performed using glass-backed silica gel (250 μ) plates, and flash chromatography utilized 230–400 mesh silica gel from Scientific Adsorbents. Neutral Alumina was used as received from Scientific Adsorbents for chromatography of acid-sensitive intermediates or products. Products were visualized by UV light, iodine, and/or the use of ceric ammonium molybdate, potassium permanganate, ninhydrin, *p*-anisaldehyde, and potassium iodoplatinate solutions.

IR spectra were recorded on a Nicolet Avatar 360 spectrophotometer. Liquids and oils were analyzed as neat films on a salt plate (transmission), whereas solids were applied to a diamond plate (ATR). Nuclear magnetic resonance spectra (NMR) were acquired on either a Varian Inova-400 or VXR-400 instrument. Chemical shifts are measured relative to tetramethylsilane, as judged by the residual partially deuterated solvent peak. Mass spectra were obtained using a Kratos MS-80 spectrometer using the ionization technique indicated. Combustion analyses were performed by Atlantic Microlab, Norcross, GA.

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[168] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. *J. Organometallics* **1996**, *15*, 1518–1520.

Ratios of diastereomers and isomeric products were measured directly from integration of ^{1}H NMR absorptions of protons common to the components. Precision was checked by varying the relaxation delay for measurements on the same compound. Where possible, ratios were corroborated using GC-mass spectrometry. Peak assignments were made from authentic samples in every case. Ratios reported generally represent a lower limit defined by multiple runs.

N,*N*-Dimethylformamide was dried using $MgSO_4$ under reduced pressure. Solid KOH, NaOH and $CsOH{\bullet}H_2O$ were pulverized under N_2 before use. Benzyltriethylammonium chloride was used as received from Aldrich. AIBN was recrystallized prior to use, and tri-*n*-butyl tin hydride (^{n}Bu$_3$SnH) was used as received from Aldrich.[169] 2′,4′,6′-Tribromo benzaldehyde **264** and 2′,4′-dibromo benzaldehyde **262** were prepared from the corresponding bromobenzenes using the procedure reported by Serwatowski.[170]

β-Chloro-α-methyl acrolein **228** was synthesized in three steps from commercially available methallyl chloride. Chlorination of methallyl chloride to give 1,2,3-Trichloro-2-methyl propane was carried out as described by Mooradian and Cloke (Caution! Reaction generates SO_2. Therefore, build up of starting material leads to a violent explosion. In order to prevent this, carefully monitored addition of methallyl chloride was necessary).[171] Conversion of 1,2,3-Trichloro-2-methyl propane into a 1:1 mixture of E and Z isomers of 3-chloro-2-methyl-2-propen-1-ol was carried out as described by Hatch et al.[172] Oxidation of the allylic alcohol was carried out as reported by Williard et al.[173] *m*CPBA was purified by washing with a buffer solution (pH = 7.4) as described by Perrin.[174] Literature procedure was followed for the synthesis of glycine *tert*-butyl ester.[175]

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[169] Two lots (purchased six months apart) from Alfa Aesar failed to effect the radical reactions.
[170] Serwatowski, J.; Luliński, S. *J. Org. Chem.* **2003**, *68*, 5384–5387.
[171] Mooradian, A.; Cloke, J. B. *J. Am. Chem. Soc.* **1946**, *68*, 785-789.
[172] Hatch, L. F.; Russ, J. J.; Gordon, L. B. *J. Am. Chem. Soc.* **1947**, *69*, 2614-2616.
[173] Williard, P.G.; Grab, L. A.; Laszlo, S. E. *J. Org. Chem.* **1983**, *48*, 1123-1125.
[174] Perrin, D. D. and Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed., Pregamon Press, Oxford, 1988.
[175] Moore, A. T.; Rydon, H. N. in "Organic Syntheses"; Wiley: NY, 1973, Collective Vol. 5, pp. 586-9.

General Procedure for Ketimine Condensations (Procedure A)

A rapidly stirred benzene solution of the amine (0.5 M), ketone (0.5 M), and 4Å MS (1:1 w/w) was stirred at 25 °C until complete conversion was achieved, as evidenced by ^{1}H NMR. The mixture was filtered through a pad of Celite and washed with Et_2O or benzene. The solvent was removed *in vacuo* to give the analytically pure ketimine which was used immediately.

The same procedure was used when the benzophenone ketimine was desired, however, benzophenone imine[176] was used in place of the ketone and dichloromethane was used as the reaction solvent.[177]

General Procedure for Aryl Aminations (Procedure B)

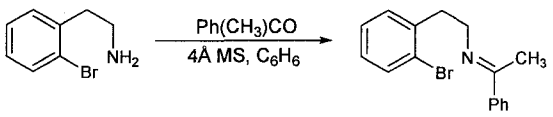
A benzene solution of the ketimine (0.01 M) was warmed to 85 °C in a round-bottomed flask equipped with a condenser. A benzene solution (1 mL) of ^{n}Bu$_3$SnH (1.1 equiv) and AIBN (0.4 equiv) was loaded into a gas-tight syringe and was attached to a syringe pump. The syringe needle was attached through a septum at the top of the condenser (w/N_2 line) so that the solution droplets would fall directly into the refluxing benzene. Following the addition, the reaction mixture was refluxed for an additional period (~1 h) and cooled to room temperature. At this point, an aliquot was removed, concentrated, and component ratios were measured by ^{1}H NMR and/or GC-MS. Two different work-up methods were used during these studies:[178]

Method 1: The solution was treated with $NaBH_4$ (1.1 equiv) and the slurry was stirred 4–5 hours. The mixture was concentrated *in vacuo*, diluted with Et_2O, and washed with water. The organic layer was separated, dried, and concentrated to furnish an oil. Flash chromatography of the crude mixture provided the analytically pure targeted compounds.

Method 2: The benzene was removed by vacuum, the residue was diluted with ether, and a sat aq KF solution (~20 equiv) was added. The mixture was stirred for 2 h (a

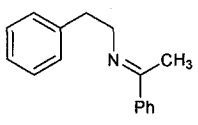
[176] For benzophenone imine synthesis: Pickard, P. L.; Tolbert, T. L. in *Organic Syntheses*; Wiley: NY, 1973, Collective Vol. 5, pp. 520-2.
[177] O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.
[178] Method 2 using the potassium fluoride was found to be more effective and easy to perform.

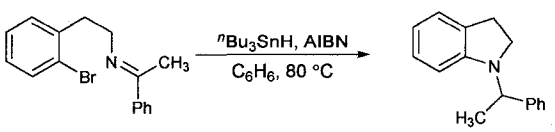
ppt usually forms at the interface) and the layers were separated. The organic layer was dried and concentrated, and the resulting oil was chromatographed.



[2-(2-Bromophenyl)ethyl]-(1-phenylethylidene)amine (136). Following the general procedure A, *ortho*-bromophenethylamine (46 mg, 231 μmol), acetophenone (27 μL, 231 μmol), and 4Å MS were stirred in benzene (2.3 mL) at room temperature for 12 h. Filtering of the mixture through Celite and removal of the solvent provided the ketimine (66.1 mg 95%) as a >95:5 mixture of stereoisomers. IR (film) 3056, 1633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.57 (d, J = 6.9 Hz, 1H), 7.40 (t, J = 3.1 Hz, 3H), 7.34 (d, J = 6.0 Hz, 1H), 7.26 (t, J = 6.3 Hz, 1H), 7.10 (t, J = 6.0 Hz, 1H), 3.79 (dd, J = 7.8, 7.2 Hz, 2H), 3.22 (dd, J = 7.8, 7.2 Hz, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.0, 142.0, 140.0, 133.0, 131.7, 129.7, 128.5, 128.1, 127.6, 126.9, 52.2, 37.8, 18.1; HRMS (EI): Exact mass calcd for $C_{16}H_{16}BrN$ $[M+H]^+$ 302.0544. Found 302.0516.

Phenethyl-(1-phenylethylidene)-amine (138). The phenethylamine ketimine was similarly prepared following the general procedure A. IR (film) 3083, 1685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.40 (t, J = 3.0 Hz, 3H), 7.31 (m, 5H), 3.76 (dd, J = 7.6, 7.5 Hz, 2H), 3.10 (dd, J = 7.6, 7.5 Hz, 2H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.9, 141.6, 140.9, 129.7, 129.3, 128.7, 128.5, 126.8, 126.3, 126.1, 54.4, 37.8, 15.7; HRMS (EI): Exact mass calcd for $C_{16}H_{17}N$ $[M]^+$ 223.1361. Found 223.1360.

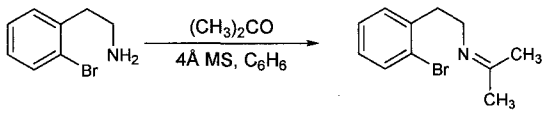




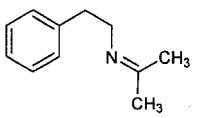
***N*-(1-Methylbenzyl) indoline (137).** Following the general procedure B, a three hour addition of a $^nBu_3SnH$ (68 μL, 0.25 mmol) and AIBN (15 mg, 93 μmol) solution in

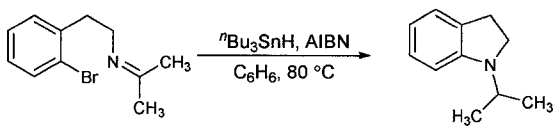
benzene (0.7 mL) to a refluxing solution of the unpurified ketimine (69.6 mg, 231 μmol) in benzene (23 mL) delivered, after flash chromatography (2% dichloromethane in hexanes), the indoline as a colorless oil (44.9 mg, 87%). R_f = 0.62 (30% CH_2Cl_2/hexanes); IR (film) 3046, 1606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 7.5 Hz, 2H), 7.29 (t, J = 7.2 Hz, 2H), 7.26 (t, J = 7.2 Hz, 1H), 7.08 (d, J = 7.2 Hz, 1H), 7.00 (t, J = 7.8 Hz, 1H), 6.6 (t, J = 7.2 Hz, 1H), 6.36 (d, J = 7.8 Hz, 1H), 4.68 (q, J = 6.8 Hz, 1H), 3.42 (dd, J = 18.1, 9.1 Hz, 1H), 3.35 (dd, J = 15.7, 7.4 Hz, 1H), 2.96 (dd, J = 8.5, 8.3 Hz, 2H), 2.58 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 151.1 143.0 128.7, 127.4, 127.3, 127.1, 124.6, 117.2, 107.5, 54.8, 48.2, 28.5, 16.8; HRMS (EI): Exact mass calcd for $C_{16}H_{17}N$ $[M]^+$ 223.1361. Found 223.1366.

Anal. Calcd for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 86.09; H, 7.76; N, 6.38.

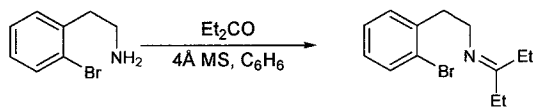


[2-(2-Bromophenyl)ethyl]-isopropylidene-amine (139a). Following the general procedure A, *ortho*-bromophenethylamine (150 mg, 750 μmol), acetone (44 mg, 750 μmol) and 4Å MS were stirred in benzene (5 mL) at room temperature for 4 h to provide the ketimine. IR (film) 3055, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.3 Hz, 1H), 7.24–7.18 (m, 2H), 7.04 (td, J = 6.9, 2.3 Hz, 1H), 3.46 (t, J = 7.5 Hz, 2H), 3.06 (t, J = 7.7 Hz, 2H), 1.99 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 168.3, 139.9, 133.0, 131.4, 128.1, 127.6, 124.9, 51.6, 37.7, 29.5, 18.6; HRMS (EI): Calcd for $C_{11}H_{15}BrN$ $[M+H]^+$ 240.0310. Found 240.0389.

Isopropylidene-phenethyl-amine (141a). Following the general procedure A, the  ketimine derived from phenethyl amine and acetone was prepared. IR (film) 3080, 1665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, J = 8.1 Hz, 2H), 7.28–7.24 (m, 3H), 3.52 (t, J = 7.8 Hz, 2H), 3.00 (t, J = 7.8 Hz, 2H), 2.05 (s, 3H), 1.74 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) ppm 169.9, 140.8, 129.1, 128.8, 126.3, 53.7, 37.7, 29.5, 18.6; HRMS (EI): Exact mass calcd for $C_{11}H_{15}N$ $[M]^+$ 161.1204. Found 161.1200.



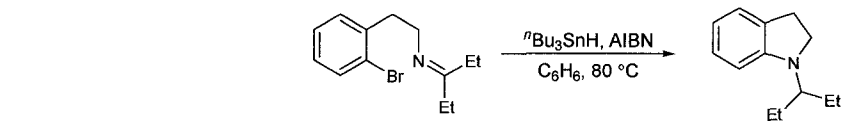
***N*-(*iso*-Propyl)-indoline (140a).** Following the general procedure B, a three-hour addition of $^nBu_3SnH$ (154 μL, 573 μmol) and AIBN (34 mg, 208 μmol) solution in benzene (1 mL) to a refluxing solution of the unpurified ketimine (125 mg, 521 μmol) in benzene (50 mL) delivered, after flash chromatography (30% CH_2Cl_2/Hexanes) 0.024 g (30%) of the desired indoline as a volatile colorless liquid. R_f = 0.1 (30% CH_2Cl_2/hexanes); IR (film) 3047, 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (t, J = 6.7 Hz, 2H), 6.59 (t, J = 7.4 Hz, 1H), 6.42 (d, J = 8.1 Hz, 1H), 3.83 (sep, J = 6.6 Hz, 1H), 3.33 (t, J = 8.5 Hz, 2H), 2.93 (t, J = 8.3 Hz, 2H), 1.15 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 151.5, 130.5, 127.5, 124.6, 117.1, 107.3, 46.0, 45.7, 28.4, 18.4; HRMS (EI): Exact mass calcd for $C_{11}H_{15}N$ $[M]^+$ 161.1204. Found 161.1201.



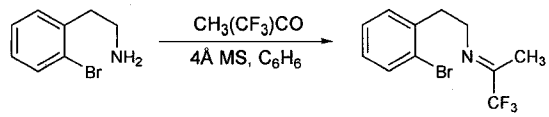
[2-(2-Bromophenyl)ethyl]-(1-ethylpropylidene)amine (139b). Following the general procedure A, *ortho*-bromophenethylamine (200 mg, 1.00 mmol) and 3-pentanone (86.0 mg, 1.00 mmol) were stirred in benzene (5 mL) at room temperature for 48 h to provide the ketimine as colorless oil (241 mg, 90%). IR (film) 3056, 1660 cm^{-1}; ^1H NMR (400

MHz, $CDCl_3$) δ 7.56 (dd, J = 7.9, 0.9 Hz, 1H), 7.32–7.24 (m, 2H), 7.10 (td, J = 7.8, 1.9 Hz, 1H), 3.61 (t, J = 7.5 Hz, 2H), 3.10 (t, J = 7.9 Hz, 2H), 2.30 (q, J = 7.5, 2H), 2.18 (q, J = 7.7 Hz, 2H), 1.12 (t, J = 7.5 Hz, 3H), 1.01 (t, J = 7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 176.2, 140.1, 132.9, 131.6, 128.0, 127.5, 124.8, 50.6, 38.0, 32.8, 24.0, 11.3, 11.1; HRMS (EI): Exact mass calcd for $C_{13}H_{19}BrN$ $[M+H]^+$ 268.0703. Found 268.0690.

(1-Ethyl-Propylidene)phenethylamine (141b). Following the general procedure A, the ketimine derived from phenethylamine and 3-pentanone was prepared. IR (film) 3084, 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.19 (m, 5H), 3.58 (t, J = 7.7 Hz, 2H), 2.95 (t, J = 7.9 Hz, 2H), 2.28 (q, J = 7.4 Hz, 2H), 2.13 (q, J = 7.7, 2H), 1.11 (t, J = 7.4 Hz, 3H), 0.97 (t, J = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 176.0, 140.9, 129.2, 128.5, 126.2, 52.8, 38.0, 32.9, 24.0, 11.4, 11.1; HRMS (FAB) Exact mass calcd for $C_{13}H_{20}N$ $[M+H]^+$ 190.1596. Found 190.1592.

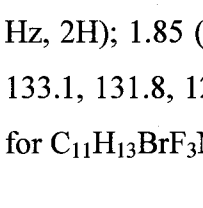


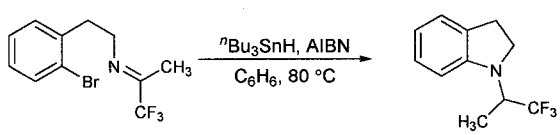
1-(1-Ethylpropyl)-2,3-dihydro-1H-indole (140b). Following general procedure B, a three hour addition of ^{n}Bu_3SnH (126 μL, 0.470 mmol) and AIBN (28 mg, 0.170 mmol) solution in benzene (1 mL) to a refluxing solution of the unpurified ketimine (114 mg, 0.425 mmol) in benzene (42 mL) delivered, after flash chromatography on silica gel (4% dichloromethane in hexanes) the desired indoline as a volatile colorless liquid (32.0 mg, 40%). R_f = 0.10 (4% CH_2Cl_2/hexanes); IR (film) 3048, 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (t, J = 7.3 Hz, 2H), 6.51 (t, J = 7.1 Hz, 1H), 6.34 (d, J = 8.1 Hz, 1H), 3.34 (t, J = 8.7 Hz, 2H), 3.24 (p, J = 7.1 Hz, 1H), 2.96 (t, J = 8.7 Hz, 2H), 1.56–1.49 (m, 4H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 152.6 129.5, 127.5, 124.6, 115.8, 105.8, 58.2, 45.5, 28.4, 24.7, 11.9; HRMS (EI): Exact mass calcd for $C_{13}H_{19}N$ $[M]^+$ 189.1517. Found 189.1527.



[2-(2-Bromophenyl)ethyl]-(2,2,2-trifluoro-1-methyl-ethylidene)amine (139c). Following the general procedure A, *ortho*-bromophenethylamine (200 mg, 999 μmol), trifluoroacetone (168 mg, 1.5 mmol), and 4Å MS were stirred in benzene (5 mL) at room temperature for 4 h to provide the ketimine as a >95:5 mixture of stereoisomers (264 mg, 90%). IR (film) 3059, 1686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.3 Hz, 1H), 7.29–7.22 (m, 2H), 7.13 (dt, J = 6.8, 2.4 Hz, 1H), 3.75 (t, J = 7.3 Hz, 2H), 3.17 (t, J = 7.3 Hz, 2H); 1.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 157.3 (q, J = 33.6 Hz), 138.6, 133.1, 131.8, 127.8, 124.7, 121.4, 118.6, 51.4, 36.6, 12.6; HRMS (EI): Exact mass calcd for $C_{11}H_{13}BrF_3N$ $[M+H]^+$ 296.0086. Found 296.0088.

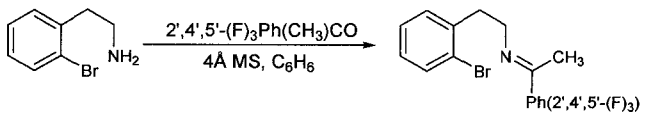
Phenethyl-(2,2,2-trifluoro-1-methylethylidene)amine (141c). Following the general procedure A, the ketimine derived from phenethylamine and trifluoroacetone was prepared. IR (film) 3088, 1686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 7.0, 7.0 Hz, 2H), 7.27 (t, J = 6.6 Hz, 1H), 7.26 (d, J = 6.9 Hz, 2H), 3.74 (t, J = 7.3 Hz, 2H), 3.06 (t, J = 7.3 Hz, 2H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 156.9 (q, J = 32.8 Hz), 139.6, 129.2, 128.8, 126.7, 120.1, 53.6, 36.4, 12.5; HRMS (EI): Exact mass calcd for $C_{11}H_{12}F_3N$ $[M]^+$ 215.0922. Found 215.0928.





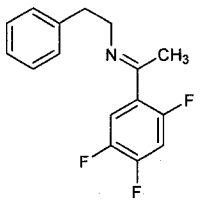
***N*-(1-Trifluoroethyl)-indoline (140c).** Following the general procedure B, a three hour addition of a $^nBu_3SnH$ (133 μL, 495 μmol) and AIBN (30 mg, 180 μmol) solution in benzene (1 mL) to a refluxing solution of the unpurified ketimine (132 mg, 450 μmol) in benzene (44 mL) provided, after flash chromatography (100% hexanes), the desired indoline as a volatile colorless liquid (80 mg, 83%). R_f = 0.15 (hexanes); IR (film) 3050,

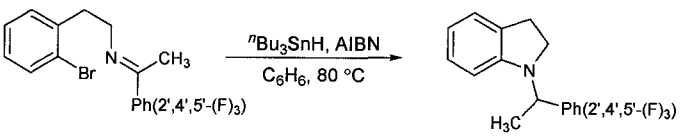
1490 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, J = 7.9 Hz, 2H), 6.65 (t, J = 7.3 Hz, 1H), 6.44 (d, J = 7.8 Hz, 1H), 4.14 (m, 1H), 3.54 (t, J = 8.5 Hz, 2H), 3.03 (t, J = 8.6 Hz, 2H), 1.38 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 150.3, 129.3, 127.5, 125.0, 118.2, 114.0, 106.3, 52.8 (q, J = 28.2 Hz), 47.1, 28.5, 10.5; HRMS (EI): Exact mass calcd for $C_{11}H_{12}F_3N$ $[M]^+$ 215.0922. Found 215.0920.



(*E*)-2-(2-bromophenyl)-N-(1-(2,4,5-trifluorophenyl)ethylidene)ethanamine (142b). Following the general procedure A, *ortho*-bromophenethylamine (100 mg, 0.503 mmol), 2',4',5'-trifluoroacetophenone (87.0 mg, 503 μmol) were stirred in benzene (5.0 mL) at room temperature for 5 h to provide the ketimine as a colorless oil (179 mg, 100%); IR (film) 3067, 1627 cm-1; 1H NMR (400 MHz, CDCl3) δ 7.59 (dd, J = 8.1, 1.1 Hz, 1H), 7.52-7.44 (m, 1H), 7.34-7.27 (m, 2H), 7.18 (td, J = 7.9, 1.9 Hz, 2H), 6.96-6.90 (m , 1H), 3.76 (t, J = 7.4 Hz, 2H), 3.22 (t, J = 7.8 Hz, 2H), 2.15 (d, J = 3.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 163.2, 139.6, 133.1, 131.6, 128.3, 127.7, 127.5, 126.9, 124.9, 118.6, 117.8, 106.3, 106.1, 106.1, 105.8, 51.8, 37.5, 18.9; HRMS (EI): Exact mass calcd for $C_{13}H_{14}BrF_3N$ $[M+H]^+$ 356.0262. Found 356.0293.

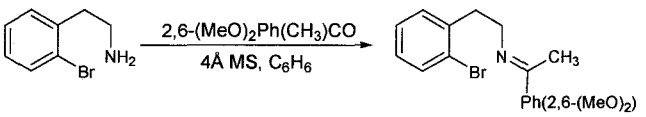
(*E*)-N-(1-(2,4,5-trifluorophenyl)ethylidene)-2-phenylethanamine (144b). Following the general procedure A, phenethylamine (50.0 mg, 0.413 mmol), 2',4',5'-trifluoroacetophenone (54.0 μL, 0.413 mmol) were stirred in benzene (4.1 mL) at room temperature for 5 h to provide the ketimine as a colorless oil (110 mg, 90%): IR (film) 3065, 1627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49-7.42 (m, 1H), 7.36-7.22 (m, 5H), 7.11 (d, J = 6.9 Hz, 1H), 6.97-6.90 (m, 1H), 3.74 (t, J = 7.4, 2H), 3.10 (t, J = 7.7 Hz, 2H), 2.12 (d, J = 3.4 Hz , 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 162.9, 140.5, 140.1, 129.2, 129.2, 128.7, 128.6, 126.5, 118.1, 117.8, 106.1, 53.9, 37.4, 18.9; HRMS (EI): Exact mass calcd for $C_{16}H_{14}NF_3$ $[M]^+$ 277.1078. Found 277.1085.





1-[1-(2,4,5-Trifluorophenyl)ethyl]-2,3-dihydro-1*H*-indole (143b). Following the general procedure B, a three-hour addition of $^{n}Bu_3SnH$ (59.0 μL, 0.219 mmol) and AIBN (11.0 mg, 68.0 μmol) solution in benzene (1 mL) to a refluxing solution of the unpurified ketimine (60.0 mg, 0.169 mmol) in benzene (17 mL) delivered, after flash chromatography (10% CH_2Cl_2/hexanes), the desired indoline (31.0 mg, 65%) as a colorless solid. R_f = 0.1 (1% EtOAc/hexanes); IR (film) 3063 , 1628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.25 (m, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 7.03-6.93 (m, 2H), 6.67 (t, *J* = 7.3 Hz, 1H), 6.26 (d, *J* = 7.8 Hz, 2H), 4.84 (q, *J* = 6.9 Hz, 1H), 3.52 (td, *J* = 7.8, 1.3 Hz, 2H), 3.03 (t, *J* = 7.9 Hz, 2H), 1.55 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 156.5, 154.2, 151.0, 148.3, 130.3, 127.6, 127.5, 124.7, 118.0, 116.2 (d, *J* = 6.0 Hz) 107.4 , 106.1 (d, *J* = 21.0 Hz), 105.8 (d, *J* = 20.5 Hz), 49.5, 49.1, 28.5, 18.2; HRMS (EI): Exact mass calcd or $C_{16}H_{14}F_3N$ $[M]^+$ 277.1078. Found 277.1088.

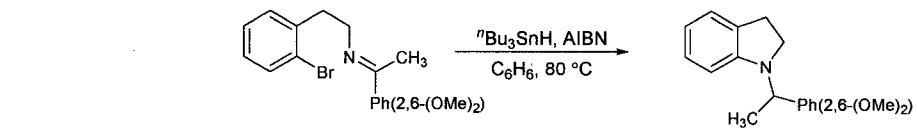
Anal. Calcd for $C_{16}H_{14}F_3N$: C, 69.30; H, 5.09; N, 5.05. Found: C, 69.39; H, 5.06; N, 5.03.



[2-(2-Bromophenyl)ethyl]-[1-(2,6-dimethoxyphenyl)ethylidene]amine (142e). Following the general procedure A, *ortho*-bromophenethylamine (200 mg, 0.999 mmol) and 2',6'-dimethoxyacetophenone (180 mg, 0.999 mmol) were stirred in benzene (10.0 mL) at room temperature for 10 h to provide the ketimine as a colorless oil (326 mg, 90%): IR (film) 2293, 1648, 1104 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.7 Hz, 1H), 7.24-7.15 (m, 3H), 7.00 (td, *J* = 6.3, 2.7 Hz, 1H), 6.56 (d, *J* = 8.3 Hz, 2H), 3.77 (s, 6H), 3.32 (t, *J* = 7.4 Hz, 2H), 3.03 (dd, *J* = 8.5, 5.8 Hz, 2H) 2.25 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 164.9, 156.7, 155.9, 140.1, 132.5, 130.9, 130.6, 129.5, 127.2,

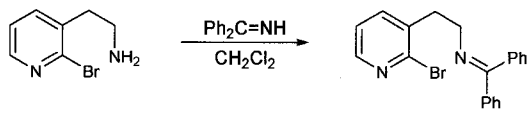
124.6, 116.3, 103.9, 103.5, 55.8, 55.6, 53.3, 37.3, 32.3, 27.7; HRMS (EI): Exact mass calcd for $C_{18}H_{21}BrNO_2$ $[M+H]^+$ 362.0756. Found 362.0750.

[1-(2,6-dimethoxyphenyl)ethylidene]phenethylamine (144e). Following the general procedure A, phenethylamine (50.0 mg, 0.413 mmol), 2',6'-dimethoxyacetophenone (74.4 mg, 0.413 mmol) were stirred in benzene (4.1 mL) at room temperature for 10 h to provide the ketimine as a colorless oil (108 mg, 87%): IR (film) 2922, 1643, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, J = 8.5 Hz, 3H), 7.18-7.13 (m, 3H), 6.58 (d, J = 8.3 Hz, 2H), 3.78 (s, 6H), 3.33 (t, J = 7.0, 2H), 2.95 (t, J = 7.9 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 164.7, 156.1, 141.1, 130.9, 129.9, 129.0, 128.4, 126.0, 116.6, 104.2, 103.9, 56.1, 55.8, 55.7, 37.5, 27.9; HRMS (EI): Exact mass calcd for $C_{18}H_{21}NO_2$ $[M]^+$, 283.1572. Found 283.1570.



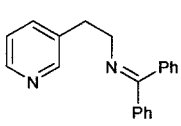
(2,6,Dimethoxyphenyl)ethyl]-2,3-dihydro-1*H*-indole (143e). Following the general procedure B, a three hour addition of $^nBu_3SnH$ (232 μL, 0.866 mmol) and AIBN (43.0 mg, 0.266 mmol) in benzene (2 mL) to a refluxing solution of the unpurified ketimine (241 mg, 0.666 mmol) in benzene (66 mL) delivered, after flash chromatography (SiO_2, 30% dichloromethane in hexanes) the desired indoline (50.0 mg, 27%) as a colorless solid. R_f = 0.10 (30% CH_2Cl_2/hexanes); IR (film) 2935, 1606 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, J = 8.3 Hz, 1H), 7.00 (t, J = 6.8 Hz, 1H), 6.98 (d, J = 1.1 Hz, 1H), 6.56 (d, J = 8.3 Hz, 2H), 6.51-6.46 (m, 2H), 5.41 (q, J = 7.1 Hz, 1H), 3.84 (2, 6H), 3.68 (dd, J = 18.3, 9.0 Hz, 1H), 3.61 (dd, J =18.7, 6.4 Hz, 1H), 2.98 (dd, J =15.7, 6.7, 1H) 2.91 (dd, J =15.7, 9 Hz 1H), 1.59 (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 159.0, 152.3, 129.5, 128.3, 127.5, 124.2, 119.5, 115.7, 105.9, 104.7, 56.0, 48.5, 46.2, 28.7, 16.4; HRMS (EI): Exact mass calcd for $C_{18}H_{21}NO_2$ $[M]^+$ 283.1572. Found 283.1581.

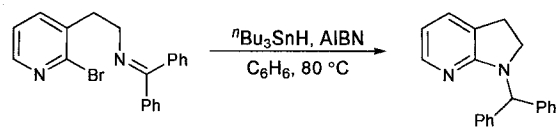
Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.56; H, 7.51; N, 4.91.



2-(2-bromopyridin-3-yl)-N-(diphenylmethylene)ethanamine (148). Following the general procedure A, 2-Bromo-3-(2-aminoethyl) pyridine (163 mg, 811 μmol) and benzophenone imine (147 mg, 811 μmol) were stirred in CH_2Cl_2 at room temperature for 8 h to provide the ketimine. IR (film) 3056, 1622 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, J = 4.7, 0.9 Hz, 1H), 7.56 (t, J = 7.8 Hz, 3H), 7.43–7.40 (m, 3H), 7.37 (d, J = 6.6 Hz, 1H), 7.32 (t, J = 7.9 Hz, 2H), 7.16 (dd, J = 7.4, 5.2 Hz, 1H); 6.96 (t, J = 3.4 Hz, 2H), 3.69 (t, J = 6.9 Hz, 2H), 3.10 (t, J = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 169.2, 158.1, 147.7, 144.5, 139.5, 137.0, 136.5, 130.0, 128.5, 128.4, 128.3, 127.5, 122.6, 52.4, 36.8; HRMS (EI): Exact mass calcd for $C_{20}H_{17}BrN_2$ $[M]^+$ 364.0575. Found 364.0587.

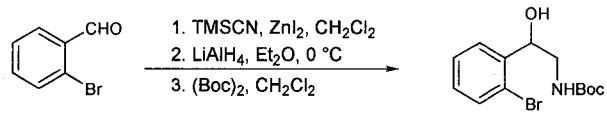
N-(diphenylmethylene)-2-(pyridin-3-yl)ethanamine (150). Following the general procedure A, 3-(2-aminoethyl)pyridine (30.0 mg, 0.106 mmol), benzophenone imine (19.0 mg, 0.106 mmol) were stirred in CH_2Cl_2 (1.1 mL) at room temperature for 8 h to provide the ketimine **150** (21.2 mg, 70%) as a colorless oil: IR (film) 3080, 1659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 4.4 Hz, 2H), 7.50 (d, J = 7.3 Hz, 2H), 7.40 (d, J = 7.8 Hz, 1H), 7.36-7.23 (m, 6H), 7.11 (dd, J = 7.7, 4.8 Hz, 1H) 6.88 (dd, J =7.2, 3.6Hz, 2H), 3.57 (t, J = 7.0, 2H), 2.93 (t, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 168.7, 150.2, 147.1, 136.3, 135.5, 129.8, 128.2, 128.2, 128.0, 127.8, 127.2, 122.9, 54.9, 34.4; HRMS (EI): Exact mass calcd for $C_{20}H_{19}N_2$ $[M]^+$ 287.1548. Found 287.1547.





***N*-(1-Phenylbenzyl)-6-azaindoline (149).** Following the general procedure B, a two-hour addition of ^{n}Bu$_3$SnH (268 μL, 997 μmol) and AIBN (60 mg, 362 μmol) solution in benzene (2 mL) to a refluxing solution of the unpurified ketimine (110 mg, 310 μmol) in benzene (30 mL) delivered, after flash chromatography (SiO_2, 5% ethyl acetate in hexanes), the desired indoline as an orange crystalline solid (50 mg, 60%). mp 101 °C; R_f = 0.1 (5% EtOAc/hexanes); IR (film) 3058, 1611 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 5.2 Hz, 1H), 7.34–7.26 (m, 10H), 7.17 (d, J = 7.0 Hz, 1H), 6.81 (s, 1H), 6.42 (t, J = 6.5 Hz, 1H), 3.34 (t, J = 8.5 Hz, 2H), 2.97 (t, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 162.8, 146.1, 140.2, 131.2, 129.1, 128.5, 127.4, 122.8, 112.4, 60.0, 45.6, 25.9; HRMS (EI): Exact mass calcd for $C_{20}H_{18}N_2$ $[M]^+$ 286.1470. Found 286.1468.

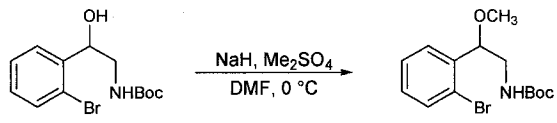
Anal. Calcd for $C_{20}H_{18}N_2$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.84; H, 6.34; N, 9.71.



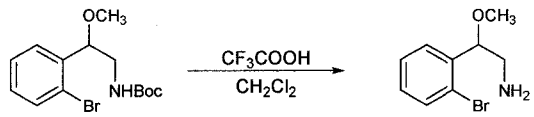
2-(2-Bromophenyl)-2-hydroxyethyl carbamic acid *tert*-butyl ester (151). Treatment of 0.215g (0.994 mmol) of 2-amino(2-bromo-phenyl)-ethanol[179] with di-*tert*-butyl dicarbonate (0.217g, 0.994 mmol) and triethylamine (0.129 ml, 0.994 mmol) in CH_2Cl_2 (20 mL) provided after chromatography (SiO_2, 20% ethyl acetate in hexanes) the carbamate as a colorless oil (260 mg, 83%). R_f = 0.10 (20% EtOAc/hexanes); IR (film) 3427 (br), 1691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, J = 7.8, 1.2 Hz, 1H), 7.47 (dd, J = 7.9, 0.8 Hz, 1H), 7.30 (t, J = 7.5 Hz 1H), 7.10 (td, J = 7.8, 1.5 Hz, 1H), 5.21(t, J= 5.4 Hz, 1H), 5.09 (d, J = 3.0 Hz, 1H), 4.50 (s, 1H), 3.48 (ddd, J = 14.2, 6.5, 3.0 Hz, 1H), 3.29-3.24 (m, 1H), 1.41(s, 9H) ; ^{13}C NMR (100 MHz, $CDCl_3$) ppm 157.8 , 141.0 , 132.8 ,

[179] Fleming, I.; Woolias, M.; *J. Chem. Soc., Perkin Trans.* 1, **1979**, *3*, 829.

129.2 , 128.2 , 127.8 , 122.0 , 80.0 , 73.4 , 46.8 , 28.6 ; HRMS (EI): Exact mass calcd for $C_{13}H_{19}BrNO_3$ $[M+H]^+$ 316.0548. Found 316.0544.

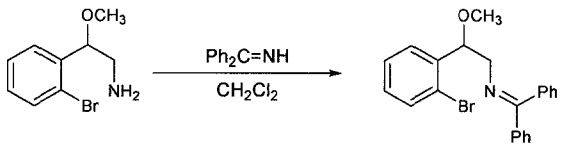


2-(2-Bromophenyl)-2-methoxyethyl carbamic acid *tert*-butyl ester (152). The carbamate (50.0 mg, 0.159 mmol) was treated with sodium hydride (7.00 mg, 0.152 mmol) at 0 °C in DMF (1 mL). Dimethyl sulfate (14.0 μL, 0.152 mmol) was added and the solution was warmed to room temperature. Stirring for 4 hours followed by aqueous work-up and flash chromatography (SiO_2, 5% ethyl acetate in hexanes) provided the ether as a colorless oil (35.0 mg, 70%). R_f = 0.10 (4% EtOAc/hexanes); IR (film) 3442, 3362, 3061, 1717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J = 8.1, 1.1 Hz, 1H), 7.41(dd , J = 7.7 , 1.8 Hz , 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.16 (td , J = 7.8, 1.6 Hz, 1H), 4.92 (s, 1H), 4.68 (br, d, J = 3.5 Hz, 1H), 3.53-3.44 (m , 1H), 3.27 (s, 3H), 3.18 (ddd, J = 12.8, 7.8, 5.0 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 177.2, 155.9, 138.4, 133.1, 129.6, 127.9, 123.6, 81.5, 79.5, 57.4, 45.4, 28.6; HRMS (EI): Exact mass calcd for $C_{14}H_{21}BrNO_3$ $[M+H]^+$ 330.0704. Found 330.0723.

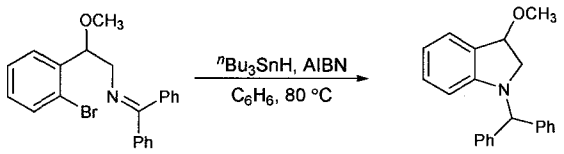


2-(2-Bromophenyl)-2-methoxyethylamine (152a). Treatment of the carbamate (14.6 mg, 0.044 mmol) with trifluoroacetic acid (10% v/v TFA:CH_2Cl_2) at room temperature for 2 h yielded the trifluoroacetate salt. This salt was dissolved in ether and washed with satd aq K_2CO_3 to give the amine in quantitative yield as a colorless oil. R_f = 0.05 (10% MeOH/hexanes); IR (film) 3384, 3311, 3062, 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.4 Hz, 1H), 7.41(dd, J = 7.8, 1.8 Hz, 1H), 7.33 (t, J = 7.1 Hz, 1H), 7.15 (td, J = 7.7, 1.8 Hz, 1H), 4.57 (dd, J = 7.5, 3.4 Hz, 1H), 3.30(s, 1H), 2.94 (br, m, 1H) , 2.79 (br, m, 1H), 1.53 (br, s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 139.2, 133.1, 131.1,

129.3, 127.9, 123.4, 68.4 HRMS (EI): Exact mass calcd for C_8H_8BrO $[M\text{-}CH_4N]^+$ 198.9759. Found 198.9758.



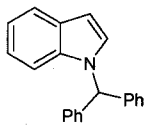
2-(2-bromophenyl)-2-methoxy-N-(diphenylmethylene)ethanamine (153). Following the general procedure A, 2-(*ortho*-Bromophenyl)-2-methoxyethylamine (43.4 mg, 189 μmol), benzophenone imine (32 μL, 189 μmol), and 4Å MS were stirred in CH_2Cl_2 at room temperature for 7 h. Removal of the solvent provided the ketimine as a colorless oil. R_f = 0.10 (4% EtOAc/hexanes); IR (film) 3058, 1626 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.3 Hz, 2H), 7.52 (dd, J = 8.1, 2.2 Hz, 1H), 7.45–7.28 (m, 8H), 7.13 (dt, J = 9.3, 1.6 Hz, 1H), 7.07 (dd, J = 7.5, 2.4 Hz, 2H), 5.05 (dd, J = 6.7, 4.5 Hz, 1H), 3.71 (dd, J = 14.0, 4.4 Hz, 1H), 3.64 (dd, J = 14.0, 6.9 Hz, 1H), 3.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 169.8, 140.1 (2C), 137.0, 132.82, 130.2, 129.1, 128.8 (2C), 128.65, 128.6, 128.54, 128.2, 127.7, 123.8, 82.8, 59.2, 57.6; HRMS (EI): Exact mass calcd for $C_{22}H_{21}BrNO$ $[M+H]^+$ 394.0808. Found 394.0795.



1-benzhydryl-3-methoxyindoline (154). Following the general procedure B, a three hour addition of $^nBu_3SnH$ (38 μL, 143 μmol) and AIBN (8.5 mg, 52 μmol) in benzene (1 mL) to a refluxing solution of the unpurified ketimine (51.2 mg, 130 μmol) in benzene (13 mL) afforded, after flash chromatography on basic alumina (10% CH_2Cl_2 in hexanes), the desired indoline as a colorless oil (29 mg, 70%). R_f = 0.15 (10% CH_2Cl_2/hexanes); IR (film) 3059, 1608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.26 (m, 11H), 7.10 (dt, J = 8.1, 1.2 Hz, 1H), 6.71 (t, J = 7.25 Hz, 1H), 6.34 (d, J = 7.9 Hz, 1H), 5.70 (s, 1H), 4.79 (dd, J = 6.7, 2.6 Hz, 1H), 3.35 (s, 3H), 3.33 (dd, J = 11.3, 2.7 Hz,

1H), 3.27 (dd, J = 11.2, 6.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 140.7, 130.1, 129.2, 128.8, 128.7, 128.4, 128.2, 127.7, 127.5, 126.1 78.9, 65.7, 56.4, 55.4; HRMS (EI): Exact mass calcd for $C_{22}H_{21}NO$ $[M]^+$ 315.1623. Found 315.1623.

1-Benzhydryl-1-H indole (156). This indole formed from the previously isolated C3-methoxy indoline **154** upon standing in air. White solid, mp 91-94°C, R_f = 0.1 (2.5% EtOAc/Hexanes); IR (film) 3059, 1610 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, J = 8.2, 0.8 Hz, 1H), 7.38-7.31 (m, 7H), 7.27 (d, J = 7.3 Hz, 1H), 7.17-7.12 (m, 6H), 6.87 (s, 1H), 6.53 (d, J = 0.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 140.1, 137.0, 130.5, 128, 9, 128.7, 127.2, 124.9, 121.8, 121.2, 120.0, 110.5, 101.6; HRMS (EI): Exact mass calcd for $C_{21}H_{17}N$ $[M]^+$ 283.1361. Found 283.1355.



General Procedure for Racemic Phase Transfer Alkylations (Procedure C)

A 0.34 M dichloromethane solution of benzophenone glycinyl imine *tert*-butyl ester (1 equiv), benzyltriethyl ammonium chloride (0.2 equiv), and benzyl halide (1.2 equiv) was treated with 50% aq NaOH (20 equiv). The mixture was stirred vigorously at room temperature for 4 h. The heterogeneous mixture was diluted with Et_2O, washed with water, dried, and concentrated prior to purification by column chromatography (neutral alumina) to yield pure racemic ketimines.

General Procedure for Asymmetric Phase Transfer Alkylations (Procedure D)

A 0.34 M dichloromethane solution of benzophenone glycinyl imine *tert*-butyl ester (1 equiv), cinchonidine or cinchonine derived catalyst (0.1 equiv) and solid $CsOH{\bullet}H_2O$ (10 equiv) was cooled to –78 °C followed by dropwise addition of benzyl halide (5 equiv). The heterogeneous mixture was stirred for the time specified (typically ~20 hours) while maintaining the low temperature. The solution was diluted with Et_2O, washed with water, dried, and concentrated prior to purification by chromatography (neutral alumina) which gave analytically pure ketimine. Absolute stereochemistry was assigned for X based on

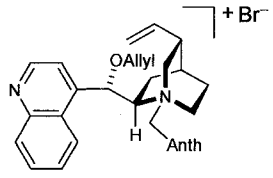
conversion to the corresponding amino acid X. The absolute stereochemistry for the other indoline α-amino acids were assigned by analogy.

General Procedure for Aryl Amination of Chiral Non-racemic Schiff Base Substrates (Procedure E)

A benzene solution of the ketimine (1 equiv) and $^{n}Bu_3SnH$ (2.2 equiv) was warmed to 85 °C followed by slow addition of AIBN (1.2 equiv) using a syringe pump over 4-5 hrs. The solution was refluxed for an additional hour before concentration. The residue was treated with a 1:1 (by volume) solution of Et_2O and satd aq KF[180] and the mixture stirred vigorously until a white solid precipitated. The organic layer was washed with water, and concentrated prior to purification by silica gel chromatography to give the target indoline.

General Procedure for Imine Reduction to Determine % ee (Procedure F)

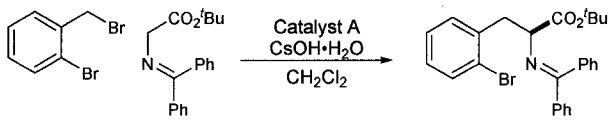
To a 0.02 M solution of ketimine (1 equiv) in dry methanol, was added $NaBH_4$ (25 equiv) at 0 °C. The mixture was warmed up to 25 °C, and stirred for 1-1.5 h. The solution was diluted with CH_2Cl_2, washed with water, dried, and concentrated prior to purification by silica gel chromatography to yield analytically pure amine for HPLC analysis.



9-*O*-Allyl-N-9-anthracenylmethylcinchoninium bromide (182). Catalyst **182** was prepared in an analogous manner to that reported for catalyst **181**.[181] Yellow solid, purified by silica gel chromatography (2% methanol in dichloromethane); mp 140–142 °C; R_f= 0.1 (2% CH_3OH/CH_2Cl_2); IR (film) 3402, 1640, 1625 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 9.02 (d, J = 4.6 Hz, 1H), 8.94 (d, J = 9.0 Hz, 1H), 8.80 (s, 1H), 8.68 (m, 1H), 8.29 (d, J = 8.9 Hz, 1H), 8.20-8.16 (m, 3H), 7.93-7.90 (m, 3H), 7.83 -7.79 (m, 1H), 7.70-

[180] Complete saturation by KF is necessary.
[181] Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414; However, in our hands the catalyst failed to crystallize, therefore it was purified by chromatography.

7.66 (m, 1H), 7.62-7.58 (m, 2H), 6.88 (bs, 1H), 6.45-6.36 (m, 1H), 6.05 (s, 2H), 5.98-5.89 (m, 1H), 5.71 (d, J = 17.3 Hz, 1H), 5.61 (d, J = 10.5 Hz, 1H), 5.18 (d, J = 10.4 Hz, 1H), 5.04 (d J = 17.2 Hz, 1H), 4.87 (s, 1H), 4.55-4.51 (m, 2H), 4.41-4.33 (m, 2H), 4.41-4.33 (m, 3H), 3.14 (t, J = 11.0 Hz, 1H), 2.82-1.75 (m, 1H), 2.54 (t, J = 11.8 Hz, 1H), 2.25 (d, J = 7.7 Hz, 1H), 1.82 (br s, 1H), 1.62 (m, 1H), 1.18 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) ppm 151.9, 150.2, 143.3, 138.3, 135.6, 135.5, 134.6, 134.0, 133.8, 132.4, 132.2, 131.9, 131.2, 130.4, 130.2, 130.0, 128.0, 127.5, 127.3, 126.8, 125.9, 125.7, 122.3, 119.9, 119.8, 119.1, 118.8, 76.5, 72.1, 69.7, 59.9, 57.9, 57.5, 39.7, 28.3, 25.6, 24.3.; HRMS (EI): Exact mass calcd for $C_{37}H_{37}NO_2$ $[M]^+$ 525.2906. Found 525.2880. $[\alpha]_D^{21}$ = +286 (*c* 1.6, $CHCl_3$)

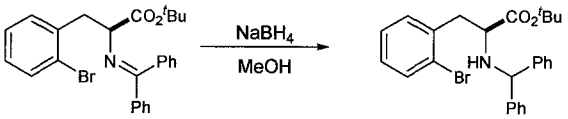


(*S*)-*tert*-butyl 3-(2-bromophenyl)-2-(diphenylmethyleneamino)propanoate (178a). Following the general procedure D, *ortho*-Bromobenzylbromide (1.97 g, 7.87 mmol), the glycinyl imine (465 mg, 1.574 mmol), and $CsOH•H_2O$ (2.35 g, 15.74 mmol) stirred for 20 h in the presence of catalyst **181** (10 mol %) at < -65 °C. Work-up according to the general procedure provided the desired phenyl alanine derivative as a colorless oil (650 mg, 89%). R_f = 0.40 (10% EtOAc/hexanes); IR (film) 3058, 1732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dt, J = 7.1, 0.9 Hz, 2H), 7.44 (dd, J = 9.0, 1.1 Hz, 1H), 7.41–7.28 (m, 6H), 7.23 (dd, J = 7.5, 1.6 Hz, 1H), 7.15 (td, J = 7.4, 1.3 Hz, 1H), 7.05 (td, J = 7.7, 1.8 Hz, 1H), 6.61 (d, J = 5.9 Hz, 2H), 4.36 (dd, J = 9.7, 4.0 Hz, 1H), 3.49 (dd, J = 13.3, 4.0 Hz, 1H), 3.25 (dd, J = 13.3, 9.7 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 170.5, 139.5, 137.7, 136.2, 132.7, 132.5, 130.1 (2C), 128.8, 128.2, 128.1, 127.93, 127.86, 127.7, 126.9, 125.2, 81.1, 65.2, 39.6, 28.1; HRMS (EI): Exact mass calcd for $C_{26}H_{27}BrNO_2$ $[M+H]^+$ 464.1225. Found 464.1241.

Anal. Calcd for $C_{26}H_{27}BrNO_2$: C, 67.24; H, 5.64; N, 3.02. Found: C, 67.36; H, 5.71; N, 2.94.

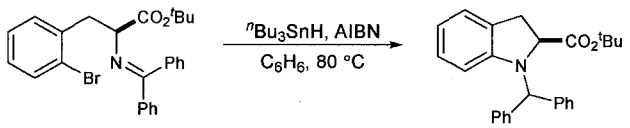
HPLC (Chiralcel OD, 2% ^{i}PrOH/hexanes, 0.5 mL/min) t_r (*R*) = 10.5 m, t_r (*S*) = 11.0 m. (*S*)- 96% ee, $[\alpha]_D^{21}$ = –265 (*c* 0.9, $CHCl_3$); (*R*)- 93% ee, $[\alpha]_D^{21}$ = +260 (*c* 2.7, $CHCl_3$).

Use of cinchonine-derived catalyst **182** gave the enantiomer as a colorless oil (189 mg, 81%).



(*S*)-*tert*-butyl 2-(benzhydrylamino)-3-(2-bromophenyl)propanoate (183a). For chiral HPLC analysis, the imine was reduced according to the General Procedure F (7 mg, 88%). Crystalline solid, mp 98–100 °C; R_f = 0.43 (10% EtOAc/hexanes); IR (film) 3324, 1724 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.8 Hz, 1H), 7.34 (dd, *J* = 8.5, 1.3 Hz, 2H), 7.29 (d, *J* = 7.0 Hz, 2H), 7.25 (d, *J* = 4.2 Hz, 2H), 7.17 (m, 7H), 4.81 (s, 1H), 3.46 (t, *J* = 7.5 Hz, 1H), 3.09 (dd, *J* = 13.4, 6.6 Hz, 1H), 3.03 (dd, *J* = 13.6, 8.6 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm, 174.1, 144.5, 142.6, 137.7, 132.6, 132.0, 128.5, 128.3, 128.1, 127.4, 127.2, 127.1, 127.0, 125.1, 81.2, 65.4, 59.6, 40.2, 28.1; HRMS (EI): Exact mass calcd for $C_{26}H_{29}BrNO_2$ $[M+H]^+$ 466.1382. Found 466.1358.

HPLC (Chiralcel AD, 2% ^{i}PrOH/hexanes, 1 mL/min) t_r (*S*) = 4.1 m, t_r (*R*) = 4.6 m. (*S*)- 95% ee, $[\alpha]_D^{21}$ = –30.6 (*c* 2.2, $CHCl_3$). (*R*)- 93% ee, $[\alpha]_D^{21}$ = +29.4 (*c* 0.9, $CHCl_3$).

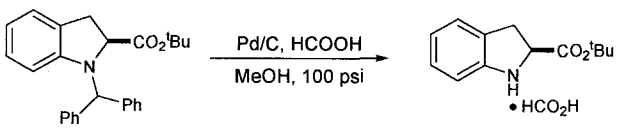


(*S*)-*tert*-butyl 1-benzhydrylindoline-2-carboxylate (179a). According to the general procedure E, use of the Schiff base (0.107 g, 0.23 mmol), Bu_3SnH (0.14 mL, 0.51 mmol), and AIBN (30 mg, 0.19 mmol) furnished, after silica gel chromatography (2% EtOAc in hexanes), a white solid (62 mg, 69%). mp 102–104 °C; R_f = 0.42 (10% EtOAc/hexanes); IR (film) 3061, 1736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* =

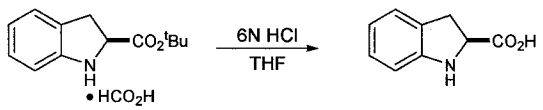
7.1 Hz, 2H), 7.37 (d, J = 7.1 Hz, 2H), 7.34–7.23 (m, 6H), 7.03 (d, J = 7.1 Hz, 1H), 6.87 (t, J = 7.7 Hz, 1H), 6.64 (t, J = 7.3 Hz, 1H), 6.01 (d, J = 7.9 Hz, 1H), 5.66 (s, 1H), 4.11 (dd J = 10.5, 5.4 Hz, 1H), 3.42 (dd, J = 15.9, 10.5 Hz, 1H), 3.0 (dd, J = 15.9, 5.4 Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 172.6, 151.2, 141.2, 140.7, 129.2, 128.5, 128.4, 127.7, 127.3, 127.2, 123.8, 117.9, 80.8, 67.1, 65.0, 34.0, 27.9; HRMS (EI): Exact mass calcd for $C_{26}H_{27}NO_2$ $[M]^+$ 385.2042. Found 385.2061.

HPLC (Chiralcel OD, 2% ^{i}PrOH/hexanes, 1 mL/min) t_r (*S*) = 4.1 m, t_r (*R*) = 4.7 m. (*S*)- 95% ee, $[\alpha]_D^{21}$ = –45.4 (*c* 1.0, $CHCl_3$). (*R*)- 93% ee, $[\alpha]_D^{21}$ = +41.9 (*c* 1.8, $CHCl_3$).

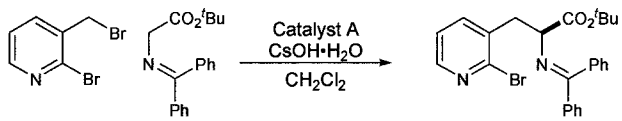
The enantiomeric indoline was similarly prepared (21.5 mg, 70%).



(*S*)-Indoline α-amino acid *tert*-butyl ester, formic acid salt (184). Indoline (*S*)-**179a** (55 mg, 142 μmol) was dissolved in dry MeOH (2 mL) and treated with 96% HCOOH (65 mg, 1.42 mmol) and 10% Pd/C (5.5 mg). The bomb was charged with hydrogen (100 psi): and the reaction was stirred for 48 h with frequent recharging of the hydrogen atmosphere. Filtration of the reaction mixture and evaporation of solvent gave a white solid (29 mg, 77%). mp 102-104 °C; R_f = 0.10 (15% EtOAc/hexanes); IR (film) 2978, 1736, 1672 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.25-7.20 (m, 3H), 7.10-7.05 (m, 1H), 4.94 (ddd, J = 11.1, 4.3, 0.8 Hz, 1H), 3.54 (dd, J = 16.8, 11.3 Hz, 1H), 3.15 (dd, J = 16.8, 4.3 Hz, 1H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, CDCl3) ppm 169.7, 157.6, 128.3, 126.1, 124.6, 109.5, 82.6, 58.6, 45.0, 32.7, 28.2; HRMS (EI): Exact mass calcd for $C_{14}H_{17}NO_3$ $[M\text{-}H_2O]^+$ 247.1208. Found 247.1215. (S)- 91% ee, $[\alpha]_D^{21}$ = –103.7 (*c* 0.74, $CHCl_3$).



(*S*)-Indoline α-amino acid ((*S*)-157). The formic acid salt **184** (32.5 mg, 123 μmol) was dissolved in 6*N* HCl (1 mL) and THF (several drops to solubilize) and refluxed for 3 h. The reaction mixture was cooled, neutralized with NaOH, and the solvent was removed by evaporation. The residue was extracted with 50% MeOH/CH_2Cl_2 and the extracts were concentrated to give a white solid (87%). $[\alpha]_D^{21}$ = –60.0 (*c* 0.40, 1*N* HCl). Literature: $[\alpha]_D^{21}$ = –114 (*c* 1.0, 1*N* HCl). The presence of (inseparable) NaCl in the synthetic material accounts for the depression of rotation.



(*S*)-*tert*-butyl 3-(2-bromopyridin-3-yl)-2-(diphenylmethyleneamino)propanoate (178b). Following the general procedure D, 2-Bromo-3-bromomethyl pyridine[182] (213 mg, 850 μmol), glycinyl imine (50 mg, 170 μmol), and CsOH•H_2O (253 mg, 1.70 mmol) were stirred for 20 h in the presence of catalyst **181** (10 mol %) while maintaining a temperature < –65 °C. Work-up according to the general procedure provided the desired alanine derivative as a white solid (61 mg, 77%). mp 93–95 °C; R_f = 0.15 (10% EtOAc/hexanes); IR (film) 3056, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 4.7, 1.9 Hz, 1H), 7.60 (dd, *J* = 8.6, 1.5 Hz, 2H), 7.56 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.41–7.28 (m, 6H), 7.12 (dd, *J* = 7.5, 4.7 Hz, 1H), 6.68 (d, *J* = 6.2 Hz, 2H), 4.40 (dd, *J* = 9.5, 4.3 Hz, 1H), 3.43 (dd, *J* = 13.7, 4.3 Hz, 1H), 3.22 (dd, *J* = 13.6, 9.4 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.1, 170.2, 148.0, 144.7, 140.7, 139.0, 135.9, 135.1, 130.3, 128.7, 128.5, 128.3, 127.9, 127.4 122.4, 81.5, 64.4, 44.7, 28.0; HRMS (EI): Exact mass calcd for $C_{25}H_{26}BrN_2O_2$ $[M+H]^+$ 465.1177. Found 465.1180.

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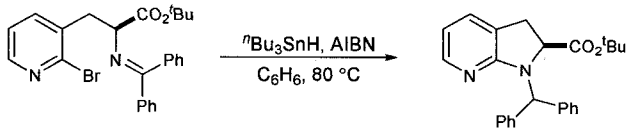
[182] Srinivasan, J. M.; Burks, H. E.; Smith, C. R.; Viswanathan, R.; Johnston, J. N. *Synthesis* (Practical Synthetic Procedures) **2005**, *2*, 330.

Anal. Calcd for $C_{25}H_{25}BrN_2O_2$: C, 64.52; H, 5.41; N, 6.02. Found: C, 64.24; H, 5.48; N, 5.96.

HPLC (Chiralcel AD, 2% ^{i}PrOH/hexanes, 1 mL/min) t_r (*R*) = 7.4 m, t_r (*S*) = 8.9 m. (*S*)- >99% ee, $[\alpha]_D^{21}$ = –245.4 (*c* 0.9, $CHCl_3$). (*R*)- 98% ee, $[\alpha]_D^{21}$ = +235.9 (*c* 1.7, $CHCl_3$).

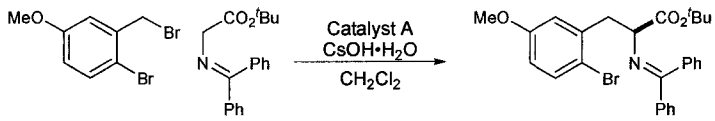
Similarly, use of cinchonine catalyst **182** gave the enantiomer as a white solid (60 mg, 76%).



(*S*)-*tert*-butyl 1-benzhydryl-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine-2-carboxylate (179b). Following the general procedure E, According to the general procedure, use of the Schiff base (123 mg, 264 μmol), Bu_3SnH (157 μL, 582 μmol), and AIBN (34.7 mg, 211 μmol) furnished, after silica gel chromatography (10% EtOAc in hexanes), a white solid (72.5 mg, 71%). mp 104–106 °C; R_f = 0.15 (10% EtOAc/hexanes); IR (film) 3060, 1740 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 5.4 Hz, 1H), 7.40 (d, *J* = 7.1 Hz, 2H), 7.30–7.17 (m, 9H), 6.49 (s, 1H), 6.46 (dd, *J* = 5.4, 1.6 Hz, 1H), 4.20 (dd, *J* = 10.7, 5.0 Hz, 1H), 3.42 (dd, *J* = 16.5, 10.7 Hz, 1H), 2.96 (dd, *J* = 16.5, 5.0 Hz, 1H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.8, 162.5, 146.4, 140.4, 140.1, 130.7, 129.8, 128.5, 128.2, 127.2, 127.0, 120.4, 112.9, 81.1, 62.5, 61.0, 32.1, 27.7; HRMS (EI): Exact mass calcd for $C_{25}H_{26}N_2O_2$ $[M]^+$ 386.1994. Found 386.1992.

HPLC (Chiralcel AD, 10% ^{i}PrOH/hexanes, 1 mL/min) t_r (*S*) = 6.0 m, t_r (*R*) = 11.3 m. (*S*)- 91% ee, $[\alpha]_D^{21}$ = –61.8 (*c* 0.9, $CHCl_3$). (*R*)- 89% ee, $[\alpha]_D^{21}$ = +58.6 (*c* 0.6, $CHCl_3$).

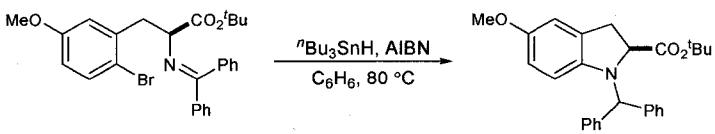
The enantiomeric indoline was similarly prepared (37 mg, 60%).



(*S*)-*tert*-butyl-3-(2-bromo-5-methoxyphenyl)-2-diphenylmethyleneamino)propanoate (178c). Following the general procedure D, 5-Methoxy-2-bromo-benzyl bromide (474 mg, 1.69 mmol), the glycinyl imine (100 mg, 339 μmol) and $CsOH•H_2O$ (505 mg, 3.39 mmol) stirred for 2 hrs in the presence of catalyst **181** (10 mol %) while maintaining a temperature < –10 °C. Work-up according to the general procedure provided the desired phenyl alanine derivative as a colorless oil (136 mg, 81%). R_f = 0.28 (10% EtOAc/hexanes); IR (film) 3058, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 7.3 Hz, 2H), 7.40–7.28 (m, 8H), 6.76 (d, J = 2.7 Hz, 1H), 6.63 (dd, J = 8.7, 3.0 Hz, 2H), 4.38 (dd, J = 9.7, 3.9 Hz, 1H), 3.62 (s, 3H), 3.43 (dd, J = 13.3, 4.0 Hz, 1H), 3.22 (dd, J = 13.2, 9.9 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 170.6, 158.4, 139.4, 138.4, 136.1, 132.9, 130.2, 128.7, 128.3, 128.1, 127.9, 127.7, 117.1, 115.5, 114.9, 81.2, 65.1, 55.2, 39.7, 28.0; HRMS (EI): Exact mass calcd for $C_{27}H_{29}BrNO_3$ $[M+H]^+$ 494.1331. Found 494.1323.

HPLC (Chiralcel AD, 2% ^{i}PrOH/hexanes, 1 mL/min) t_r (*R*) = 4.6 m, t_r (*S*) = 5.4 m. (*S*)- 94% ee $[\alpha]_D^{21}$ = –211.7 (*c* 1.0, $CHCl_3$). (*R*)- 91% ee, $[\alpha]_D^{21}$ = +201.1 (*c* 0.9, $CHCl_3$).

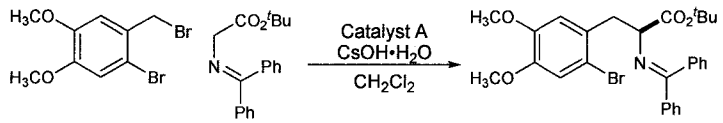
Similarly use of cinchonine based catalyst **182** gave the enantiomer as a colorless oil (120 mg, 74%).



(*S*)-*tert*-butyl 1-benzhydryl-5-methoxyindoline-2-carboxylate (179c). According to the general procedure E, use of the Schiff base (69.2 mg, 140 μmol), Bu_3SnH (188 μL, 700 μmol), and AIBN (37 mg, 224 μmol) furnished, after chromatography on neutral alumina

(2% EtOAc in hexanes), a colorless oil (26 mg, 45%). R_f = 0.1 (3% EtOAc/hexanes); IR (film) 3060, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, J = 8.3, 1.4 Hz, 2H), 7.39 (d, J = 7.1 Hz, 2H), 7.33–7.22 (m, 6H), 6.68 (d, J = 2.4 Hz, 1H), 6.42 (dd, J = 8.6, 2.6 Hz, 1H), 5.89 (d, J = 8.6 Hz, 1H), 5.59 (s, 1H), 4.07 (dd, J = 10.2, 5.1 Hz, 1H), 3.70 (s, 3H), 3.38 (dd, J = 15.8, 10.2 Hz, 1H), 2.96 (dd, J = 15.9, 5.0 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 172.6, 152.7, 145.4, 141.6, 140.9, 129.3, 129.1, 128.4, 128.3, 128.2, 127.2, 127.0, 111.6, 111.3, 109.3, 79.8, 67.6, 65.3, 55.8, 34.1, 27.9; HRMS (EI): Exact mass calcd for $C_{27}H_{29}NO_3$ $[M]^+$ 415.2147. Found 415.2160.
HPLC (Chiralcel OD, 2% ^{i}PrOH/hexanes, 1 mL/min) t_r (*S*) = 5.4 m, t_r (*R*) = 6.0 m. (*S*)-91% ee $[\alpha]_D^{21}$ = –41.2 (*c* 1.3, $CHCl_3$). (*R*)- 87% ee, $[\alpha]_D^{21}$ = +37.5 (*c* 0.7, $CHCl_3$).

The enantiomeric indoline was similarly prepared (24.3 mg, 55%).

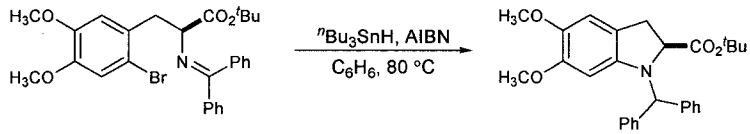


(*S*)-2-(Benzhydrylideneamino)-3-(2-bromo-4,5-dimethoxyphenyl)propionic acid *tert*-butyl ester ((*S*)-178d). Following general procedure D, 1-bromo-2-bromomethyl-4,5-dimethoxybenzene[183] (787 mg, 2.54 mmol), the glycinyl imine (150 mg, 0.508 mmol), and $CsOH•H_2O$ (757 mg, 5.08 mmol) were stirred in CH_2Cl_2 for 15 h in the presence of the cinchonidine derived catalyst **181** (10 mol %) while maintaining a temperature ≤–65 °C. Work-up according to the general procedure provided the desired product as a white solid (226 mg, 85%). mp 99–100 °C; R_f=0.13 (10% EtOAc/hexanes); IR (film) 3057, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.3 Hz, 2H), 7.39–7.28 (m, 6H), 6.92 (s, 1H), 6.71 (s, 1H), 6.62 (br d, J = 6.5 Hz, 2H), 4.29 (dd, J = 9.9, 3.8 Hz, 1H), 3.85 (s, 3H), 3.63 (s, 3H), 3.39 (dd, J = 13.4, 3.8 Hz, 1H), 3.20 (dd, J = 13.3, 10.1 Hz, 1H), 1.48 (s 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 170.6, 170.4, 148.0, 147.7, 139.3, 136.0, 130.2, 129.5, 128.7, 128.2, 128.0, 127.9, 127.7, 115.0, 114.8, 81.2, 65.4, 56.1, 55.7, 39.0, 28.0; HRMS (EI): Exact mass calcd for $C_{28}H_{31}BrNO_4$ $[M+H]^+$ 524.1436. Found 524.1418.

[183] Landais, Y.; Robin, J. P.; Lebron, A. *Tetrahedron* **1991**, *47*, 3787.

Similarly, use of cinchonine derived catalyst **182** gave the enantiomer as a white solid (256 mg, 95%).

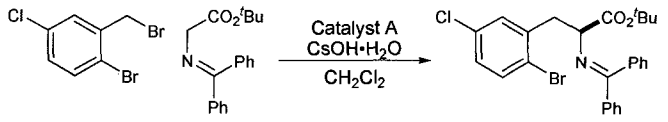
HPLC (Chiralcel OD, 2% ^{i}PrOH/hexanes, 1 mL/min): t_r (*S*) = 7.1 m, t_r (*R*) = 8.5 m. (*S*)- 92% ee, $[\alpha]_D^{23}$ = –202.5 (*c* 1.4, $CHCl_3$). (*R*)- 97% ee, $[\alpha]_D^{25}$ = +214.3 (*c* 0.8, $CHCl_3$).



(*S*)-1-Benzhydryl-5,6-dimethoxy-2,3-dihydro-1*H*-indole-2-carboxylic acid *tert*-butyl ester ((*S*)-179d). Following the general procedure E, the ketimine (41.6 mg, 79.0 μmol), $^{n}Bu_3SnH$ (107 μL, 397 μmol), and AIBN (15.6 mg, 95.0 μmol) gave, following chromatography (neutral alumina, 5% EtOAc in hexanes), the indoline as a colorless oil (18.0 mg, 50%). R_f= 0.13 (10% EtOAc/hexanes); IR (film) 3061, 1733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 6.9, 5.5 Hz, 4H), 7.34–7.22 (m, 6H), 6.67 (s, 1H), 5.65 (s, 1H), 5.62 (s 1H), 4.10 (dd, *J* = 10.1, 5.2 Hz, 1H), 3.78 (s, 3H), 3.41 (s, 3H), 3.35 (dd, *J* = 15.6, 10.3 Hz, 1H), 2.93 (dd, *J* = 15.0, 5.1 Hz, 1H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 172.6, 148.4, 145.6, 141.7, 141.5, 140.7, 132.4, 130.1 129.1, 128.5, 128.4, 128.3, 127.4, 127.2, 118.2, 109.8, 96.3, 80.9, 67.5, 65.5, 57.0, 55.5, 33.7, 27.9; HRMS (EI): Exact mass calcd for $C_{28}H_{31}NO_4$ $[M]^+$, 445.2253. Found, 445.2167.

The enantiomeric indoline was similarly prepared (27.7 mg, 50%).

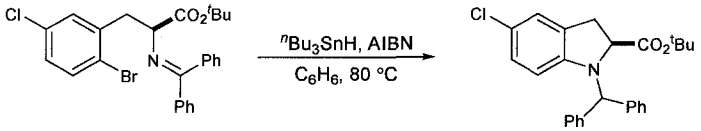
HPLC (Chiralcel AD, 2% ^{i}PrOH/hexanes, 1 mL/min): t_r (*R*) = 7.9 m, t_r (*S*) = 8.6 m. (*S*)- 82% ee, $[\alpha]_D^{25}$ = –18.0 (*c* 0.8, $CHCl_3$). (*R*)- 82% ee, $[\alpha]_D^{25}$ = +18.5 (*c* 2.2, $CHCl_3$).



(*S*)-*tert*-butyl 3-(2-bromo-5-chlorophenyl)-2-(diphenylmethyleneamino)propanoate (178e). Following the general procedure D, 5-Chloro-2-bromo benzyl bromide (1.16 g, 4.06 mmol), the glycinyl imine (200 mg, 667 mmol) and $CsOH•H_2O$ (1.01 g, 6.77 mmol) stirred for 22 hrs in the presence of catalyst **181** (10 mol %) while maintaining a temperature <–60 °C. Work-up according to the general procedure provided the desired phenyl alanine derivative as a white solid (250 mg, 74%); mp 98–100 °C; R_f = 0.43 (10% EtOAc/hexanes); IR (film) 3059, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, J = 8.5, 1.3 Hz, 2H), 7.39–7.29 (m, 6H), 7.26 (s, 1H), 7.20 (d, J = 2.4 Hz, 1H), 7.01 (dd, J = 8.5, 2.6 Hz, 1H), 6.73 (br d, J = 6.9 Hz, 2H), 4.31 (dd, J = 9.3, 4.6 Hz, 1H), 3.38 (dd, J = 13.4, 4.6 Hz, 1H), 3.24 (dd, J = 13.4, 9.3 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.1, 170.3, 139.5, 139.3, 136.1, 133.5, 132.8, 132.4, 130.3, 130.1, 128.8, 128.5, 128.3, 128.2, 128.0, 127.7, 122.9, 81.5, 65.0, 39.4, 28.0; HRMS (EI): Exact mass calcd for $C_{26}H_{25}ClNO_2$ $[M - Br]^+$ 418.1574. Found 418.1586.

HPLC (Chiralcel OD, 2% ^{i}PrOH/hexanes, 1 mL/min) t_r (*S*) = 4.1 m, t_r (*R*) = 4.6 m. (*S*)- 93% ee $[\alpha]_D^{21}$ = –194.3 (*c* 2.6, $CHCl_3$). (*R*)- 94% ee, $[\alpha]_D^{21}$ = +194.6 (*c* 0.74, $CHCl_3$).

Similarly, use of cinchonine-derived catalyst **182** gave the enantiomer as a white solid (240 mg, 71%).



(*S*)-*tert*-butyl 1-benzhydryl-5-chloroindoline-2-carboxylate (179e). According to the general procedure E, use of the Schiff base (50 mg, 100 μmol) $^nBu_3SnH$ (81 μL, 300 μmol) and AIBN (26.3 mg, 160 μmol) furnished, after silica gel chromatography (1% EtOAc in hexanes), a colorless oil (23 mg, 55%). R_f = 0.45 (10% EtOAc/hexanes); IR

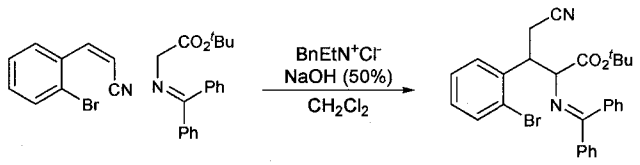
(film) 3062, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 6.9 Hz, 2H), 7.38–7.25 (m, 8H), 6.98 (s, 1H), 6.81 (dd, J = 8.5, 1.9 Hz, 1H), 5.87 (d, J = 8.5 Hz, 1H), 5.64 (s, 1H), 4.12 (dd, J = 10.3, 4.7 Hz, 1H), 3.38 (dd, J = 16.0, 10.4 Hz, 1H), 2.96 (dd, J = 16.3, 4.7 Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 172.1, 149.7, 141.0, 140.2, 129.2, 128.6, 128.5, 128.0, 127.5, 127.3, 127.0, 124.1, 122.6, 109.8, 81.2, 66.9, 65.2, 33.6, 27.8; HRMS (EI): Exact mass calcd for $C_{26}H_{26}ClNO_2$ $[M]^+$ 419.1652. Found 419.1657.

HPLC (Chiralcel AD, 2% ^{i}PrOH/hexanes, 1 mL/min) t_r (*S*) = 4.2 m, t_r (*R*) = 4.9 m. (*S*)- 93% ee $[\alpha]_D^{21}$ = –59.8 (*c* 1.2, $CHCl_3$). (*R*)- 94% ee, $[\alpha]_D^{21}$ = +63.4 (*c* 1.0, $CHCl_3$).

The enantiomeric indoline was similarly prepared (25.2 mg, 60%).

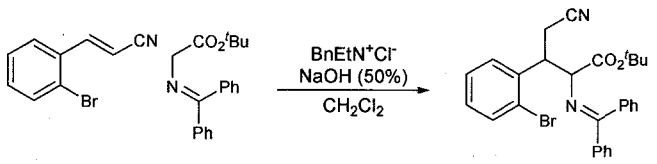
General Procedure for Two Component Phase Transfer-Catalyzed Michael Additions (Procedure G).

A dichloromethane solution of the Schiff base (1 equiv, 0.34M), benzyl triethyl ammonium chloride (20 mol%), and the Michael acceptor (1.2 equiv) was treated with 50% aq NaOH (20 equiv). The resulting mixture was rapidly stirred at room temperature for 4-8 hours and then diluted with ether. The organic layer was separated, washed with water, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography to furnish the analytically pure Michael adduct.

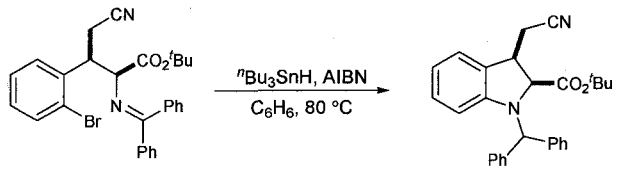


2-(Benzhydrylideneamino)-3-(2-bromophenyl)-4-cyanobutyric acid *tert*-butyl ester (*anti*-192). Following the general procedure G, nitrile *Z*-**191** (100 mg, 480 μmol) and Schiff base **177** (101 mg, 342 μmol) furnished the desired Michael adducts *syn*-**192** and *anti*-**192** in a 1.4:1 ratio (155 mg, 89%); (*anti*-**192**) R_f = 0.1 (6% EtOAc/hexanes); IR (film) 3061, 2977, 2930, 2244, 1736, 1623 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (dd, J =7.8, 1.1 Hz, 1H), 7.75 (dd, J = 7.1, 1.5 Hz, 2H), 7.59 (dd, J = 7.9, 1.1 Hz, 1H), 7.49-

7.45 (m, 4H), 7.42-7.34 (m, 3H), 7.29-7.27 (m, 2H), 7.16 (td, J = 7.9, 1.6 Hz, 1H), 4.56 (d, J = 5.6 Hz, 1H), 4.26 (ddd, J = 9.3, 6.5, 5.6 Hz, 1H), 3.00 (dd, J = 16.8, 9.3 Hz, 1H); 2.79 (dd, J = 16.8, 6.5 Hz, 1H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 173.2, 168.7, 139.0, 138.7, 135.6, 132.8, 130.7, 129.7, 129.0, 128.8, 128.3, 128.0, 127.9, 127.8, 125.0, 118.1, 81.7, 66.4, 43.0, 27.5, 20.3; HRMS (EI): Exact mass calcd for $C_{28}H_{27}BrN_2O_2$ $[M]^+$ 502.1256. Found 502.1267.

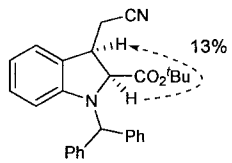


2-(Benzhydrylideneamino)-3-(2-bromophenyl)-4-cyanobutyric acid *tert*-butyl ester (*syn*-192). Following the general procedure G, nitrile *E*-**191** (99.0 mg, 480 μmol) and Schiff base **177** (117 mg, 397 μmol) furnished the desired Michael adducts *syn*-**192** and *anti*-**192** in a 6.5:1 ratio (178 mg, 70%); (*syn*-**192**) mp 142-145°C; R_f = 0.1 (8% EtOAc/hexanes); IR (film) 3060, 2977, 2931, 2245, 1730, 1624, 1151 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, J = 8.6, 1.5 Hz , 2H), 7.57 (dd, J = 8.1, 1.1 Hz, 1H), 7.47-7.33 (m, 6H), 7.29-7.21 (m, 2H), 7.15 (td, J = 8.1, 2.0 Hz, 1H), 6.71 (d, J =7.1 Hz, 2H), 4.44 (ddd, J = 9.5, 5.1, 4.6 Hz, 1H), 4.36 (d, J = 5.1 Hz, 1H), 3.32 (dd, J = 16.5, 9.5 Hz, 1H); 3.06 (dd, J =17.1, 4.6 Hz, 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 172.6, 168.7, 138.7, 137.4, 135.5, 133.1, 130.6, 128.9, 128.7, 128.6, 128.2, 128.0, 127.4, 127.2, 118.4, 81.9, 66.9, 53.4, 43.5, 27.7, 18.1; HRMS (EI): Exact mass calcd for $C_{28}H_{27}BrN_2O_2$ $[M]^+$ 502.1256. Found 502.1265.

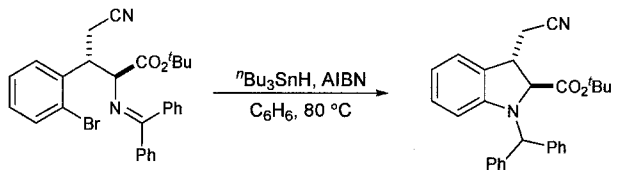


(*cis*)-1-Benzhydryl-3-cyanomethyl-2,3-dihydro-1*H*-indole-2-carboxylic acid *tert*-butyl ester (*cis*-197). According to the general procedure E, use of *syn*-**192** (110 mg, 218 μmol), ^{n}Bu$_3$SnH (130 μL, 480 μmol), and AIBN (29.0 mg, 174 μmol) provided after chromatography (6% ethyl acetate in hexanes), the desired indoline as a colorless oil

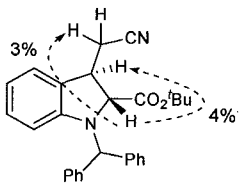
(56.0 mg, 61%). R_f = 0.10 (10% EtOAc/hexanes); IR (film) 3062, 2249, 1733, 1603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (td, *J* = 8.5, 1.1 Hz, 4H), 7.36-7.24 (m, 6H), 7.20 (d, *J* = 7.4 Hz, 1H), 6.95 (t, *J* = 7.7 Hz, 1H), 6.73 (td, *J* = 7.4, 0.7 Hz, 1H), 6.07 (d, *J* = 7.9 Hz, 1H) 5.58 (s, 1H), 4.27 (d, *J* = 8.9 Hz, 1H), 3.93 (m, 1H) 2.80 (dd, *J* = 16.8, 7.9 Hz, 1H), 2.33 (dd, *J* = 16.8, 7.4 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 169.2, 150.8, 141.2, 139.8, 129.2, 128.7, 128.7, 128.2, 127.7, 127.3, 122.8, 118.6, 118.4, 110.1, 82.6, 69.1, 66.9, 40.6, 28.0, 22.6, 18.5, 10.2; HRMS (EI): Exact mass calcd for $C_{28}H_{28}N_2O_2$ $[M]^+$ 424.2151. Found 424.2171.



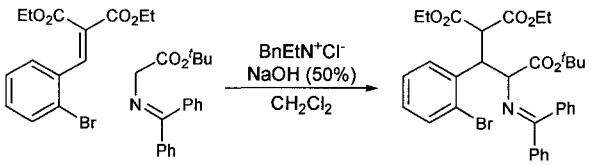
NOE measurements



(*trans*)-1-Benzhydryl-3-cyanomethyl-2,3-dihydro-1*H*-indole-2-carboxylic acid *tert*-butyl ester (*trans*-197). According to the general procedure E, use of *anti*-**192** (64.0 mg, 127 μmol), $^nBu_3SnH$ (74.9 μL, 279 μmol), and AIBN (17.0 mg, 102 μmol) provided, after chromatography (6% ethyl acetate in hexanes), the indoline as a colorless solid (50 mg, 80%). mp 148-150 °C; R_f = 0.1 (7% EtOAc/hexanes); IR (film) 3065, 2249, 1733, 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ7.42 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.37 (dd, *J* = 8.7, 1.6 Hz, 2H), 7.33-7.24 (m, 6H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.95 (t, *J* =6.9 Hz, 1H), 6.71 (t, *J* = 7.4 Hz, 1H), 6.04 (d, *J* =8.1 Hz, 1H) 5.69 (s, 1H), 3.82 (d, *J* = 3.8Hz, 1H), 3.46 (ddd, *J* = 3.8, 2.0, 1.5 Hz, 1H) 2.75 (d, *J* = 1.5 Hz, 1H), 2.73 (d, *J* =2.0 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 170.9, 150.3, 141.2, 140.1, 129.1, 128.7, 128.0, 127.8, 127.6, 127.4, 123.8, 118.7, 117.8, 110.1, 81.8, 69.9, 66.9, 42.5, 31.6, 29.7, 27.9, 23.2, 22.6, 14.1; HRMS (EI): Exact mass calcd for $C_{28}H_{28}N_2O_2$ $[M]^+$ 424.2151. Found 424.2144.



NOE measurements



2-(Benzhydrylidene-amino)-3-(2-bromo-phenyl)-4-ethoxycarbonyl-pentanedioic acid 1-tert-butyl ester 5-ethyl ester (*syn/anti*-199). According to the general procedure G, a solution of alkylidene malonate **198** (400 mg, 1.22 mmol) and Schiff base **177** (82 mg, 361 μmol) furnished, following chromatography (neutral alumina, 15% diethyl ether in hexanes), the desired adducts in a 1:1 *syn:anti* ratio as a colorless oil (685 mg, 90%); *syn*-**199** : R_f = 0.20 (12% EtOAc/hexanes); IR (film) 2980, 1733, 1622 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.72-7.70 (m, 2H), 7.49 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.44-7.31 (m, 7H), 7.09-7.05 (m, 3H), 4.68 (dd, *J* = 11.3, 5.4 Hz, 1H), 4.61 (d, *J* = 5.4 Hz, 1H), 4.19 (d, *J* = 11.3 Hz, 1H), 4.19-4.03 (m, 2H), 4.02-3.83 (m, 2H), 1.14 (t, *J* = 6.8 Hz, 3H), 1.14 (s, 9H), 0.98 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 172.5, 169.2, 167.9, 167.6, 139.4, 138.4, 136.0, 132.4, 131.1, 130.5, 128.9, 128.7, 128.6, 128.2, 128.0, 127.54, 127.49, 126.0, 100.6, 81.5, 65.9, 64.7, 61.4, 55.2, 44.3, 27.5, 13.9, 13.6; *anti*-**199** : R_f = 0.25 (12% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.6, 1.3 Hz, 2H), 7.51 (d, *J* = 7.7 Hz, 1H), 7.41-7.30 (m, 6H), 7.19-7.12 (m, 2H), 7.02 (td, *J* = 7.8, 1.8 Hz, 1H), 6.85 (d, *J* = 6.7 Hz, 2H), 4.96 (dd, *J* = 10.1, 4.7 Hz, 1H), 4.39 (d, *J* = 10.2 Hz, 1H), 4.20 (d, *J* = 4.8 Hz, 1H), 4.16-4.07 (m, 2H), 3.95-3.83 (m, 2H), 1.32 (s, 9H), 1.20 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.4, 169.0, 167.9, 167.8, 139.5, 139.1, 136.1, 132.9, 130.5, 129.2, 129.0, 128.4, 128.0, 127.9, 127.3, 127.0, 125.7, 81.3, 68.2, 61.4, 61.2, 54.3, 46.1, 27.7, 13.9, 13.6; HRMS (EI): Exact mass calcd for $C_{29}H_{36}{}^{79}BrNO_6$ $[M-C_4H_9]^+$ 564.1022. Found 564.1009.

(*cis*)-2-(1-Benzhydryl-2-*tert*-butoxycarbonyl-2,3-dihydro-*1H*-indol-3-yl)-malonic acid diethyl ester (*cis*-200). According to the general procedure E, use of *syn*-**199** (135 mg, 217 μmol), $^{n}Bu_3SnH$ (263 μL, 975 μmol) and AIBN (43 mg, 260 μmol) provided after column chromatography (15% diethyl ether in hexanes), the indoline as a colorless oil (108 mg, 92%); R_f = 0.25 (20% EtOAc/hexanes); IR (film) 3058, 2985, 1737, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.4 Hz, 2H), 7.39 (d, *J* = 6.8 Hz, 2H), 7.34-7.23 (m, 6H), 6.91 (t, *J* = 7.7 Hz, 1H), 6.81 (d, *J* = 7.4 Hz, 1H), 6.63 (t, *J* = 7.4 Hz, 1H), 6.04 (d, *J* = 7.7 Hz, 1H), 5.58 (s, 1H), 4.47 (dd, *J* = 11.7, 8.1 Hz, 1H), 4.40-4.31 (m, 4H), 4.09-4.01 (m, 1H), 3.59 (d, *J* = 11.8 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), (s, 9H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 169.8, 168.3, 167.3, 151.4, 150.4, 142.5, 140.0, 129.6, 128.7, 128.6, 128.1, 127.8, 127.6, 126.9, 126.7, 122.2, 118.0, 109.6, 82.1, 69.2, 66.8, 62.1, 61.6, 52.9, 43.5, 27.7, 14.0, 13.8; HRMS (EI): Exact mass calcd for $C_{33}H_{37}NO_6$ $[M]^+$, 543.2621. Found 543.2637.

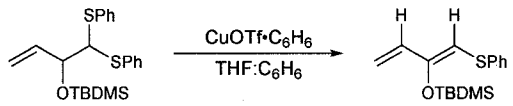
Anal. Calcd for $C_{39}H_{47}NO_8$: C, 71.21; H, 7.20; N, 2.13. Found: C, 71.11; H, 7.36; N, 2.14. Relative stereochemistry was assigned to be *cis* based on coupling constant correlation with that of *cis*-**197**.

(*trans*)-2-(1-Benzhydryl-2-tert-butoxycarbonyl-2,3-dihydro-1H-indol-3-yl)-malonic acid diethyl ester (*trans*-200). Adduct *anti*-**199** was cyclized according to the general procedure E to furnish indoline *trans*-**200** as a colorless oil (84% yield); R_f = 0.25 (20% EtOAc/hexanes); IR (film) 3058, 2985, 1737, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ

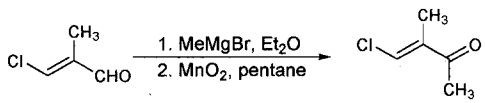
7.45 (d, J = 7.2 Hz, 2H), 7.41 (d, J = 7.0 Hz, 2H), 7.34-7.22 (m, 6H), 7.13 (d, J = 7.4 Hz, 1H), 6.89 (t, J = 7.5 Hz, 1H), 6.62 (t, J = 7.4 Hz, 1H), 6.01 (d, J = 7.9 Hz, 1H), 5.69 (s, 1H), 4.24-4.14 (m, 4H), 3.96 (d, J = 1.9 Hz, 1H), 3.85 (dd, J = 9.5, 1.9 Hz, 1H), 3.78 (d, J = 9.5 Hz, 1H), 1.30 (s, 9H), 1.23 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.1, 167.7, 167.6, 150.4, 142.2, 140.3, 129.5, 128.7, 128.5, 128.4, 127.5, 127.2, 127.0, 125.1, 118.1, 109.7, 81.1, 68.6, 66.6, 61.7, 61.5, 55.9, 45.0, 27.8, 14.1, 13.9; HRMS (EI): Exact mass calcd for $C_{33}H_{37}NO_6$ $[M]^+$ 543.2621. Found 543.2637. Anal. Calcd for $C_{39}H_{37}NO_8$: C, 71.21; H, 7.20; N, 2.13. Found: C, 71.11; H, 7.36; N, 2.14. Relative stereochemistry was assigned to be *trans* based on coupling constant correlation with that of *trans*-**197**.

[1-(Bis-phenylsulfanyl-methyl)-allyloxy]-*tert*-butyl-dimethyl-silane (222). A solution of the alcohol[184] (5.0 g, 17.3 mmol) in THF (10 mL) was canulated into DMF (16 mL). To this solution, *tert*-butyl dimethyl silyl chloride (5.08 g, 33.7 mmol) and imidazole (4.78 g, 70.2 mmol) were added. After 3 h of stirring, the reaction mixture was diluted with ether and washed with H_2O. The organic layer was separated, dried, and concentrated to an oil that was purified by flash chromatography (SiO_2, 2% ether in hexanes) to give the desired product as a colorless oil (5.69 g, 82% yield). R_f = 0.10 (2% Et_2O/hexanes); IR (film) 3074, 1579 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (m, 4H), 7.43-7.23 (m, 6H), 6.19 (ddd, J = 17.2, 10.3, 5.8 Hz, 1H), 5.31 (ddd, J = 17.1, 10.3, 1.6 Hz, 2H), 4.50-4.48 (m, 1H), 4.44 (d, J = 5.2 Hz, 1H), 0.91 (s, 9H), 0.01 (s, 3H), –0.01(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 137.5, 135.5, 135.1, 132.4, 132.0, 128.8 (2C), 127.5, 127.3, 116.9, 75.4, 66.6, 25.7, 18.2, -4.5, -4.9 ; HRMS (EI): Exact mass calcd for $C_{22}H_{30}SiOS_2$ $[M]^+$ 402.1507. Found 402.1491.

[184] Cohen, T.; Ruffner, R. J.; Shull, D. W.; Daniewski, W. M.; Ottenbrite, R. M.; Alston, P. V. *J. Org. Chem.* **1978**, *43*, 4052-4055.



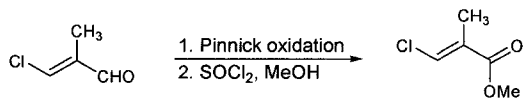
***tert*-Butyl-dimethyl-(1-phenylsulfanylmethylene-allyloxy)-silane (223).** Copper(I) triflate-benzene complex (4.83 g, 9.60 mmol) was combined with benzene (106 mL) in a two-necked flask fitted with a reflux condenser. The silyl ether (2.36 g, 5.85 mmol), Hunig's base (8.40 mL, 48.0 mmol), and 3-*tert*-butyl-4-hydroxy-5-methyl phenyl sulfide (86.0 mg, 240 μmol) were dissolved in THF (21 mL) and canulated into the two-necked flask. The resulting red solution was refluxed for 6 h, and then diluted with H_2O and ether after cooling to rt. The organic layer was dried and concentrated to an oil that was purified by flash chromatography (SiO_2, 1% triethylamine in hexanes) to furnish the diene as a yellow oil (1.30 g, 76% yield). R_f = 0.10 (100% hexanes); IR (film) 3062, 1618 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 7.3 Hz, 2H), 7.38-7.33 (m, 2H), 7.26 (t, J = 7.3 Hz, 1H), 6.32 (dd, J = 17.1, 10.7 Hz, 1H), 5.70 (s, 1H), 5.47 (d, J = 17.1 Hz, 1H), 5.15 (d, J = 10.7 Hz, 1H), 1.10 (s, 9H), 0.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 150.9, 136.7, 133.6, 128.9, 128.5, 126.1, 113.3, 107.6, 29.6, 26.0, -3.4 ; HRMS (EI): Exact mass calcd for $C_{16}H_{24}ClSiOS$ $[M]^+$ 292.1317. Found 292.1311.



4-Chloro-3-methyl-but-3-en-2-one (231). A solution of methyl magnesium bromide (33.6 mL, 3.0 M in ether), in ether (70 mL) was cooled to 0 °C and treated with a solution of β-chloro-α-methyl acrolein[185] (10.0g, 95.7 mmol) as a pre-dissolved solution in ether (16 mL). The mixture was warmed to room temperature and quenched with an ether-ice mixture, followed by an aqueous work-up to give the alcohol in sufficient purity for oxidation.

[185] See general experimental details in the beginning of this section for references.

The alcohol (11.53 g, 95.7 mmol) was added to a slurry of MnO_2[186] (83.2 g, 957 mmol) in pentane (300 mL) and stirred vigorously for 22 hours. Additional MnO_2 (8.32 g, 95.7 mmol) was added and the mixture was stirred for an additional 7 h. The mixture was filtered over Celite and concentrated to a yellow oil that was purified by flash chromatography (SiO_2, 8% ether in hexanes) to furnish the ketone as a yellow oil (4.3 g, 38%). R_f = 0.10 (6% Et_2O/hexanes); IR (film) 3094, 1678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (s, 1H), 2.30 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 195.7, 140.3, 133.6, 25.9, 12.0; HRMS (EI): Exact mass calcd for C_5H_7ClO $[M]^+$ 118.0182. Found 118.0182.

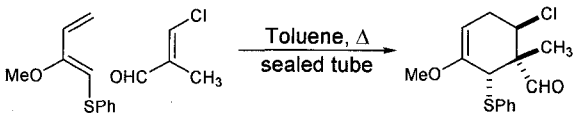


3-Chloro-2-methyl-acrylic acid methyl ester (232). Using the procedure reported by Hillis,[187] β-chloro-α-methyl acrolein (5.00g, 47.8 mmol) was dissolved in ^{t}BuOH (62 mL). To this solution, *iso*-amylene (34.0 mL, 320 mmol) and $NaClO_2$ (6.99 g, 77.3 mmol) were added. A separate addition flask was charged with $NaH_2PO_4 \cdot H_2O$ (8.58 g, 62.2 mmol) and dissolved in H_2O (50 mL). The solution of $NaH_2PO_4 \cdot H_2O$ was added dropwise to the aldehyde, resulting in a yellow solution. The mixture was stirred for 18 h at room temperature, concentrated, diluted with H_2O, and extracted with hexanes. The aqueous phase was acidified to pH 2 (5% HCl), saturated with sodium chloride, and extracted with ether. The organic layer was dried and concentrated to furnish the crude acid as a pale yellow solid (2.45 g, 44% yield). This material was found to be sufficiently pure (^1H NMR) for the esterification reaction.

β-Chloro-α-methyl acrylic acid (2.61 g, 22.2 mmol) was dissolved in CH_3OH (22.2 mL). The solution was stirred and cooled to 0 °C. Thionyl chloride (3.56 mL, 48.8 mmol) was added dropwise to the solution, while the temperature was maintained at 0 °C. After addition was complete, the reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was diluted with ether and poured onto

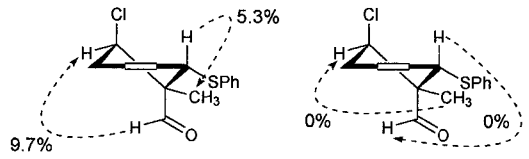
[186] 88% "activated" purchased from Acros Chemicals.
[187] Hillis, L. R.; Ronald, R. C. *J. Org. Chem.* **1985**, *50*, 470-473.

crushed ice, and the organic layer was dried and concentrated. Flash chromatography (SiO_2, 2% ether in hexanes) of the resulting oil furnished the desired product as a yellow oil (1.31 g, 44% yield). R_f = 0.50 (10% Et_2O/hexanes); IR (film) 3100, 1729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.26 (m, 1H), 3.73 (s, 3H), 1.95 (d, J = 1.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.0, 132.1, 130.9, 52.1, 13.0; HRMS (EI): Exact mass calcd for $C_5H_7ClO_2$ $[M+H]^+$ 135.0213. Found 135.0211.

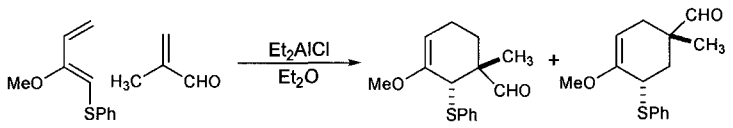


6-Chloro-3-methoxy-1-methyl-2-phenylsulfanyl-cyclohex-3-enecarbaldehyde (233). Cohen's diene[188] (82.3 mg, 428 μmol), β-chloro-α-methyl acrolein[189] (504 μL, 7.14 mmol), *tert*-butyl-4-hydroxy-5-methyl phenylsulfide (12.8 mg, 35.7 μmol), hydroquinone (3.93 mg, 35.7 μmol), Hunig's base (375 μL, 2.14 mmol), and dry toluene (1.40 mL) were added to a silanized[184] sealed tube. The contents were heated to 140 °C for 40 hours. The cooled reaction mixture was then concentrated to a residue that was purified by flash chromatography (3% ethyl acetate in hexanes) to furnish the desired *endo* adduct as a yellow oil (56.0 mg, 44%). About 10% of the regioisomeric adduct was also isolated. R_f = 0.1 (3% EtOAc/hexanes); IR (film) 3062, 1727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.44 (dd, J = 8.2, 1.8 Hz, 2H), 7.33-7.27 (m, 3H), 4.39 (dd, J = 10.5, 6.2 Hz, 1H), 4.64 (dd, J = 4.8, 2.8 Hz, 1H), 3.60 (s, 3H), 3.55 (s, 1H), 2.79 (dt, J = 17.2, 5.6 Hz, 1H), 2.42 (ddd, J = 16.8, 10.4, 1.6 Hz, 1H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 202.7, 152.6, 135.0, 132.4, 129.1, 127.9, 93.1, 91.8, 56.4, 56.4, 55.0, 52.5, 30.8, 13.6; HRMS (EI): Exact mass calcd for $C_{15}H_{17}ClO_2S$ $[M]^+$ 296.0638. Found 296.0647.

[188] Cohen, T.; Ruffner, R. J.; Shull, D. W.; Fogel, E. R. *Org. Synth.* **1980**, *59*, 202.
[189] For synthesis: see general experimentals section in the beginning of this chapter.

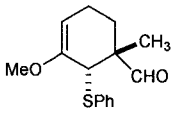


NOE measurements
-OMe group omitted for clarity

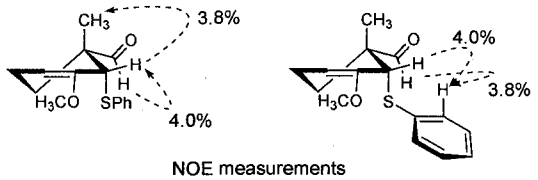


3-Methoxy-1-methyl-2-phenylsulfanyl-cyclohex-3-enecarbaldehyde (238).

The diene (24.6 mg, 128 μmol) and methacrolein (11.7 μL, 141 μmol) were dissolved in Et_2O (0.6 mL). The mixture was cooled to 0 °C, diethyl aluminum chloride (141 μL, 141 μmol, 1.0 M in hexanes) was added, and the mixture was stirred vigorously for 2 hours prior to warming to room temperature. Water (1 mL), and ether (5.0 mL) were added, and the organic layer was dried over $MgSO_4$ and concentrated. The resulting oil was purified by flash chromatography on silica gel (6% ethyl acetate in hexanes) to give the product as a colorless oil and a 1:1 mixture of regioisomeric adducts in 38% and 45% yields respectively.

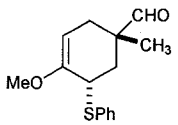


(10.0 mg, 38%); R_f = 0.1 (6% EtOAc/hexanes); IR (film) 3055, 1727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 7.49 (dd, J = 8.4, 1.6 Hz, 2H), 7.29–7.20 (m, 3H), 4.71 (dd, J = 4.8, 2.8 Hz, 1H), 3.59 (s, 3H), 3.42 (s, 1H), 2.21 (dt, J = 18.0, 5.2 Hz, 1H), 2.12–2.04 (m, 1H) 1.83–1.75 (m, 1H), 1.67 (dd, J = 14.0, 6.4 Hz, 1H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 202.6, 152.7, 136.1, 132.5, 129.0, 127.5, 95.2, 54.7, 53.7, 51.0, 23.6, 19.5, 18.7; HRMS (EI): Exact mass calcd for $C_{15}H_{18}ClO_2S$ $[M]^+$ 262.1028. Found 262.1021.

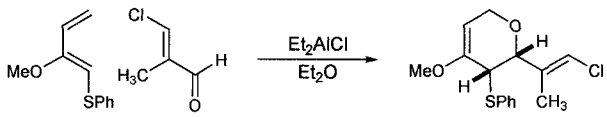


NOE measurements

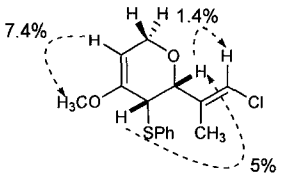
4-Methoxy-1-methyl-5-phenylsulfanyl-cyclohex-3-enecarbaldehyde (239).



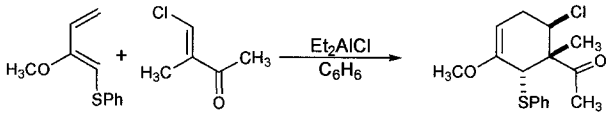
(12.0 mg, 45%); R_f = 0.1 (8% EtOAc/hexanes); IR (film) 3058, 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.30~7.21 (m, 3H), 4.77 (t, J = 4.0 Hz, 1H), 3.83 (t, J = 5.2 Hz, 1H), 3.56 (s, 3H), 2.60 (dd, J = 17.2, 4.4 Hz, 1H), 2.13 (dd, J = 14.0, 5.2 Hz, 1H), 1.94 (dd, J = 14.0, 5.6 Hz, 1H), 1.86 (dd, J = 17.2, 3.2 Hz, 1H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 203.4, 152.0, 134.7, 132.0, 129.0, 127.2, 95.1, 54.7, 44.9, 44.5, 37.0, 29.0, 21.0; HRMS (EI): Exact mass calcd for $C_{15}H_{18}ClO_2S$ $[M]^+$ 262.1028. Found 262.1026.



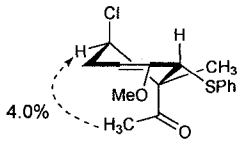
((*E*)-1-chloroprop-1-en-2-yl)-3,6-dihydro-4-methoxy-3-(phenylthio)-2H-pyran (240). The aldehyde (61.0 μL, 858 μmol) was dissolved in Et_2O (0.75 mL) and cooled to 0 °C. Diethylaluminum chloride (103 μL, 1.8 M in toluene) was added to this solution. After stirring for 15 min, the diene (90.0 mg, 468 μmol) was added. The reaction mixture was quenched by addition of water after stirring for 7 h at 0 °C. The mixture was diluted with ether and the organic layer was washed with water, dried, and concentrated. Flash Chromatography on silica gel (2% ethyl acetate in hexanes) furnished the product as a yellow oil (76.0 mg, 51% yield). IR (film) 3105, 1671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, J = 8.1, 1.9 Hz, 2H), 7.30~7.24 (m, 3H), 6.34 (m, 1H), 4.68 (dd, J = 3.4, 1.9 Hz, 1H), 4.30 (dd, J = 15.0, 3.4 Hz, 1H), 4.24 (m, 1H), 4.23 (dt, J = 14.9, 1.9 Hz, 1H), 3.60 (s, 3H), 3.58 (m, 1H), 1.42 (d, J = 0.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 152.7, 135.0, 134.5, 134.2, 128.2, 127.4, 116.7, 94.4, 79.3, 65.0, 54.6, 50.6, 14.2; HRMS (EI): Exact mass calcd for $C_{15}H_{17}ClO_2S$ $[M]^+$ 296.0638. Found 296.0641.



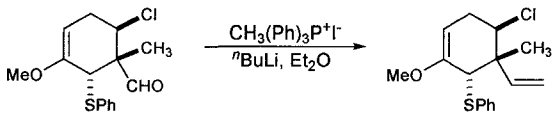
NOE measurements



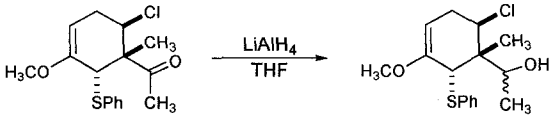
1-(6-Chloro-3-methoxy-1-methyl-2-phenylsulfanyl-cyclohex-3-enyl)-ethanone (242). Diethyl aluminum chloride (3.00 ml, 1.8 M in toluene) was added to the ketone (604 mg, 5.10 mmol) at room temperature. The resulting orange solution was cooled to 0 °C and the diene (1.23 g, 6.37 mmol) was canulated as a solution in benzene (6 ml). The solution was stirred overnight at room temperature, diluted with ether, and treated with 1M NaOH to precipitate the inorganic salts. The solution was filtered, washed with water, dried, and concentrated to an oil that was purified by flash chromatography (SiO_2, 3% ethyl acetate in hexanes with 1% triethylamine) to furnish the product as a yellow oil (520 mg, 51% yield based on a 52% conversion) (3:1 regioselectivity ^1H NMR) and recovered diene (590 mg, 30%). R_f = 0.40 (10% EtOAc/hexanes); IR (film) 3058, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 8.0, 2.0 Hz, 2H), 7.27-7.22 (m, 3H), 4.59 (dd, J = 10.4, 6.8 Hz, 1H), 4.54 (dd, J = 4.4, 2.8 Hz, 1H), 3.55 (s, 3H), 3.53 (s, 1H), 2.70 (dt, J = 17.2, 5.2 Hz, 1H), 2.34 (ddd, J = 16.8, 10.0, 2.0 Hz, 1H), 2.07 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 206.4, 193.6, 159.1, 152.3, 133.0, 128.8, 127.9, 93.0, 97.5, 74.2, 54.9, 31.9, 27.7, 16.5; HRMS (EI): Exact mass calcd for $C_{16}H_{19}ClO_2S$ $[M]^+$ 310.0794. Found 310.0803.



NOE measurements

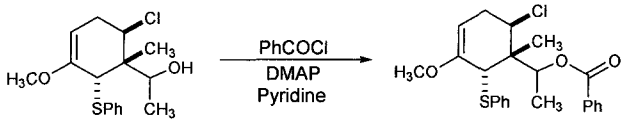


(5-Chloro-2-methoxy-6-methyl-6-vinyl-cyclohex-2-enylsulfanyl)-benzene (243). Methyltriphenylphosphonium iodide (549 mg, 1.36 mmol) was dissolved in Et_2O (7 mL) and cooled to –78 °C. *n*-Butyllithium (490 μL, 1.18 mmol) was added, followed by addition of the aldehyde (268 mg, 905 μmol) as a solution in Et_2O (2.0 mL). After stirring for 45 min at –78 °C, the reaction mixture was allowed to warm to room temperature and stirred overnight. The solution was diluted with ether, washed with water, dried, and concentrated to a residue that was purified by flash chromatography (1% ethyl acetate in hexanes) to furnish the product as a yellow oil (136 mg, 51% yield). R_f = 0.5 (2% EtOAc/hexanes); IR (film) 3076, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.30-7.22 (m, 3H), 6.23 (dd, *J* = 14.0, 10.4 Hz, 1H), 5.14 (dd, *J* = 14.4, 2.8 Hz, 2H), 4.59 (t, *J* = 7.6 Hz, 1H), 4.35 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.55 (s, 3H), 3.52 (s, 1H), 2.76 (dt, *J* = 17.6, 4.8 Hz, 1H), 2.42 (ddd, *J* = 13.2, 9.2, 0.8 Hz, 1H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 153.7, 142.4, 137.1, 131.9, 128.6, 126.9, 115.4, 92.5, 61.7, 59.5, 54.8, 45.8, 31.6, 17.1; HRMS (EI): Exact mass calcd for $C_{16}H_{19}ClOS$ $[M]^+$ 294.0845. Found 294.0846.

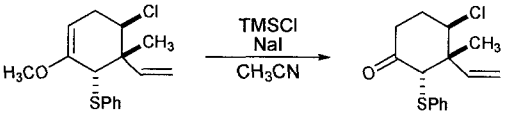


1-(6-Chloro-3-methoxy-1-methyl-2-phenylsulfanyl-cyclohex-3-enyl)-ethanol (245). The ketone (462 mg, 1.49 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. Lithium aluminum hydride (56.4 mg, 1.49 mmol) was added and the solution was allowed to warm to room temperature and stir for 3 h. The mixture was cooled to 0 °C, diluted with ether and quenched by dropwise addition of water. Treatment with 1M NaOH (10 mL) precipitated the inorganic salts. The solution was filtered and the organic layer was separated, dried, and concentrated to an oil that was purified by flash chromatography (SiO_2, 6% Et_2O/hexanes) to give the alcohol as a colorless oil and

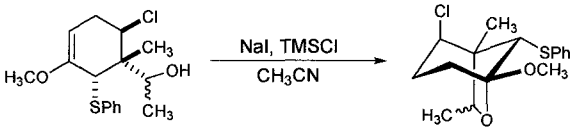
inseparable mixture (1:1) of diastereomers (370 mg, 80%). R_f = 0.10 (6% Et_2O/hexanes); IR (film) 3589, 3473 (br), 3062, 1664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59-7.54 (m, 4H), 7.35-7.27 (m, 6H), 4.64 (dd, *J* = 10.8, 6.4 Hz, 1H), 4.55 (dd, *J* = 10.0, 6.0 Hz, 1H), 4.51-4.47 (m, 2H), 4.30–4.25 (m, 1H), 4.04–3.96 (m, 1H), 3.63 (d, *J* = 11.2 Hz, 1H), 3.54 (s, 1H), 3.50 (s, 3H), 3.46 (s, 3H), 3.43 (s, 1H), 3.20 (s, 1H), 2.73-2.64 (m, 2H), 2.47-2.36 (m, 2H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.24 (d, *J* = 5.2 Hz, 3H), 1.12 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 154.2, 153.8, 135.3, 134.1, 133.1, 132.8, 128.93, 128.85, 128.0, 127.7, 93.2, 92.4, 73.1, 72.6, 62.3, 58.83, 58.80, 55.5, 54.6, 54.5, 46.4, 46.2, 32.7, 31.9, 18.0 (2C), 17.2, 13.4; HRMS (EI): Exact mass calcd for $C_{16}H_{21}ClO_2S$ $[M]^+$ 312.0951. Found 312.0952.



6-Chloro-3-methoxy-1-methyl-2-(phenylthio)cyclohex-3-enyl)ethyl benzoate (247). The alcohol **245** (56.5 mg, 181 μmol) was dissolved in pyridine (0.72 mL) and cooled to 0 °C, followed by the addition of 4-dimethylamino pyridine (16.6 mg, 136 μmol). Benzoyl chloride (63.2 μL, 544 μmol) was added dropwise at 0 °C. The solution turned turbid in 15 minutes upon warming to room temperature. This heterogeneous mixture was stirred vigorously at room temperature for 10 h, after which it was diluted with 50 mL of CH_2Cl_2. The organic layer was washed twice with water, dried and concentrated. Flash chromatography (SiO_2, 10% Et_2O/hexanes) gave the benzoate **247** as a mixture of diastereomers and colorless oil (38.0 mg, 50%). R_f = 0.10 (10% Et_2O/Hexanes); IR (film) 3066, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 7.3, 1.2 Hz, 2H), 7.57–7.51 (m, 3H), 7.44 (t, *J* = 7.9 Hz, 2H), 7.23-7.15 (m, 3H), 5.37 (q, *J* = 6.5 Hz, 1H), 4.70 (dd, *J* = 10.6, 6.6 Hz, 1H), 4.46 (m, 1H), 3.68 (s, 1H), 3.32 (s, 3H), 2.79 (ddd, *J* = 17.2, 6.5, 4.7 Hz, 1H), 3.66 (ddd, *J* = 17.3, 10.6, 3.0 Hz, 1H); 1.45 (d, *J* = 6.5 Hz, 3H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.6, 155.3, 135.6, 133.3, 132.7, 130.5, 130.0, 128.5, 128.2, 127.4, 91.7, 74.3, 58.5, 55.4, 54.3, 46.4, 32.3, 16.2, 14.8; HRMS (EI): Exact mass calcd for $C_{23}H_{26}ClO_3S$ $[M]^+$ 416.1213. Found 416.1223.



4-Chloro-3-methyl-2-phenylsulfanyl-3-vinyl-cyclohexanone (248). Using the procedure described by Cohen,[190] the enol ether (58.7 mg, 199 μmol) and NaI (29.8 mg, 199 μmol) were combined in CH_3CN (4 ml). Trimethylsilyl chloride (25.2 μL, 199 μmol) was added dropwise to this mixture at room temperature causing the solution to turn orange. After stirring for 15 minutes, the mixture was diluted with CH_2Cl_2 (5 mL) and was purified by filtration through a plug of silica gel-alumina to furnish the product as a yellow oil (32.3 mg, 58% yield). R_f = 0.1 (10% EtOAc/hexanes); IR (film) 3059, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 6.8 Hz, 2H), 7.31̃7.27 (m, 3H), 6.00 (dd, J = 17.6, 10.8 Hz, 1H), 5.33 (dd, J = 10.8, 5.6 Hz, 1H), 5.26 (dd, J = 17.6, 5.2 Hz, 1H), 4.48 (dd, J = 8.4, 4.0 Hz, 1H), 3.80 (s, 1H), 3.07̃2.99 (m 1H), 2.59̃2.52. m, 1H), 2.50̃2.43 (m, 1H), 2.26̃2.17 (m, 1H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 204.2, 140.3, 134.3, 131.8, 129.1, 127.7, 116.8, 65.7, 63.5, 49.6, 35.7, 31.0, 20.6; HRMS (EI): Exact mass calcd for $C_{15}H_{17}ClOS$ $[M]^+$ 280.0689. Found 280.0674.

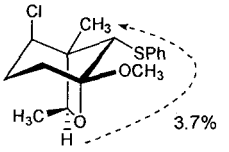


2-Chloro-5-methoxy-1,7-dimethyl-8-phenylsulfanyl-6-oxa-bicyclo[3.2.1]octane (249). The alcohol (87.0 mg, 279 μmol) and sodium iodide (46.0 mg, 307 μmol) were combined in CH_3CN (5.5 mL). Trimethylsilyl chloride (35.4 μL, 279 μmol) was added dropwise, resulting in a deep orange solution. The reaction mixture was stirred for 3 h and quenched by dropwise addition of methanol. The mixture was washed with water, dried, and concentrated to an oil that was purified by flash chromatography (SiO_2, 4% ether in

[190] Kosarych, Z.; Cohen, T. *Tetrahedron Lett.* **1980**, *21*, 3959-3962.

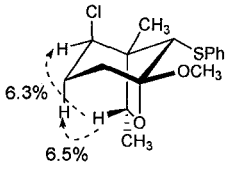
hexanes) to furnish the product as a colorless oil (60 mg, 69%) (1:1 mixture of diastereomers separable by chromatography).

Diastereomer – 1: R_f = 0.42 (20% Et_2O/hexanes); IR (film) 3062, 1579 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, J = 8.0, 1.6 Hz, 2H), 7.28 (td, J = 8.0, 1.6 Hz, 2H), 7.17 (t, J = 7.6 Hz, 1H), 4.46 (q, J = 6.8 Hz, 1H), 4.28 (d, J = 4.8 Hz, 1H), 4.15 (s, 1H), 3.45 (s, 3H), 2.48-2.38 (m, 1H), 2.22 (dd, J = 12.8, 6.4 Hz, 1H), 2.18-1.96 (m, 2H), 1.24 (d, J = 6.8 Hz, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 137.0, 129.2, 128.8, 125.8, 107.0, 80.7, 66.0, 60.3, 54.4, 51.5, 30.3, 29.7, 18.4, 12.0; HRMS (EI): Exact mass calcd for $C_{16}H_{21}ClO_2S$ $[M]^+$ 312.0945. Found: 312.0949.

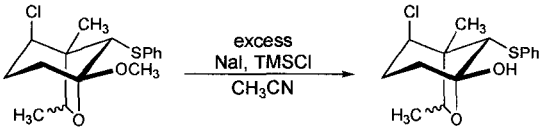


NOE measurements

Diastereomer – 2: R_f = 0.33 (20% Et_2O/hexanes); IR (film) 3058, 1583 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, J = 8.4, 1.2 Hz, 2H), 7.29 (t, J = 7.2 Hz, 2H), 7.18 (tt, J = 6.8, 1.2 Hz, 1H), 4.11 (d, J = 4.4 Hz, 1H), 4.02 (s, 1H), 3.94 (q, J = 6.8 Hz, 1H), 3.46 (s, 3H), 2.42-2.32 (m, 1H), 2.24 (dd, J = 13.2, 6.0 Hz, 1H), 2.10-1.97 (m, 2H), 1.41 (d, J = 6.8 Hz, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 137.8, 129.5, 128.8, 125.9, 107.3, 80.4, 68.5, 59.1, 54.1, 51.7, 30.4, 29.4, 20.6, 18.1; HRMS (EI): Exact mass calcd for $C_{16}H_{22}ClO_2S$ $[M+H]^+$ 313.1023. Found: 313.1033.

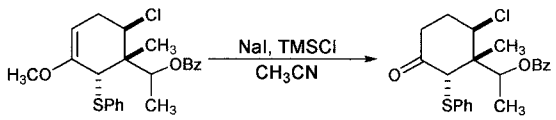


NOE measurements



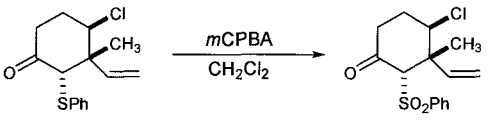
2-Chloro-1,7-dimethyl-8-phenylsulfanyl-6-oxa-Bicyclo[3.2.1]octan-5-ol (250). The ketal (27.0 mg, 86.0 μmol) and sodium iodide (129 mg, 862 μmol) were combined in

CH_3CN (1.7 mL). The solution was cooled to 0 °C and trimethylsilyl chloride (91.3 μL, 862 μmol) was added dropwise resulting in a dark yellow solution. The mixture was allowed to warm to room temperature and stir vigorously for 7 h, diluted with CH_2Cl_2 and quenched with satd aq NH_4Cl. The organic layer was washed with satd aq K_2CO_3, dried, and concentrated to an oil that was purified by flash chromatography (SiO_2, 20% ether in hexanes) to furnish the product as a colorless oil (22 mg, 87% yield). R_f = 0.10 (20% Et_2O/hexanes); IR (film) 3459, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.44 (m, 4H), 7.36–7.25 (m, 6H), 4.36 (s, 1H), 4.35 (s, 1H), 4.31 (d, J = 4.8 Hz, 1H), 4.16 (q, J = 6.7 Hz, 1H), 4.14 (dd, J = 4.7, 1.2 Hz, 1H), 3.90 (s, 1H), 3.85 (s, 1H), 3.49 (q, 1H), 2.52–2.36 (m, 2H), 2.18–2.11 (m, 4H), 2.08–2.01 (m, 2H), 1.40 (s, 3H), 1.33 (s, 3H), 1.29 (d, J = 6.7 Hz, 3H), 1.26 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 136.2, 130.7, 130.5, 129.5, 129.3, 128.5, 127.2, 127.1, 103.3, 103.2, 80.1, 78.8, 68.0, 65.6, 65.5, 63.4, 53.4, 45.9, 32.7, 32.2, 30.0, 29.1, 20.4, 18.7, 18.1, 12.0; HRMS (EI): Exact mass calcd for $C_{15}H_{19}ClO_2S$ $[M]^+$ 292.0794. Found 292.0795.

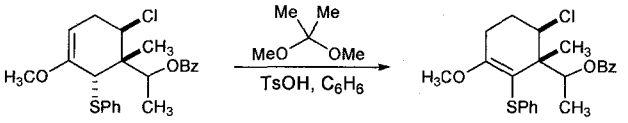


Benzoic acid 1-(6-chloro-1-methyl-3-oxo-2-phenylsulfanyl-cyclohexyl)-ethyl ester (252). The benzoate (21.4 mg, 52.0 μmol) and sodium iodide (8.54 mg, 57.2 μmol) were combined in CH_3CN (1 mL) and cooled to 0 °C prior to the addition of trimethylsilyl chloride (6.61 μL, 52.0 μmol), resulting in a deep orange colored solution. After 15 minutes of stirring, the solution was diluted with CH_2Cl_2 and quenched with satd aq NH_4Cl. The organic layer was concentrated to an oil that was purified by flash chromatography (15% ether in hexanes) to give the product as a yellow oil (38 mg, 73%). R_f = 0.10 (15% Et_2O/hexanes); IR (film) 3060, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, J = 8.5, 1.3 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.7 Hz, 4H), 7.32-7.24 (m, 3H), 5.51 (q, J = 6.6 Hz, 1H), 4.73 (dd, J = 7.7, 3.4 Hz, 1H), 3.92 (s, 1H), 3.15–3.05 (m, 1H), 2.69-2.61 (m, 2H), 2.30 (ddd, J = 20.9, 8.1, 5.4 Hz, 1H), 1.55 (d, J =

6.6 Hz, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 202.7, 165.3, 134.7, 133.8, 131.1, 129.8, 129.6, 129.2, 128.4, 127.7, 74.8, 64.2, 62.3, 49.8, 35.5, 31.0, 20.8, 15.2; HRMS (EI): Exact mass calcd for $C_{22}H_{23}ClO_3S$ $[M+H]^+$ 402.1056. Found 402.1055.

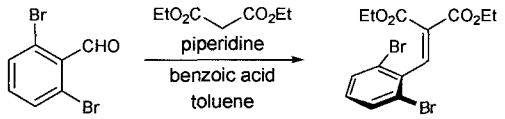


2-Benzenesulfonyl-4-chloro-3-methyl-3-vinyl-cyclohexanone (254). *m*-CPBA (34.3 mg, 199 μmol) was added to the ketone (25.4 mg, 90.4 μmol) in CH_2Cl_2 (0.9 mL) at 0 °C and the mixture was allowed to stir for 3 h. The solution was diluted with CH_2Cl_2 (5 mL) and washed with H_2O. The organic layer was dried and concentrated to an oil that was purified by flash chromatography (SiO_2, 20% ethyl acetate in hexanes) to furnish the product as a colorless oil (25.0 mg, 89% yield). R_f = 0.1 (20 % EtOAc/hexanes); IR (film) 3065, 1734, 1309, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, J = 8.8, 1.2 Hz, 2H), 7.66 (t, J = 10.8 Hz, 1H), 7.55 (t, J = 8.0 Hz, 2H), 6.24 (dd, J = 17.2, 10.8 Hz, 1H), 5.16 (d, J = 10.8 Hz, 1H), 5.14 (d, J = 17.2 Hz, 1H), 5.12 (dd, J = 8.8, 4.4 Hz, 1H), 4.01 (d, J = 1.6 Hz, 1H), 3.05-2.97 (m, 1H), 2.64-2.50 (m, 2H), 2.52-2.14 (m, 1H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 199.4, 139.8, 139.4, 134.2, 129.1, 128.6, 116.7, 82.7, 61.3, 49.4, 39.4, 31.1, 18.9; HRMS (EI): Exact mass calcd for $C_{15}H_{17}ClO_3S$ $[M]^+$ 312.0587. Found 312.0572.



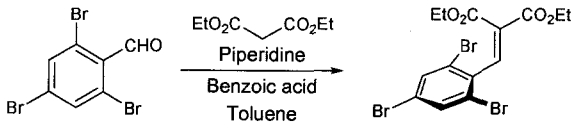
6-Chloro-3-methoxy-1-methyl-2-(phenylthio)cyclohex-2-enyl)ethyl benzoate (256). The benzoate **247** (18.0 mg, 43.0 μmol) was dissolved in 2,2-dimethoxy propane (0.6 mL) and treated with pyridinium *p*-toluene sulfonate (13.0 mg, 52 μmol). The solution was refluxed for 4 h. The solvent was removed, and the residue purified by flash chromatography (SiO_2, 20% ether in hexanes) to give the vinyl sulfide as a colorless oil

(18.0 mg, 100%). R_f = 0.10 (20% Et_2O/Hexanes); IR (film) 3058, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.3 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.28-7.17 (m, 4H), 7.06 (t, *J* = 7.3 Hz, 1H), 5.04 (q, *J* = 6.3 Hz, 1H), 4.52 (d, *J* = 2.4 Hz, 1H), 3.54 (s, 3H), 2.83 (m, 1H), 2.69-2.62 (m, 1H), 2.50 (dd, *J* = 17.5, 6.6 Hz, 1H), 2.23-2.19 (m, 1H), 1.45 (s, 3H), 1.44 (d, *J* = 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.6, 161.0, 139.1, 133.4, 130.5, 129.8, 128.7 (2C), 126.0, 124.6, 106.5, 76.9, 63.8, 55.7, 49.0, 26.9, 22.6, 21.4, 19.5, 16.2; HRMS (EI): Exact mass calcd for $C_{23}H_{25}ClO_3S$ $[M]^+$ 416.1198. Found 416.1213.

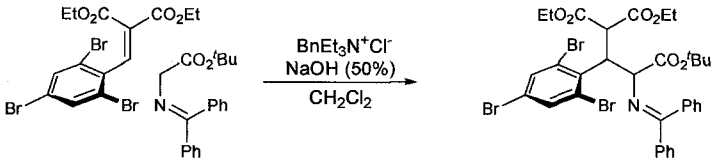


2-(2,6-Dibromo-benzylidene)-malonic acid diethyl ester (266).[191] 2,4-Dibromobenzaldehyde (2.00 g, 7.58 mmol), diethyl malonate (1.15 mL, 7.58 mmol), piperidine (225 μL, 2.27 mmol) and benzoic acid (122 mg, 2.27 mmol) were dissolved in toluene (8 mL). 4Å MS were added and the solution was refluxed overnight. After cooling to room temperature, the mixture was diluted with CH_2Cl_2, was filtered over Celite, and concentrated to a brown oil. Flash chromatography (SiO_2, 15% ether in hexanes) yielded the product as a yellow oil (1.4 g, 44%). R_f = 0.50 (20% Et_2O/hexanes); IR (film) 2972, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.06 (t, *J* = 8.4 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.3 Hz, 3H), 1.00 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 163.5, 163.4, 144.1, 136.2, 131.4, 130.4, 122.4, 61.9, 61.2, 14.1, 13.6; HRMS (EI): Exact mass calcd for $C_{14}H_{14}{}^{79}Br^{81}BrO_4$ $[M+Na]^+$ 428.9136. Found 428.9134.

[191] Gu, J. X.; Holland, H. L. *Synth. Commun.* **1998**, *28*, 3305-3315.

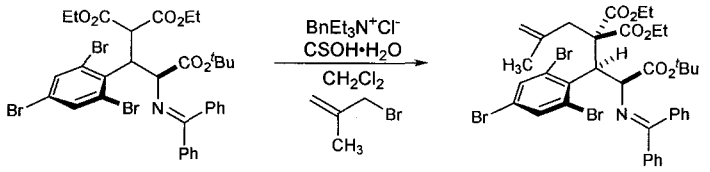


2-(2,4,6-Tribromo-benzylidene)-malonic acid diethyl ester (268). 2,4,6-Tri-bromo benzaldehyde (500 mg, 1.46 mmol) was dissolved in toluene (2.0 mL) and diethyl malonate (240 mg, 1.46 mmol), piperidine (43.4 μL, 438 μmol), and benzoic acid (53.5 mg, 438 μmol) were added. 4Å MS were added and the reaction mixture was refluxed overnight. After cooling the solution to room temperature, it was diluted with CH_2Cl_2, filtered over Celite and concentrated to give a brown oil. Flash chromatography (SiO_2, 5% ether in hexanes) gave the corresponding alkylidene malonate as a colorless oil (171 mg, 32%). R_f = 0.50 (20% Et_2O/hexanes); IR (film) 3010, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ7.73 (s, 2H), 7.59 (s, 1H), 4.36 (q, J = 7.1 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 163.3, 163.2, 143.2, 143.1, 135.3, 134.0, 133.9, 131.7, 122.7 (2C), 62.0, 61.4, 14.1, 13.7; HRMS (EI): Exact mass calcd for $C_{14}H_{14}{}^{79}Br_2{}^{81}BrO_4$ $[M+H]^+$ 484.8422. Found 484.8410.



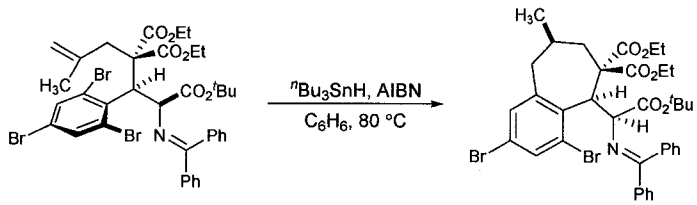
2-(Benzhydrylidene-amino)-4-ethoxycarbonyl-3-(2,4,6-tribromo-phenyl)-pentanedioic acid 1-*tert*-butyl ester 5-ethyl ester (269). Following the general procedure G, alkylidine malonate (560 mg, 1.16 mmol), Schiff base (341 mg, 1.16 mmol), and benzyltriethylammonium chloride (52.5 mg, 231 μmol) were dissolved in CH_2Cl_2 (3.4 mL). 50% NaOH (920 μL) was added and the mixture was stirred vigorously for 5 h. The reaction mixture was diluted with CH_2Cl_2, washed with H_2O, and the separated organic layer was filtered, dried, and concentrated to an oil. Flash chromatography (SiO_2, 15% ether in hexanes) furnished the product as a colorless oil (475 mg, 53%). The ratio of diastereomers = 4:1 (^1H NMR). R_f = 0.17 (20%

Et_2O/hexanes); IR (film) 3063, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74–7.70 (m, 3H), 7.56 (d, J = 2.0 Hz, 1H), 7.50–7.42 (m, 3H), 7.40 (d, J = 7.2 Hz, 1H), 7.34 (t, J = 7.6 Hz, 2H), 7.28–7.25 (m, 2H), 5.50 (t, J = 10.4 Hz, 1H), 4.98 (d, J = 10.0 Hz, 1H), 4.32 (d, J = 10.8 Hz, 1H), 4.10–4.04 (m, 1H), 3.95–3.82 (m, 3H), 1.20 (s, 9H), 1.01 (q, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.8, 168.8, 167.4, 167.1, 138.9, 137.2, 136.5, 135.9, 134.8, 130.7, 129.1, 128.6, 128.5, 127.9, 124.1, 121.2, 81.3, 66.3, 61.4, 54.1, 47.8, 29.7, 27.6, 13.6; HRMS (EI): Exact mass calcd for $C_{33}H_{35}{}^{79}Br_2{}^{81}BrNO_6$ $[M+H]^+$ 779.9949. Found 779.9899.

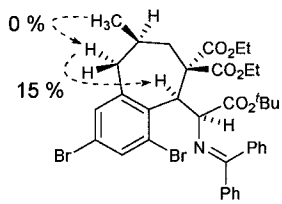


4-(Benzhydrylidene-amino)-2-ethoxycarbonyl-2-(2-methyl-allyl)-3-(2,4,6-tribromo-phenyl)-pentanedioic acid 5-*tert*-butyl ester 1-ethyl ester (271). The Schiff base (183 mg, 235 μmol) was dissolved in CH_2Cl_2 (0.7 mL) and benzyltriethyl ammonium chloride (10.7 mg, 47.0 μmol) and $CsOH•H_2O$ (395 mg, 2.35 mmol) were added. The resulting reddish solution was treated with methallyl bromide (119 μL, 1.18 mmol). The solution was stirred overnight prior to dilution with CH_2Cl_2 and a water wash. The organic layer was dried and concentrated, and the crude oil was purified by flash chromatography (SiO_2, 15% ether in hexanes with 1% Et_3N) to furnish the desired product as a colorless oil (100 mg, 51%). The ratio of diastereomers was > 20:1 (^1H NMR); R_f = 0.10 (15% Et_2O/hexanes); IR (film) 3062, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 2.0 Hz, 1H), 7.67-7.65 (m, 3H), 7.43-7.28 (m, 8H), 5.90 (d, J = 11.3 Hz, 1H), 5.68 (d, J = 11.3 Hz, 1H), 4.79 (d, J = 1.3 Hz, 1H), 4.73 (s, 1H), 4.28-4.09 (m, 3H), 4.02-3.94 (m, 1H), 2.56 (d, J = 13.6 Hz, 1H), 2.40 (d, J = 13.6 Hz, 1H), 1.69 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H), 0.91 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 170.1, 170.0, 169.6, 169.5, 141.8, 140.3, 137.0, 136.5, 135.1, 132.3, 129.9, 129.1, 128.3, 128.2, 127.7, 127.5, 125.3, 121.6, 116.0, 80.5, 64.2, 61.1, 61.0, 59.8, 56.1, 42.6, 27.1, 24.2, 13.7,

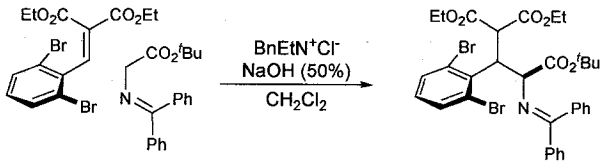
13.6; HRMS (EI): Exact mass calcd for $C_{37}H_{41}{}^{79}Br_2{}^{81}BrNO_6$ $[M+H]^+$ 834.0463. Found 834.0453.



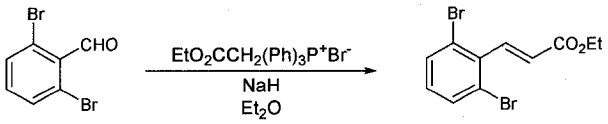
5-[(Benzhydrylidene-amino)-*tert*-butoxycarbonyl-methyl]-2,4-dibromo-8-methyl-5,7,8,9-tetrahydro-benzocycloheptene-6,6-dicarboxylic acid diethyl ester (273). To a refluxing (85 °C) benzene (13.4 mL) solution of the ketimine (112 mg, 134 μmol) and ^{n}Bu$_3$SnH (19.9 μL, 148 μmol) was added AIBN (21.2 mg, 160 μmol) dissolved separately in benzene (1 mL) via a syringe pump over 4h. The solution was cooled to room temperature and concentrated. Flash chromatography (SiO_2, 12% ether in hexanes) furnished the product as a colorless oil (61.0 mg, 60%). Ratio of diastereomers was > 20:1 (^{1}H NMR). R_f = 0.10 (15% Et_2O/hexanes); IR (film) 3065, 1748, 1738, 1733, 1717 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 6.8 Hz, 2H), 7.64 (d, J = 2.0 Hz, 1H), 7.45 (dd, J = 5.2, 1.6 Hz, 2H), 7.38-7.36 (m, 2H), 7.30 (t, J = 8.0 Hz, 2H), 7.20 (dd, J = 6.8, 3.2 Hz, 2H), 7.00 (d, J = 2.0 Hz, 1H), 5.56 (d, J = 9.2 Hz, 1H), 4.69 (d, J = 9.6 Hz, 1H), 4.08-3.92 (m, 3H), 3.87–3.81 (m, 1H), 3.07 (dd, J = 14.8, 1.6 Hz, 1H), 2.39–2.23 (m, 4H), 1.17–1.11 (m, 6H), 1.00 (s, 9H), 0.88 (d, J = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.1, 171.0, 170.5, 168.4, 143.3, 138.9, 137.7, 136.5, 133.6, 133.1, 131.5, 130.5, 129.0, 128.6, 128.3, 127.7, 127.4, 120.1, 80.9, 64.6, 61.6, 61.1, 56.4, 50.9, 41.9, 36.5, 28.8, 27.2, 27.1, 17.8, 13.7; HRMS (EI): Exact mass calcd for $C_{37}H_{41}{}^{79}Br^{81}BrNO_6$ $[M+Na]^+$ 778.1178. Found 778.1171.



NOE measurements

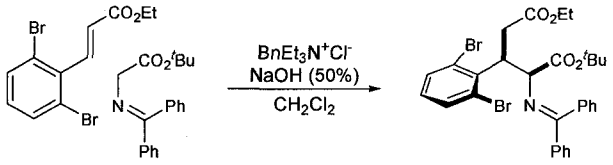


2-(Benzhydrylidene-amino)-3-(2,6-dibromo-phenyl)-4-ethoxycarbonyl-pentanedioic acid 1-*tert*-butyl ester 5-ethyl ester (276). Following the general procedure G, the alkylidene malonate (206 mg, 508 μmol), benzyltriethylammonium chloride (23.1 mg, 102 μmol) and Schiff base (150 mg, 508 μmol) were dissolved in CH_2Cl_2 (1.5 mL). 50% NaOH (410 μL, 10.2 mmol) was added and the solution was stirred vigorously overnight. The mixture was diluted (CH_2Cl_2) and washed with water. The organic layer was separated, dried, and concentrated to an oil that was purified by flash chromatography (SiO_2, 15% ether in hexanes with 1% Et_3N) to give the product as a colorless oil (176 mg, 49%). Ratio of diastereomers was > 20:1 (^1H NMR). R_f = 0.10 (20% Et_2O/hexanes); IR (film) 3059, 1760, 1738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, J = 7.3, 1.2 Hz, 2H), 7.55 (dd, J = 8.1, 0.9 Hz, 1H), 7.47–7.36 (m, 6H), 7.32 (t, J = 7.8 Hz, 1H), 7.26 (dd, J = 7.9, 2.1 Hz, 2H) 6.85 (t, J = 7.9 Hz, 1H); 5.54 (t, J = 10.2 Hz, 1H), 5.05 (d, J = 9.9 Hz, 1H), 4.33 (d, J = 10.6 Hz, 1H), 4.09–4.01 (m, 1H); 3.88–3.77 (m, 3H); 1.13 (s, 9H), 0.99 (t, J = 7.1 Hz, 3H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.6, 168.9, 167.5, 167.2, 138.9, 137.7, 136.5, 133.7, 132.6, 130.6, 130.3, 129.2, 129.1, 128.5, 128.4, 128.2, 128.2, 127.9, 127.8, 124.0, 80.9, 66.4, 61.6, 61.3, 54.2, 48.2, 27.9, 27.5, 13.6, 13.5; HRMS (EI): Exact mass calcd for $C_{33}H_{35}{}^{79}Br_2{}^{81}BrNO_6$ $[M+Na]^+$ 724.0708. Found 724.0699.



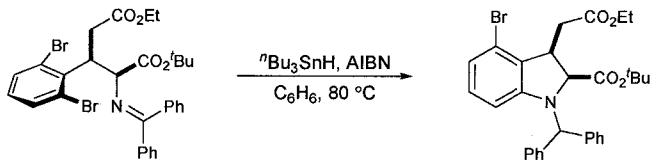
(*E*)-3-(2,6-Dibromophenyl)-acrylic acid ethyl ester (278). (Carbethoxymethyl)triphenylphosphonium bromide (11.2 g, 31.4 mmol) was dissolved in Et_2O (10.5 mL) and treated with the aldehyde (6.9 g, 26.2 mmol) at 0 °C. NaH (820 mg,

34.0 mmol) was added and the solution was stirred and allowed to warm to room temperature. After stirring overnight, the solution was refluxed for 4 h, cooled to rt, diluted with 200 mL of Et_2O:hexanes (1:1) and filtered over Celite. The filtrate was concentrated to give a crude oil that was purified by flash chromatography (SiO_2, 5% ether in hexanes) to give the product as a colorless oil (5.47 g, 79%). Ratio of *E*:*Z* isomer was >20:1 (^{1}H NMR). R_f = 0.10 (5% Et_2O/hexanes); IR (film) 2981, 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 16.3 Hz, 1H), 7.56 (d, *J* = 16.3 Hz, 1H), 7.01 (t, *J* = 8.1 Hz, 1H), 7.01 (t, *J* = 8.1 Hz, 1H), 6.39 (d, *J* = 16.3 Hz, 1H), 4.29 (q, *J* = 7.3 Hz, 2H), 1.35 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 165.8, 142.2, 142.1, 135.6, 132.5, 132.4, 130.3, 126.9, 123.9, 60.8, 14.1; HRMS (EI): Exact mass calcd for $C_{11}H_{11}{}^{79}Br_2{}^{81}BrO_2$ $[M+H]^+$ 334.9105. Found 334.9108.



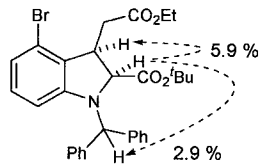
2-(Benzhydrylidene-amino)-3-(2,6-dibromophenyl)-pentanedioic acid 1-*tert*-butyl ester 5-ethyl ester (281). Following the general procedure G, the enoate (5.47 g, 16.5 mmol), Schiff base (4.86 g, 16.5 mmol), and benzyltriethylammonium chloride (748 mg, 3.29 mmol) were dissolved in CH_2Cl_2 (48 mL) and treated with 50% NaOH (13.2 mL, 330 mmol). The mixture was stirred vigorously overnight, diluted with CH_2Cl_2, and washed with water. The separated organic layer was dried and concentrated to an oil that was purified by flash chromatography (SiO_2, 10% ether in hexanes) to give the product as a colorless oil (8.80 g, 75%). Ratio of diastereomers was >20:1 (^{1}H NMR). R_f = 0.10 (10% Et_2O/hexanes); IR (film) 3055, 1735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 7.1, 1.3 Hz, 2H), 7.56 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.52–7.29 (m, 8H), 7.23–7.20 (m, 2H), 6.88 (t, *J* = 7.9 Hz, 1H), 5.08–5.03 (m, 2H), 4.07–3.90 (m, 2H), 2.98 (ddd, *J* = 15.4, 5.2, 3.8 Hz, 1H), 2.85 (ddd, *J* = 15.4, 3.8, 1.7 Hz, 1H), 1.12 (s, 9H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.7, 169.5, 139.0, 138.5, 136.8, 134.0, 132.6, 130.5, 129.3, 129.0, 128.9, 128.6, 128.4, 128.2, 127.9 (2C), 123.5, 80.6, 66.2, 60.4, 45.9,

35.1, 27.9, 27.4, 13.9; HRMS (EI): Exact mass calcd for $C_{30}H_{32}{}^{79}Br^{81}BrNO_4$ $[M+H]^+$ 630.0677. Found 630.0665.

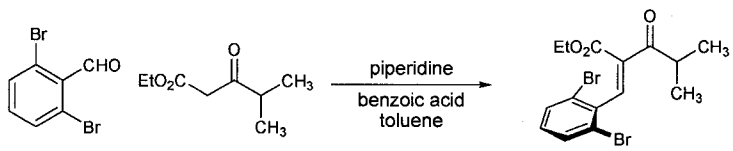


1-Benzhydryl-4-bromo-3-ethoxycarbonylmethyl-2,3-dihydro-1H-indole-2-carboxylic acid *tert*-butyl ester (282). Following the general procedure E, ketimine (4.15 g, 6.59 mmol) was dissolved in benzene (650 mL) and treated with $^nBu_3SnH$ (1.95 mL, 7.25 mmol). AIBN (950 mg, 5.78 mmol) was dissolved separately in benzene (25 mL) and added dropwise over 4 h via a syringe pump to the refluxing ketimine solution. The solution was refluxed for a further 1 h before cooling to rt. The solvent was removed *in vacuo*, and the oil was dissolved in Et_2O and treated with satd aq KF for 4 h. The resulting white precipitate was filtered over Celite and the filtrate was washed with water. The separated organic layer was dried and concentrated and the resulting oil was purified by flash chromatography (SiO_2, 4% ether in hexanes) to give the indoline as a white crystalline solid (1.50 g, 40%). Ratio of diastereomers was > 20:1 (^1H NMR). mp 146–148 °C; R_f = 0.10 (10% Et_2O/hexanes); IR (film) 3065, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.24 (m, 10H), 6.77 (d, J = 8.1 Hz, 1H), 6.70 (t, J = 7.9 Hz, 1H), 5.96 (d, J = 7.8 Hz, 1H), 5.53 (s, 1H), 4.36 (d, J = 8.8 Hz, 1H), 4.25–4.12 (m, 2H), 4.11–4.06 (m, 1H), 3.37 (dd, J = 18.1, 3.1 Hz, 1H), 2.77 (dd, J = 18.1, 10.5 Hz, 1H), 1.35 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.6, 169.8, 152.1, 140.7, 139.0, 129.22, 129.19, 129.0, 128.6, 128.5, 127.8, 127.6, 127.2, 122.0, 118.3, 108.7, 82.1, 68.7, 66.3, 60.5, 41.1, 33.5, 27.7, 14.0; HRMS (EI): Exact mass calcd for $C_{30}H_{32}{}^{79}BrNO_4$ $[M]^+$ 549.1515. Found 549.1508.

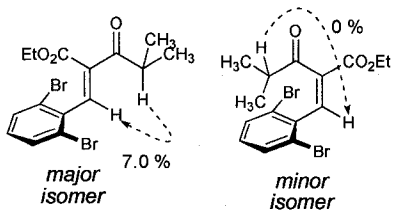
Anal. Calcd for $C_{30}H_{32}N$: C, 65.46; H, 5.86; N, 2.54. Found: C, 65.22; H, 5.95; N, 2.46.



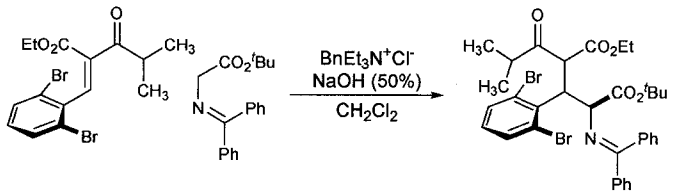
NOE measurements



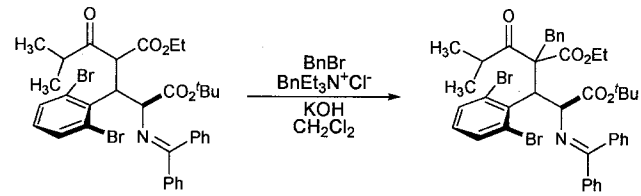
4-(2,6-Dibromo-benzylidene)-2-methyl-octane-3,5-dione (286). 2,4-Dibromo benzaldehyde (500 mg, 1.89 mmol), ethyl isobutyrylacetate (152.5 μL, 1.46 mmol), piperidine (56.1 μL, 567 μmol), and benzoic acid (69.0 mg, 567 μmol) were dissolved in toluene (1.0 mL). 4Å MS were added and the reaction mixture was refluxed for 20 h. After cooling the solution to room temperature, it was diluted with CH_2Cl_2, filtered over Celite and concentrated to a brown oil. Flash chromatography (SiO_2, 4% ether in hexanes) furnished the product as a yellow oil (171 mg, 32%). ^1H NMR showed a 3:1 mixture of *Z* and *E* stereoisomers. R_f = 0.54 (20% Et_2O/hexanes); IR (film) 3076, 2976, 1730, 1701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ7.61 (s, 1H), 7.56 (d, *J* = 8.1 Hz, 4H), 7.41 (s, 1H), 7.08 (t, *J* = 8.2 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.28 (sept, *J* = 6.6 Hz, 1H), 2.66 (sept, *J* = 7.0 Hz, 1H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.24 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 204.4, 202.4, 164.3 (2C), 142.0, 141.9, 141.05, 141.00, 137.9, 137.6, 136.7, 135.9, 131.6 (2C), 131.3 (2C), 130.6, 130.2, 122.5, 122.3, 61.7, 61.1, 40.4, 37.9, 18.2 (2C), 17.9 (2C), 14.0, 13.4; HRMS (EI): Exact mass calcd for $C_{15}H_{16}{}^{79}Br^{81}BrO_3$ $[M+H]^+$ 404.9524. Found 404.9519.



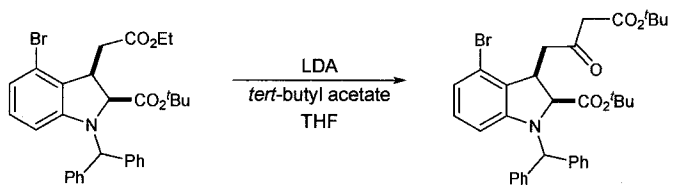
NOE measurements



2-(Benzhydrylidene-amino)-3-(2,6-dibromo-phenyl)-4-isobutyryl-pentanedioic acid 1-*tert*-butyl ester 5-ethyl ester (287). Following the general procedure G, the alkylidene malonate (1.53 g, 3.79 mmol), benzyltriethylammonium chloride (99.0 mg, 438 μmol) and Schiff base (646 mg, 2.19 mmol) were dissolved in CH_2Cl_2 (11 mL). Solid NaOH (876 mg, 21.9 mmol) was added and the solution was stirred vigorously for 4 h at room temperature. Dilution with CH_2Cl_2 was followed by an aqueous wash. The separated organic layer was dried and concentrated to an oil that was purified by flash chromatography (SiO_2, 15% ether in hexanes with 1% Et_3N) to a colorless gum (1.09 g, 71%). Characterized as an inseparable 1:1 mixture of diastereomers: R_f = 0.10 (15% Et_2O/hexanes); IR (film) 3060, 1733, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 7.4, 1.2 Hz, 2H), 7.61–7.53 (m, 5H), 7.50–7.27 (m, 15H), 7.19–7.16 (m, 2H), 6.90–6.80 (m, 2H), 5.70 (t, J = 9.7 Hz, 1H), 5.54 (t, J = 10.0 Hz, 1H), 5.06 (d, J = 9.9 Hz, 1H), 5.00 (d, J = 9.4 Hz, 1H), 4.76 (d, J = 9.9 Hz, 1H), 4.69 (d, J = 10.6 Hz, 1H), 4.00 (dq, J = 10.9, 7.1, 1H), 3.82–3.69 (m, 3H), 2.84 (sep, J = 6.7 Hz, 1H), 2.73 (sep, J = 7.0 Hz, 1H), 1.11 (s, 9H), 1.10 (s, 9H), 0.99 (t, J = 7.3 Hz, 3H), 0.96 (d, J = 6.8 Hz, 6H), 0.91 (t, J = 7.1 Hz, 3H), 0.78 (d, J = 6.7 Hz, 3H), 0.77 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 207.3, 204.0, 171.1, 171.3, 169.0, 168.8, 167.6, 167.6, 167.5, 139.1, 139.0, 138.5, 137.7, 136.6, 133.7 (2C), 133.0, 132.6, 130.6, 130.5 (2C), 129.2, 129.1 (2C), 128.5 (2C), 128.3 (2C), 127.8 (2C), 127.6, 124.2, 123.4, 80.8 (2C), 66.4, 66.0, 61.5, 61.0, 60.8, 59.3, 48.5, 48.1, 41.2, 40.0, 27.4, 18.8, 18.3, 18.2, 13.6, 13.5; HRMS (EI): Exact mass calcd for $C_{34}H_{37}{}^{79}Br_2{}^{81}BrNO_5$ $[M]^+$ 699.1018. Found 699.1027.

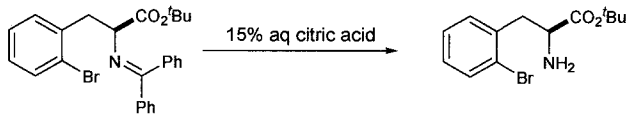


4-(Benzhydrylidene-amino)-2-benzyl-3-(2,6-dibromo-phenyl)-2-isobutyryl-pentanedioic acid 5-*tert*-butyl ester 1-ethyl ester (288). The Schiff base **287** (25.0 mg, 36.0 μmol), benzyltriethyl ammonium chloride (8.20 mg, 36.0 μmol), and solid KOH (20.2 mg, 360 μmol) were dissolved in CH_2Cl_2 (0.2 mL). Resulting red solution was treated with benzyl bromide (42.8 μL, 360 μmol) and stirred for 36 h. The mixture was diluted with CH_2Cl_2, washed with water, and the organic layer was dried and concentrated. The resulting oil was purified by flash chromatography (SiO_2, 15% ether in hexanes with 1% Et_3N) to a pale yellow solid (18.0 mg, 50%, dr = 5:1 by ^1H NMR; mp 65–71 °C; R_f = 0.10 (10% Et_2O/hexanes); IR (film) 3059, 1733, 1729, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 7.0, 1.5 Hz, 2H), 7.61 (dd, *J* = 7.9, 1.2 Hz, 2H), 7.54 (d, *J* = 8.1, 1.2 Hz, 1H), 7.48–7.36 (m, 8H), 7.14–7.11 (m, 5H), 6.90 (t, *J* = 7.9 Hz, 1H), 5.86 (d, *J* = 11.0 Hz, 1H), 5.56 (d, *J* = 11.0 Hz, 1H), 4.00 (d, *J* = 13.0 Hz, 1H), 3.82 (d, *J* = 13.0 Hz, 1H), 3.74 (dq, *J* = 10.9, 7.3 Hz, 1H), 3.58–3.49 (m, 2H), 2.88 (sept, *J* = 6.7 Hz, 1H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.99 (s, 9H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.81 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 210.8, 170.7, 170.4, 139.4, 138.4, 138.3, 136.7, 135.4, 134.7, 133.2, 130.9, 130.2, 129.3, 129.2, 128.5, 128.1, 128.0, 127.8, 127.6, 127.4, 126.2, 125.8, 80.8, 68.8, 65.5, 60.6, 54.2, 39.6, 27.1, 21.0, 20.4, 13.2; HRMS (EI): Exact mass calcd for $C_{41}H_{44}{}^{79}Br^{81}BrNO_5$ $[M+H]^+$ 790.1566. Found 790.1564.



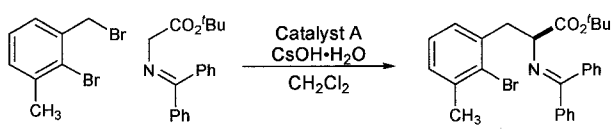
***tert*-Butyl 3-(3-(*tert*-butoxycarbonyl)-2-oxopropyl)-1-benzhydryl-4-bromoindoline-2-carboxylate (292).** Diisopropylamine (3.08 mL, 22.0 mmol) was dissolved in THF (10 mL) and cooled to –78 °C. ^{n}BuLi (9.2 mL, 2.5 M in hexanes, 23.0 mmol) was added dropwise and the solution was stirred at –78 °C for 30 min. *tert*-Butyl acetate (2.82 mL, 20.9 mmol) was added dropwise and the solution allowed to stir at –78 °C for 30 min. The indoline (1.21g, 2.09 mmol) in THF was canulated slowly into the enolate solution at –78 °C. The reaction mixture was allowed to warm to room temperature overnight, and diluted with Et_2O and water. The organic layer was dried and concentrated to an oil that was purified by flash chromatography (SiO_2, 5-10% ether in hexanes) to give the keto-ester **292** as a colorless oil (1.23 g, 95% yield).[192] R_f = 0.10 (10% Et_2O/hexanes); IR (film) 3057, 1739, 1728, 1712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.27 (m, 10H), 6.75 (d, J = 8.1 Hz, 1H), 6.68 (t, J = 8.1 Hz, 1H), 5.95 (d, J = 7.9 Hz, 1H), 5.47 (s, 1H), 4.31 (d, J = 8.6 Hz, 1H), 4.19–4.14 (m, 1H), 3.47 (d, J = 15.4 Hz, 1H), 3.33 (d, J = 15.4 Hz, 1H), 3.31 (dd, J = 19.0, 9.7 Hz, 1H), 3.31 (dd, J = 19.0, 2.8 Hz, 1H), 1.49 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 200.8, 170.4, 166.1, 151.3, 140.0, 138.4, 130.0, 129.12, 129.05, 128.6, 128.5, 128.3, 127.8, 127.3, 121.7, 118.3, 109.0, 82.1, 81.8, 68.2, 65.9, 50.7, 42.0, 39.4, 27.92, 27.88; HRMS (EI): Exact mass calcd for $C_{34}H_{38}{}^{79}BrNO_4Na$ $[M+Na]^+$ 642.1831. Found 642.1826.

[192] Product obtained from chromatography contained ^{t}butyl acetoacetate (b.p. 85 °C/20 mmHg) as an impurity which was removed by heating under vacuum (45 °C/2 mmHg).



(*S*)-2-Amino-3-(2-bromophenyl)-propionic acid *tert*-butyl ester ((*S*)-339).[193] Imine **(*S*)-178a** (599 mg, 1.29 mmol) was dissolved in THF (7.7 mL) and treated with aq 15% citric acid (3.9 mL). The mixture was stirred vigorously for 5 h at room temperature, diluted with water (10 mL) and extracted twice with ether. The pH of the aqueous layer was adjusted from 2 to 10 by dropwise addition of satd K_2CO_3 solution. The aqueous layer was thoroughly extracted with ethyl acetate, the combined organic layers were dried and concentrated, and the residue was purified by silica gel chromatography (2% methanol in dichloromethane) to furnish the amine as a colorless oil (348 mg, 90%). R_f= 0.67 (10% MeOH/hexanes); IR (film) 3382, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.3 Hz, 1H), 7.26–7.21 (m, 2H), 7.11–7.07 (m, 1H), 3.73 (t, J = 7.3 Hz, 1H), 3.20 (dd, J = 13.6, 5.8 Hz, 1H), 2.87 (dd, J = 13.6, 8.3 Hz, 1H), 1.53 (br, s, 2H) 1.41 (s, 9H); ^{13}C NMR

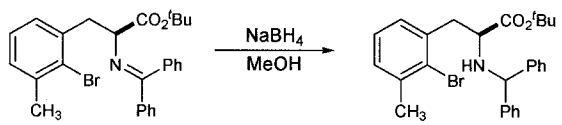
(100 MHz, $CDCl_3$) ppm 174.1, 137.4, 132.8, 131.6, 128.2, 127.2, 124.8, 81.1, 54.8, 41.7, 27.9; HRMS (EI): Exact mass calcd for $C_{13}H_{19}BrNO_2$ $[M+H]^+$ 300.0599. Found 300.0647. HPLC (Chiralcel AD, 5% ^{i}PrOH/hexanes, 1 mL/min): t_r (*R*) = 9.2 m, t_r (*S*) = 10.3 m. 95% ee: $[\alpha]_D^{21}$ =+29.3 (*c* 1.0, $CHCl_3$).



(*S*)-2-(Benzhydrylideneamino)-1-(2-bromo-3-methylphenyl)propionic acid *tert*-butyl ester (((*S*)-341a). Following the general procedure D, 2-bromo-3-bromomethyltoluene[194] (750 mg, 2.84 mmol), glycinyl imine (168 mg, 0.568 mmol), and $CsOH•H_2O$ (847 mg,

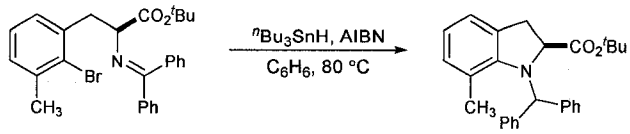
[193] Lygo, B.; Wainwright, P.G. *Tetrahedron. Lett.* **1997**, *38*, 8595.
[194] 2-Bromo-*m*-xylene was converted to the corresponding benzyl bromide: Rebek, J.; Costello, T.; Wattley, R. *J. Am. Chem. Soc. 107*, **1985**, 7487.

5.68 mmol) were stirred in CH_2Cl_2 for 20 h in the presence of the cinchonidine derived catalyst **181** (10 mol %) while maintaining a temperature ≤–78 °C. Work-up according to the general procedure provided the desired product as a white solid (233 mg, 86%). mp = 92–94 °C; R_f= 0.38 (10% EtOAc/hexanes); IR (film) 3056, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.40–7.25 (m, 6H), 7.09–7.04 (m, 3H), 6.55 (br d, *J* = 5.0 Hz, 2H), 4.42 (dd, *J* = 9.8, 3.9 Hz, 1H), 3.53 (dd, *J* = 13.3, 3.9 Hz, 1H), 3.24 (dd, *J* = 13.4, 9.9 Hz, 1H), 2.35 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.8, 170.5, 139.5, 138.2, 137.8, 136.2, 130.2, 130.0, 128.8, 128.7 (2C), 128.1, 127.9 (2C), 127.6 (2C), 126.3, 81.1, 64.9, 40.2, 28.1, 23.9; HRMS (EI): Exact mass calcd for $C_{27}H_{29}BrNO_2$ $[M+H]^+$ 478.1382. Found 478.1325.



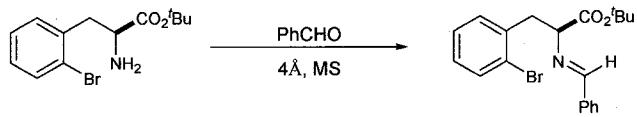
(*S*)-2-(Benzhydrylamino)-3-(2-bromo-3-methylphenyl)propionic acid tert-butyl ester (((*S*)-342). Following general procedure F, addition of $NaBH_4$ (3.77 mg, 99.5 μmol) to imine (9.50 mg, 19.9 μmol) in MeOH (1.0 mL) furnished, after flash chromatography (SiO_2, 2% ethyl acetate in hexanes), the amine as a white solid (8 mg, 83%). mp 116–118 °C; R_f=0.43 (10% EtOAc/hexanes); IR (film) 3323, 1723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 8.2, 1.5 Hz, 2H), 7.28 (td, *J* = 6.3, 1.8 Hz, 2H), 7.22 (t, *J* = 1.3 Hz, 1H), 7.20–7.13, (m, 7H), 7.09-7.07 (m, 1H), 4.81 (s, 1H), 3.50 (t, *J* = 7.7 Hz, 1H), 3.13 (dd, *J* = 13.4, 6.9 Hz, 1H), 3.06 (dd, *J* = 13.4, 5.0 Hz, 1H), 2.43 (s, 3H), 2.21 (br s, 1H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 174.1, 138.4, 138.0, 129.6, 128.9, 128.4, 128.2, 127.7, 127.4, 127.3, 127.1, 126.3, 117.9, 112.8, 95.4, 81.1, 65.4, 59.4, 41.0, 28.0, 24.0; HRMS (EI): Exact mass calcd for $C_{27}H_{31}BrNO_2$ $[M+H]^+$ 480.1538. Found 480.1560.

HPLC (Chiralcel OD, 2% ^{i}PrOH/hexanes, 1 mL/min): t_r (*S*) = 4.9 m, t_r (*R*) 5.6 m. (*S*)-88% ee $[\alpha]_D^{21}$ =–35.2 (*c* 0.8, $CHCl_3$). (*R*)- 86% ee, $[\alpha]_D^{24}$ = +33.2 (*c* 0.5, $CHCl_3$).



1-Benzhydryl-7-methyl-2,3-dihydro-1*H*-indole-2-carboxylic acid *tert*-butyl ester ((*S*)-343a). Following the general procedure E, use of the ketimine (41.0 mg, 86.0 μmol), $^{n}Bu_3SnH$ (51.0 μL, 0.189 mmol), and AIBN (17 mg, 0.103 mmol) provided, following chromatography (SiO_2, 1% ethyl acetate in hexanes), the racemic indoline as a colorless oil (5.00 mg, 15%).[195] R_f= 0.40 (10% EtOAc/hexanes); IR (film) 3059, 1743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.9 Hz, 2H), 7.39-7.30 (m, 4H), 7.26-7.20 (m, 2H), 6.97 (td, *J* = 7.8, 1.1 Hz, 3H), 6.85 (d, *J* = 7.1 Hz, 1H), 6.79 (t, *J* = 7.4 Hz, 1H), 5.95 (s, 1H), 4.05 (dd, *J* = 7.3, 5.2 Hz, 1H), 2.61 (d, *J* = 5.9 Hz, 2H), 2.37 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 173.2, 150.9, 141.2, 140.4, 132.1, 130.1, 128.9, 128.7, 128.2, 128.0, 127.4, 126.9, 123.6, 121.6, 121.5, 80.5, 68.2, 61.7, 35.0, 27.9, 18.5; HRMS (EI): Exact mass calcd for $C_{27}H_{29}NO_2$ $[M]^+$, 399.2198. Found 399.2203.

HPLC (Chiralcel AD, 0.5% ^{i}PrOH/hexanes, 0.5 mL/min): t_r (*S*) = 10.0 m, t_r (*R*) = 10.6 m.

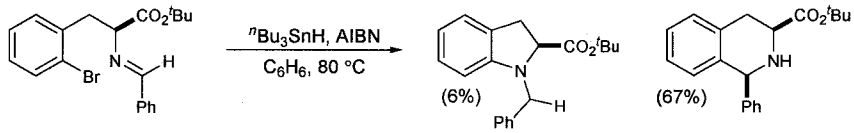


2-(Benzylidene amino)-3-(2-bromophenyl)-propionic acid *tert*-butyl ester ((*S*)-341c). Following the general procedure A, amine (*S*)-**339** (250 mg, 833 μmol), benzaldehyde (85.0 μL, 833 μmol), and 4Å MS in benzene (0.8 mL) after 10 h provided the aldimine (330 mg, 100%), as a >95: 5 mixture of stereoisomers and a colorless oil. IR (film) 3062, 1733, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.71 (dd, *J* = 7.7, 1.5 Hz, 2H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.42-7.35 (m, 3H); 7.21 (d, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.04 (td, *J* = 8.9, 1.3 Hz, 1H), 4.25 (dd, *J* = 8.2, 5.8 Hz, 1H), 3.56 (dd, *J* = 13.6, 5.8 Hz, 1H), 3.19 (dd, *J* = 13.6, 8.3 Hz, 1H) 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$)

[195] The mass balance consisted of unreacted starting material and reduced aryl bromide (ArH).

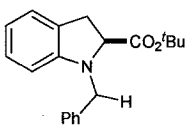
ppm 170.5, 163.5, 137.1, 135.7, 132.6, 130.9, 128.4, 128.3, 128.2, 127.0, 124.8, 81.4, 72.9, 39.8, 28.0; HRMS (EI): Exact mass calcd for $C_{20}H_{23}BrNO_2$ $[M+H]^+$ 388.0912. Found 388.0917.

HPLC (Chiralcel OD, 2% ^{i}PrOH/hexanes, 1 mL/min): t_r (*S*) = 5.4 m, t_r (*R*) = 6.3 m. (*S*)- 94% ee $[\alpha]_D^{21}$ =–140.1 (*c* 1.5, $CHCl_3$).



Following the general procedure E, use of aldimine (*S*)-**341c** (224 mg, 577 μmol), ^{n}Bu_3SnH (171 μL, 635 μmol), and AIBN (76.0 mg, 462 μmol) furnished, after silica gel chromatography (3-5% ethyl acetate in hexanes, the indoline **343c** (10.4 mg, 6%) as a colorless oil and tetrahydroisoquinoline **344** (119.0 mg, 67%) as a colorless solid.

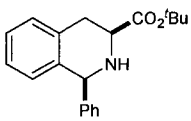
(*S*)-1-Benzyl-2,3-dihydro-1-H-indole-2-carboxylic acid *tert*-butyl ester ((*S*)-343c).



R_f=0.42 (10% EtOAc/hexanes); IR (film) 3026, 1736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.0 Hz, 1H), 7.33 (t, *J* = 7.0 Hz, 2H), 7.28–7.24 (m, 2H), 7.07–7.01 (m, 2H), 6.68 (t, *J* = 7.5 Hz, 1H), 6.40 (d, *J* = 7.8 Hz, 1H), 4.56 (d, *J* = 15.6 Hz, 1H), 4.30 (d, *J* = 15.7 Hz, 1H) 4.16 (dd *J* = 10.2, 8.2 Hz, 1H), 3.36 (dd, *J* = 15.9, 10.2 Hz, 1H), 3.19 (dd, *J* = 15.9, 8.2 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.9, 151.6, 130.3, 128.5, 127.71, 127.67, 127.1, 124.1, 122.4,

117.9, 107.0, 81.4, 66.2, 52.1, 33.4, 28.0; HRMS (EI): Exact mass calcd for $C_{20}H_{23}NO_2$ $[M]^+$, 309.1729. Found 309.1744.

HPLC (Chiralcel OD, 1% ^{i}PrOH/hexanes, 0.5 mL/min): t_r (*S*) = 14.5 m, t_r (*R*) = 17.7 m. (*S*)- 81% ee, $[\alpha]_D^{25}$ =–5.3 (*c* 0.3, $CHCl_3$).

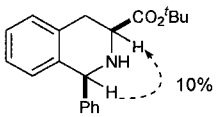


(*S*)-1-Phenyl-1,2,3,4-tetrahydro isoquinoline-3-carboxylic acid *tert*-butyl ester (344). mp 116-119 °C; R_f= 0.25 (10% EtOAc/hexanes); IR (film) 2975, 1726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.30 (m, 5H), 7.16 (dd, *J* = 14.4, 7.5 Hz, 2H), 7.05 (td, *J* = 7.9, 1.9 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 5.14 (s, 1H), 3.81 (dd, *J* = 9.0, 6.5 Hz, 1H), 3.15 (d, *J* = 6.9 Hz, 2H), 2.47 (br, s,

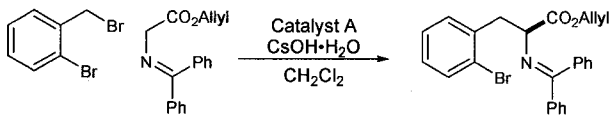
1H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.7, 143.9, 138.5, 134.1, 129.1, 128.8, 128.4, 127.6, 127.5, 126.2, 125.9, 81.5, 63.2, 57.0, 32.8, 28.0; HRMS (EI): Exact mass calcd for $C_{20}H_{23}NO_2$ $[M]^+$, 309.1729. Found 309.1715.

Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64, H, 7.49, N, 4.53. Found : C, 77.36, H, 7.55, N, 4.43.

HPLC (Chiralcel AD, 10% ^{i}PrOH/hexanes, 1.0 mL/min): t_r (*S*) = 6.0 m, t_r (*R*) = 8.9 m. (*S*)- 95% ee, $[\alpha]_D^{25}$ =–8.8 (*c* 1.0, $CHCl_3$).



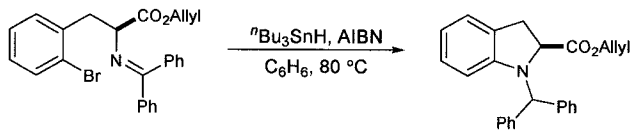
NOE measurements



2-(Benzhydrylidene-amino)-3-(2-bromophenyl)-propionic acid allyl ester ((*S*)-341d). Following the general procedure D, *ortho*-bromobenzyl bromide (501 mg, 1.79 μmol), glycine allyl ester benzophenone imine (100 mg, 357 μmol), $CsOH•H_2O$ (532 mg, 3.57 mmol), and the cinchonidine derived catalyst **181** (21.8 mg, 36.0 mmol) were stirred in CH_2Cl_2 (1.05 mL) at–78 °C for 7 hours. Workup according to the general procedure and flash chromatography (neutral alumina, 4% ethyl acetate in hexanes) gave the desired phenyl alanine derivative as a colorless oil (100 mg, 62% yield). R_f= 0.20 (10% EtOAc/hexanes); IR (film) 3062, 1748, 1618 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.3 Hz, 2H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.39 (t, *J* = 6.3 Hz, 2H), 7.36– 7.30 (m, 4H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.06 (td, *J* = 8.8, 1.5, Hz, 1H), 6.62 (bs s, 2H), 5.94 (ddd, *J* = 18.3, 10.5, 5.6 Hz, 1H), 5.34 (dd, *J* = 18.3, 1.1 Hz, 1H), 5.25 (d, *J* = 10.5 Hz, 1H); 4.74-4.65 (m, 2H), 4.58 (dd, *J* = 9.8, 3.8 Hz, 1H), 3.58 (dd, *J* = 13.2, 4.2 Hz, 1H), 3.31 (dd, *J* = 13.2, 10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 171.2, 171.1, 139.1, 137.0, 135.7, 132.7, 132.5, 131.9, 130.9, 130.0, 128.7, 128.3, 128.2, 128.1

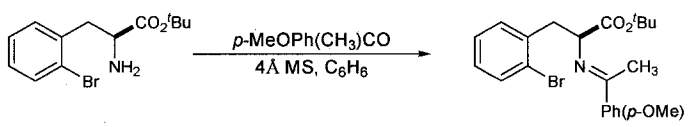
(2C), 127.5, 126.9, 118.0, 65.5, 64.3, 39.5; HRMS (EI): Exact mass calcd for $C_{25}H_{23}BrNO_2$ $[M+H]^+$ 448.0912. Found 448.0915.

HPLC (Chiralcel OD, 2% ^{i}PrOH/hexanes, 1 mL/min): t_r (*R*) = 5.9 m, t_r (*S*) = 6.6 m. (*S*)-76% ee $[\alpha]_D^{21}$ =–265.5 (*c* 0.5, $CHCl_3$).



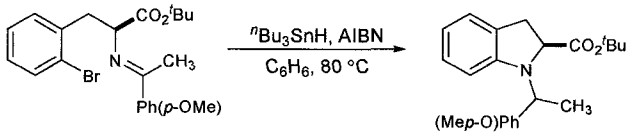
1-Benzhydryl-2,3-dihydro-1H-indole-2-carboxylic acid allyl ester ((*S*)-343d). According to the general procedure E, Schiff base (40.2 mg, 94.0 μmol), ^{n}Bu_3SnH (55.7 μL, 0.207 mmol) and AIBN (12.3 mg, 75.0 μmol) furnished after workup and chromatography (SiO_2, 4% ethyl acetate in hexanes), (*S*)-**343d** as a colorless oil (26.0 mg, 75% yield). R_f= 0.35 (10% EtOAc/hexanes); IR (film) 3055, 1744 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 1.6 Hz, 2H), 7.46-7.24 (m, 8H), 7.05 (d, *J* = 7.2 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 6.61 (t, *J* = 7.2 Hz, 1H), 6.07 (d, *J* = 4.0 Hz, 1H), 5.83–5.73 (m, 1H), 5.66 (s, 1H), 5.21 (d, *J* =1.2 Hz, 1H), 5.18 (dd, *J* = 4.8, 1.2 Hz, 1H), 4.44–4.35 (m, 2H), 4.27 (dd, *J* = 10.0, 5.6 Hz, 1H), 3.45 (dd, *J* = 15.6, 10.4 Hz, 1H), 3.07 (dd, *J* = 16.0, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 173.2, 151.1, 140.8, 140.6, 131.7, 129.0, 128.6, 128.5 (3C), 127.5 (2C), 127.4, 123.9, 118.4, 118.2, 109.3, 67.2, 65.3, 64.5, 34.0; HRMS (EI): Exact mass calcd for $C_{25}H_{23}NO_2$ $[M]^+$ 369.1729. Found 369.1745.

HPLC (Chiralcel AD, 2% ^{i}PrOH/hexanes, 1 mL/min): t_r (*R*) = 6.6 m, t_r (*S*) = 10.6 m. (*S*)-38% ee $[\alpha]_D^{21}$ =–17.9 (*c* 0.7, $CHCl_3$).



(*S*)-3-(2-bromophenyl)-2-[1-(4-methoxyphenyl)-ethylideneamino]-propionic acid *tert*-butyl ester ((*S*)-341e). Following the general procedure A, amine (*S*)-**339** (107 mg,

356 μmol), *para*-methoxyacetophenone (53.0 mg, 356 μmol), and 4Å MS in toluene (0.36 mL) after 36 h at reflux provided the desired ketimine as a colorless oil (115 mg, 75%) and > 95:5 mixture of stereoisomers (^{1}H NMR); IR (film) 2974, 1730, 1678 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.9 Hz, 2H), 7.28-7.21 (m, 2H), 7.17-7.11 (m, 2H), 6.85 (d, J = 8.9 Hz, 2H), 4.58 (dd, J = 8.9, 5.5 Hz, 1H), 3.85 (s, 3H), 3.55 (dd, J = 13.4, 5.2 Hz, 1H), 3.15 (dd, J = 13.4, 8.9 Hz, 1H), 1.91 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 166.8, 137.7, 132.8, 130.1, 129.0, 128.5, 128.3, 128.2, 128.1, 127.3, 113.6, 113.3, 81.1, 63.8, 55.3, 40.0, 29.7, 28.0; HRMS (EI): Exact mass calcd for $C_{22}H_{27}BrNO_3$ $[M+H]^+$ 432.1174. Found 432.1172. (*S*)- 87% ee $[\alpha]_D^{21}$ = –43.1 (*c* 0.7, $CHCl_3$).



(*S*)-1-[1-(4-methoxy phenyl) ethyl]-2,3-dihydro-1H-indole-2-carboxylic acid *tert*-butyl ester ((*S*)-343e). Following the general procedure E, the ketimine (36.0 mg, 86.0 μmol), ^{n}Bu$_3$SnH (51.0 μL, 189 μmol), and AIBN (11.3 mg, 69.0 μmol) furnished, after silica gel chromatography (1% ether in hexanes), the desired indoline (15.0 mg, 50%) as a 3:1 mixture of diastereomers.

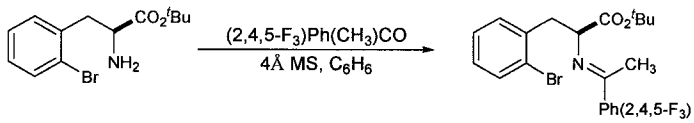
Minor diastereomer: R_f= 0.55 (10% EtOAc/hexanes); IR (film) 2974, 1741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.6 Hz, 2H), 7.01 (d, J = 7.0 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 8.6 Hz, 2H), 6.63 (t, J = 7.0 Hz, 1H), 6.26 (d, J = 7.9 Hz, 1H), 4.49 (q, J = 7.0 Hz, 1H), 4.36 (t, J = 9.5 Hz, 1H), 3.80 (s, 3H), 3.42 (dd, J = 15.9, 10.4 Hz, 1H), 3.06 (dd, J = 15.9, 9.2 Hz, 1H), 1.51 (d, J = 7.0 Hz, 3H), 1.39 (s, 9H) ; ^{13}C NMR (100 MHz, $CDCl_3$) ppm 173.5, 158.5, 151.7, 136.2, 128.2 (2C), 127.5, 123.8, 117.9, 113.8, 108.6, 81.0, 64.2, 57.6, 55.2, 34.5, 27.9, 19.3; HRMS (EI): Exact mass calcd for $C_{22}H_{27}NO_3$ $[M]^+$ 353.1991. Found 353.2008.

HPLC (Chiralcel OD, 2% ^{i}PrOH/hexanes, 0.5 mL/min): t_r (2*S*) = 11.0 m, t_r (2*R*) = 13.2 m. (*S*)- 32% ee, $[\alpha]_D^{21}$ = +2.1 (*c* 0.5, $CHCl_3$).

Major diastereomer: R_f= 0.45 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) □ 7.41 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 7.0 Hz, 1H), 6.87-6.83 (m, 3H), 6.58 (t, J = 6.9 Hz, 1H), 6.08 (d, J = 7.9 Hz, 1H), 4.60 (q, J = 7.0 Hz, 1H), 4.28 (dd, J = 10.3, 7.4 Hz, 1H), 3.80 (s, 3H), 3.37 (dd, J = 16.0, 10.5 Hz, 1H), 3.08 (dd, J = 15.9, 7.4 Hz, 1H), 1.51 (d, J = 6.9 Hz, 3H), 1.47 (s, 9H) ; ^{13}C NMR (100 MHz, $CDCl_3$) ppm 173.4, 148.1, 139.3, 127.9 (2C), 127.2, 124.0, 117.5, 113.7 (2C), 108.9, 64.4, 62.9, 55.2, 55.1, 33.8, 28.0, 16.5.

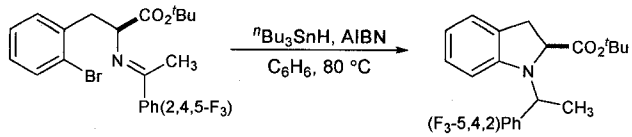
Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.77; H, 7.77; N, 3.95.

HPLC (Chiralcel OD, 2% ^{i}PrOH/hexanes, 0.5 mL/min): t_r (2*S*) = 13.0 m, t_r (2*R*) = 15.0 m. (*S*)- 32% ee, $[\alpha]_D^{21}$ = –7.2 (*c* 1.1, $CHCl_3$).



(*S*)-3-(2-Bromophenyl)-2-[1-(2′,4′,5′-trifluorophenyl)-ethylideneamino]-propionic acid *tert*-butyl ester ((*S*)-341f). Following the general procedure A, amine (*S*)-**339** (107 mg, 356 μmol), 2′4′5′-trifluoroacetophenone (46.6 μL, 356 μmol), and 4Å MS in toluene (0.36 mL) after 30 h at reflux provided the desire ketimine (115 mg, 70%) as a colorless oil; IR (film) 3065, 1734, 1618 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 7.7 Hz, 1H), 7.24-7.23 (m, 2H), 7.14-7.10 (m, 2H), 6.90 (td, J = 9.9, 6.3 Hz, 1H), 4.65 (dd, J = 9.1, 5.1 Hz, 1H), 3.61 (dd, J = 13.4, 5.1Hz, 1H), 3.19 (dd, J = 13.4, 9.1 Hz, 1H), 1.96 (d, J = 3.4 Hz, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 169.9, 165.0, 155.2, 150.6, 137.1, 132.6 (2C), 128.4, 127.1, 127.0, 124.7, 117.8 ($J_{C\text{-}F}$ = 14.5 Hz, 1C), 105.7 (m, 2C), 81.7, 65.6, 63.3, 39.6, 28.0; HRMS (EI): Exact mass calcd for $C_{21}H_{22}BrF_3NO_2$ $[M+H]^+$ 456.0786. Found 456.0781.

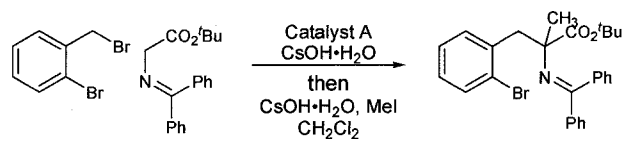
HPLC (Chiralcel OD, 2% ^{i}PrOH/hexanes, 0.5 mL/min): t_r (*S*) = 8.6 m, t_r (*R*) = 11.8 m. (*S*)- 87% ee, $[\alpha]_D^{21}$ = –66.4 (*c* 0.6, $CHCl_3$).



(*S*)-1-[1-(2,4,5-trifluorophenyl)ethyl]-2,3-dihydro-1H-indole-2-carboxylic acid *tert*-butyl ester ((*S*)-343f). Following the general procedure E, the ketimine (90.0 mg, 196 μmol), $^{n}Bu_3SnH$ (116 μL, 434 μmol), and AIBN (26.0 mg, 158 μmol) furnished after silica gel chromatography (1% ethyl acetate in hexanes) the desired indoline (52.0 mg, 70%) as a colorless oil and a 3:1 inseparable mixture of diastereomers. R_f= 0.58 (10% EtOAc/hexanes); IR (film) 3062, 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87-7.80 (m, 1H), 7.05 (d, *J* = 7.3 Hz, 1H), 7.00-6.91 (m, 2H), 6.70 (t, *J* = 6.8 Hz, 1H), 6.08 (d, *J* = 7.9 Hz, 1H), 4.71 (dd, *J* = 14.0, 7.0 Hz, 1H), 4.48 (t, *J* = 10.2 Hz, 1H), 3.48 (dd, *J* = 15.7, 10.2 Hz, 1H), 3.13 (dd, *J* = 15.8, 10.1 Hz, 1H), 1.51-1.50 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 173.4, 151.1, 128.5, 127.7, 127.4, 127.0, 124.0, 123.9, 118.6, 118.1 (d J_{C-F} = 19.7 Hz, 1C), 107.9, 105.3 (m 2C), 81.7, 64.1, 51.9, 34.5, 27.9, 18.4; HRMS (EI): Exact mass calcd for $C_{21}H_{22}NF_3O_2$ $[M]^+$ 377.1603. Found 377.1599.

Anal. Calcd for $C_{21}H_{22}NF_3O_2$: C, 66.83; H, 5.88; N, 3.71. Found: C, 66.86; H, 5.80; N, 3.62.

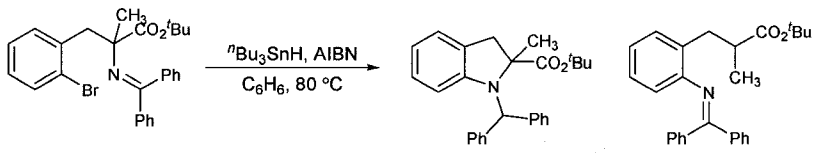
HPLC (Chiralcel AD, 1% $^{i}PrOH$/hexanes, 0.25 mL/min): major diastereomer: t_r (2*S*) = 17.2 m, t_r (2*R*) = 20.2 m; minor diastereomer : t_r (2*S*) = 18.6 m, t_r (2*R*) = 19.5 m. (2*S*)- 82% ee, $[\alpha]_D^{21}$ = –4.9 (*c* 0.7, $CHCl_3$).



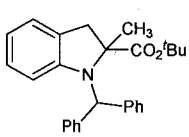
2-(Benzhydrylidene-amino)-3-(2-bromophenyl)-2-methyl-propionic acid *tert*-butyl ester (353). As an adaptation of the general procedure D, methyl iodide (22.2 μL, 355 μmol), Schiff base (100 mg, 339 μmol), $CsOH•H_2O$ (126 mg, 845 μmol), and cinchonidine derived catalyst (20.6 mg, 34.0 μmol), were stirred in toluene (1 mL) at room temperature for 3.5 h. Additional $CsOH•H_2O$ (252 mg, 1.69 mmol), catalyst (20.6

mg, 34.0 μmol) and *ortho*-bromobenzyl bromide (114 mg, 407 μmol), were added and the reaction mixture was stirred vigorously for an additional 18 h at room temperature. The reaction mixture was diluted with ether and water (1:1). The organic layer was separated, the aqueous layer was extracted with ether, and the combined ether layers were dried and concentrated. Flash chromatography (neutral alumina, 0.50% ethyl acetate in hexanes) gave the desired ketimine as a colorless oil (76.0 mg, 46%). The catalyst was recovered by washing the aqueous layer with CH_2Cl_2. R_f=0.40 (10% EtOAc/hexanes); IR (film) 3058, 1730, 1628 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.68 (dd, J = 7.3, 1.6 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.54 (t, J = 8.4 Hz, 1H), 7.34–7.28 (m, 6H), 7.21 (td, J = 8.8, 0.8 Hz, 1H), 7.06 (d, J = 6.4 Hz, 3H), 3.48 (d, J = 14.0, Hz, 1H), 3.38 (d, J = 14.0, Hz, 1H), 1.32 (s, 9H), 1.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 173.7, 166.5, 141.5, 138.5, 137.6, 132.6, 129.8, 128.5, 128.5, 128.3, 128.1, 127.9, 127.8 (2C), 126.8, 126.4, 81.0, 68.3, 46.6, 27.9, 23.7; HRMS (EI): Exact mass calcd for $C_{27}H_{29}BrNO_2$ $[M+H]^+$ 478.1382. Found 478.1363.

HPLC (Chiralcel OD, 1% ^{i}PrOH/hexanes, 0.5 mL/min): t_r (minor) = 8.9 m, t_r (major) = 10.8 m. (*S*)-22% ee.



Following the general procedure E, Schiff base (41.0 mg, 86.0 μmol), ^{n}Bu$_3$SnH (51.0 μL, 0.189 mmol) and AIBN (11.3 mg, 69 μmol) furnished after chromatography (neutral alumina, 20% dichloromethane in hexanes), the indoline as a colorless oil (16.0 mg, 48% yield) and the aryl imine as a yellow oil (15.0 mg, 45% yield).

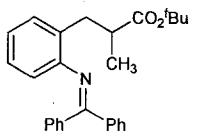


1-Benzhydryl-4-bromo-2-methyl-2,3-dihydro-1H-indole-2-carboxylic acid *tert*-butyl ester (354). R_f=0.54 (10% EtOAc/hexanes); IR (film) 3065, 1727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.26 (m, 10H), 7.02 (d, J = 7.2 Hz, 1H), 6.72 (t, J = 7.6 Hz, 1H), 6.54 (t, J = 8.0 Hz, 1H), 5.80 (s, 1H), 5.75 (d, J = 8.0 Hz, 1H), 3.67 (d, J = 16.0 Hz, 1H), 3.03 (d, J = 16.0 Hz, 1H), 1.40 (s, 9H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 173.7, 148.7, 142.2, 140.7, 128.64,

127.59, 128.4, 128.1, 127.1, 126.9, 126.8, 125.7, 123.9, 116.2, 108.8, 81.6, 71.2, 62.3, 42.5, 27.8, 24.8; HRMS (EI): Exact mass calcd. for $C_{27}H_{29}NO_2$ $[M]^+$ 399.2198. Found 399.2185.

Anal. Calcd for $C_{27}H_{29}NO_2$: C, 81.17; H, 7.32; N, 3.51. Found: C, 81.15; H, 7.52; N, 3.47.

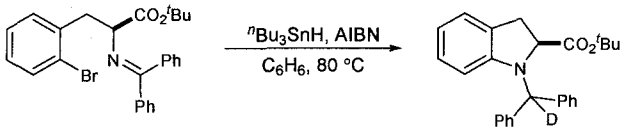
HPLC (Chiralcel AD, 1% ^{i}PrOH/hexanes, 1.0 mL/min): t_r = 3.8 m, 4.0 m.

3-[2-(Benzhydrylidene-amino)-phenyl]-2-methyl-propionic acid *tert*-butyl ester (355). 

R_f=0.17 (50% CH_2Cl_2/hexanes); IR (film) 3058, 1723, 1621 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.2 Hz, 2H), 7.48 (d, J = 7.2 Hz, 1H), 7.32–7.25 (m, 3H), 7.15 (dd, J = 7.2, 1.6 Hz, 2H), 7.10 (d, J = 7.2 Hz, 1H), 6.92 (td, J = 7.2, 1.2 Hz, 1H), 6.87 (td, J = 7.2, 1.2 Hz, 1H), 6.40 (d , J = 8.0 Hz, 1H), 2.95–2.83 (m, 2H), 2.63 (dd, J = 12.4, 6.8 Hz, 1H), 1.36 (s, 9H), 1.14 (d, J = 6.8, Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 176.1, 166.6, 139.5, 130.7, 130.5, 129.9, 129.3, 129.0 (2C), 128.6, 128.1, 127.9, 126.3, 123.2, 119.9, 79.8, 39.9, 36.4, 29.7, 28.0, 17.2; HRMS (EI): Exact mass calcd. for $C_{27}H_{29}NO_2$ $[M]^+$ 399.2198. Found 399.2212.

Anal. Calcd for $C_{27}H_{29}NO_2$: C, 81.17; H, 7.32; N, 3.51. Found: C, 81.37; H, 7.36; N, 3.46.

HPLC (Chiralcel AD, 1% ^{i}PrOH/hexanes, 1.0 mL/min): t_r = 4.7 m, 5.1 m.



(*S*)-1-Benzhydryl-2,3-dihydro-1*D*-indole-2-carboxylic acid *tert*-butyl ester (359). According to the general procedure E, the Schiff base (18.6 mg, 40.0 μmol), ^{n}Bu_3SnD (23.8 μL, 0.088 mmol) and AIBN (5.25 mg, 0.032 mmol) furnished after work-up and chromatography (SiO_2, 2% ethyl acetate in hexanes) the desired product as a colorless oil (13.9 mg, 90% yield). R_f= 0.42 (10% EtOAc/hexanes); IR (film) 3061, 1730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.1 Hz, 2H), 7.37 (d, J = 7.1 Hz, 2H), 7.34–7.23 (m, 6H), 7.03 (d, J = 7.1 Hz, 1H), 6.87 (t, J = 7.7 Hz, 1H), 6.64 (t, J = 7.3 Hz, 1H), 6.01 (d, J = 7.9 Hz, 1H), 4.11 (dd J = 10.5, 5.4 Hz, 1H), 3.42 (dd, J = 15.9, 10.5 Hz, 1H), 3.00

(dd, J = 15.9, 5.4 Hz, 1H), 1.33 (s, 9H); ^{2}H NMR (60 MHz, $CDCl_3$) δ 5.60 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) ppm 172.6, 151.2, 141.1, 140.6, 129.2, 128.5 (2C), 128.4 (2C), 127.7, 127.3, 127.2, 123.8, 117.9, 109.2, 80.8, 66.6 (t, J = 21.3 Hz), 65.0, 34.0, 27.9; HRMS (EI): Exact mass calcd for $C_{26}H_{26}DNO_2$ $[M]^+$ 386.2104. Found 386.2102.

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1999-2005	Ph.D. Studies in Synthetic Organic Chemistry, Department of Chemistry, Indiana University, Bloomington, Indiana.
1997-1999	Master of Science, General Chemistry, Indian Institute of Technology, Kanpur, India.

Research Experience:

1999-present — **Graduate Research Fellow with Prof. Jeffrey N. Johnston**
Indiana University, Bloomington, Indiana
Discovery and Development of Free Radical-Mediated Amination Reactions and their Application to the Asymmetric Synthesis of Indoline α-Amino Acids.
Discovery of ACCRI (Azacyclopentenyl Carbinyl Radical Isomerizations).
Studies Toward the Total Synthesis of (+)-Ambiguine G.

1998-1999 — **Research Fellow with Prof. Javed Iqbal**
Indian Institute of Technology, Kanpur, India
Synthesis of Cyclic Peptides as β- and γ- Turn Mimics-Potent HIV Protease Inhibitors

1998 — **Summer Research with Prof. K. K. Balasubramanian**
Studies in Photochemically Induced Radical Cyclizations to form Benzopyrans

Teaching Experience:

Fall 1999	Undergraduate Laboratory Organic Chemistry (Prof. Zafar)
Spring 2000	Undergraduate General Organic Chemistry II (Prof. Montgomery)
Fall 2000	Graduate Organic Synthesis I (Prof. Johnston) Undergraduate Honors Laboratory Organic Chemistry (Prof. Montgomery)
Spring 2001	Honors General Organic Chemistry II (Prof. Johnston)

Spring 2002	Undergraduate General Organic Chemistry II (Prof. Johnston)
Fall 2002	Undergraduate Honors Laboratory Organic Chemistry (Dr. Mullins)

Honors and Awards

2003	Lubrizol Fellowship (IU)
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Publications

"Free Radical-Mediated Aryl Amination: Convergent Two- and Three-Component Couplings to Chiral 2,3-Disubstituted Indolines", Smith C. R.; Prabhakaran E. N.; Viswanathan R.; Johnston J. N. *to be submitted.*

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Patents

Johnston, J. N.; Viswanathan, R. Amination Process U.S. Patent 6,670,479, 2003.

Presentations

"Free Radical-Mediated Aryl Amination in Alkaloid Synthesis: Studies Directed Toward the Total Synthesis of (+)-ambiguine G" Rajesh Viswanathan and Jeffrey N. Johnston. Presented at the 53rd Natural Products Gordon Research Conference, July 25-30, 2004, Tilton, New Hampshire. Poster 59.

"The First Azacyalopentenyl Carbinyl Radical Isomerization (ACCRI): Discovery, Development and Potential Biological Implications." Rajesh Viswanathan, Daniel Mutnick, and Jeffrey N. Johnston. Presented at the 38th National Organic Symposium, June 8-12, 2003, Bloomington, Indiana. Poster C126.

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