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Catalytic methods for the synthesis of spirooxindoles, pyrroloindolines, and flavanones

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Catalytic methods for the synthesis of spirooxindoles, pyrroloindolines, and flavanones

by

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DEDICATION

This thesis is dedicated to the Blessed Virgin Mary, on whose constant intercession I rely for help with everything in life. It is also dedicated to my lovely wife Kaity, who has waited with angelic patience for my arrival at this point, and to all of my family and friends who have struggled with me through the years.

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GLOSSARY OF TERMS

$AgClO_4$	silver perchlorate
$Cu(OTf)_2$	copper (II) triflate
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
ee	enantioenrichment
ESI	Electrospray Ionization
GC	Gas Chromatography
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
IR	Infrared
$Mg(NTf)_2$	magnesium Triflimide
MHz	Megahertz
M	Molar
MS	Molecular Sieves
NaTFA	Sodium Trifluoroacetate
NEt_3	Triethylamine
NMR	Nuclear Magnetic Resonance
$Pd(TFA)_2$	Palladium (II) trifluoroacetate
QTOF	Quadrupole Time of Flight
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography

t_R	retention time
UV	Ultraviolet

ACKNOWLEDGMENTS

I have a lot of individuals to whom I owe a debt of gratitude for my growth and development during my graduate school years. First and foremost, I am thankful to God whose gracious providence and guiding hand throughout my entire life have brought me to this point. I am also thankful for my lovely wife Kaity who has shown inexhaustible love, support, and patience throughout the ups and downs of graduate student life. I'm excited to find out what our future holds.

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I am also thankful to my lab mates. I appreciate your understanding of the fact that seven days without a pun makes one week (weak). Thank you for listening to all of them my puns. I understand that a glossary of terms is optional under ISU dissertation standards, but I included a glossary of terms for you to gloss over. I'm glad you guys have slapped a neon all the chemistry jokes I've shared.

Ryan, I think you know that one time a guy walked into the greenhouse looking for a pickle plant and I told him we didn't have any. This should sound familiar. I grateful that you introduced me to Ron Swanson and Sherlock, and I'm glad we got to go to Pacifichem during our time here.

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I am thankful also to the United States taxpayers for funding the research in this thesis. I hope that everything I have disclosed in this thesis will be for the betterment of society. You work very hard to earn the money for the taxes you pay and you deserve an acknowledgement.

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Additionally, having lived in Iowa for the past five years, I have gained a great appreciation for agriculture. I have run through the Iowa countryside almost every morning while I have been here at ISU, and nothing gets me excited like seeing a huge combine out in field harvesting corn. To the people who work the land in Iowa and around the world, thank you for your hard work. I think of you every time I sit down to eat.

To all of my other family and friends who have touched my life in so many ways, thank you for everything you have done for me. I hope I am as much of a blessing to you as you are to me.

Finally, I have a special message for my brother, William Gerten: cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow cow. That is the word "cow" 30 times. You can take this dissertation seriously.

ABSTRACT

This thesis discloses catalytic, enantioselective dipolar cycloadditions to deliver new nitrogen-containing heterocycles and formal hydroarylations of olefins that have previously not been possible.

Catalytic, enantioselective, dearomative cycloadditions of stabilized, α-substituted azomethine ylides with 3-nitroindoles occur in the presence of a catalytic complex generated from $Cu(OTf)_2$ and (*R*)-Difluorphos. These reactions set four contiguous stereocenters, two of which are fully substituted. Overcoming the barrier of breaking aromaticity, this catalyst system delivers pyrrolo[3, 4*b*]indoles with *exo´*-selectivity in moderate-to-good yields (39-85%) with high diastereoselectivity (up to 98 : 1 : 1 dr) and enantioselectivity (up to 96% ee).

Catalytic, enantioselective, dipolar cycloadditions of highly reactive nitrile imines with methyleneindolinones occur in the presence of a catalyst generated from $Mg(NTf_2)_2$ and a chiral aminoindanol-derived bisoxazoline ligand. The catalyst system designed overcomes a rapid competing background reaction to deliver spiro[pyrazolin-3,3′-oxindoles] in up to 98% yield and 99% ee.

Conjugate additions of arylboronic acids to challenging 2-alkylchromones occur in aqueous medium in the presence of a catalyst system generated from $Pd(TFA)_2$ and 1,10-phenanthroline. This system overcomes the problem of competing protodeboronation and biaryl-forming reactions to deliver 2-alkyl-2-aryl-chromanones in up to 90% yield, providing a new and effective means of generating a fully substituted carbon center.

In all of these projects, effective catalyst design principles were established to overcome challenges that made these types of reactions previously impossible.

CHAPTER 1

ARENES AND HETEROARENES AS 2 π-ELECTRON REACTION PARTNERS IN CATALYTIC, ASYMMETRIC, DEAROMATIVE CYCLOADDITIONS: A REVIEW

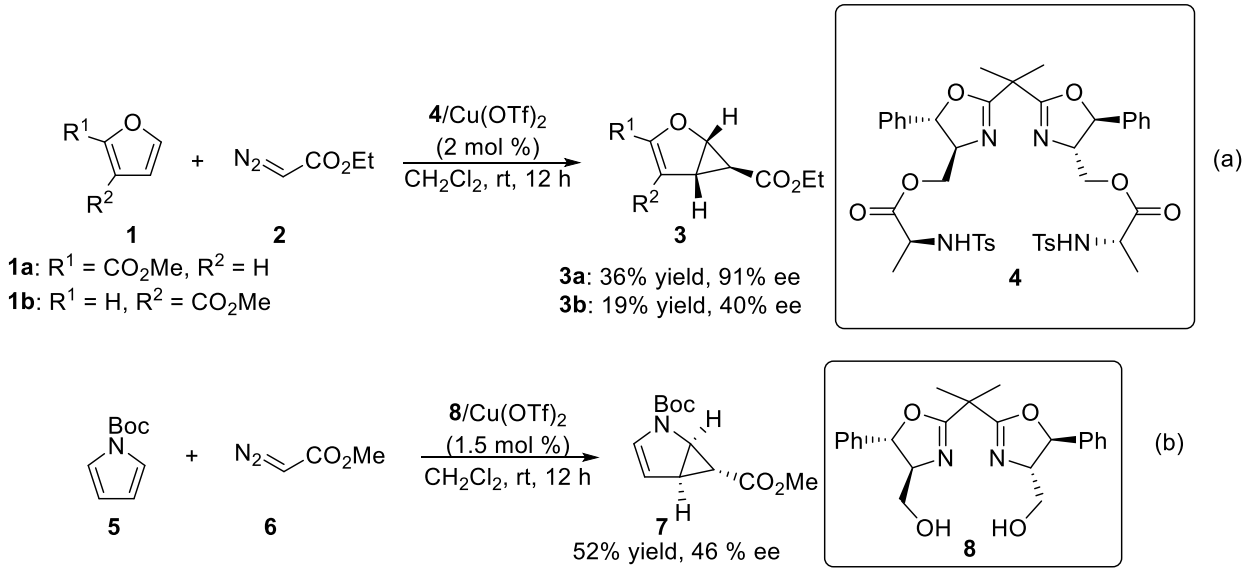
General Introduction

Dearomative cycloadditions of arenes and heteroarenes offer the potential to generate novel polycyclic systems in a rapid and elegant manner. As 2 π-electron partners in catalytic, enantioselective cycloadditions, aromatic systems are challenging substrates due to the high energy barrier of breaking aromaticity.[1] In recent years, the potential synthetic utility of asymmetric cycloadditions with arenes as 2 π-electron partners has led to increased investigations into these types of reactions, which are the focus of this review. Aromatic compounds as 4 π-electron partners have been explored in catalytic, asymmetric synthesis.[2] The electron-rich nature of these species renders them effective as dienes in many reactions.[3] A recent review included reports of such dienes as 4 π-electron partners,[4] and these reactions are not included here. This review is organized by reaction type, and includes catalytic, enantioselective dearomative cycloadditions via carbenoid species, chiral Lewis acid catalysis, cascade reactions involving allylic substitution, chiral phosphoric acid catalysis, and iminium ion organocatalysis.

Enantioselective dearomative cycloadditions via carbenoid species

In 2003, Reiser and coworkers reported the first catalytic, asymmetric cyclopropanations of aromatic compounds via metal carbenoid species (Scheme 1).[5] These cyclopropanations took place in the presence of chiral catalysts formed from copper (II) and bisoxazoline ligands. Methylfuran-2-carboxylate **1a** reacted smoothly in the presence of the **4**/$Cu(OTf)_2$ to deliver

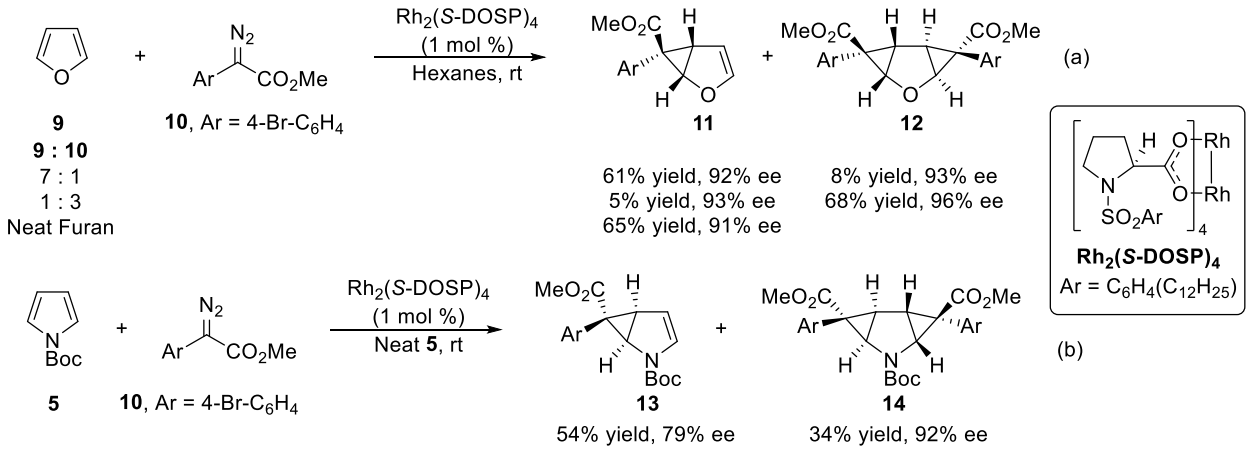
cyclopropanated furan **3a** in 36% yield and 91% ee (Scheme 1a). Methylfuran-3-carboxylate **1b** reacted with **2** in the presence of the catalyst to furnish **3b** in 19% yield and 40% ee (Scheme 1a). The investigators propose a hydrogen-bonding interaction between the amino-moiety of **4** and the carbonyl group of the ester in **1a** that allows for the delivery of high enantioselectivity in product **3a**. This hydrogen-bonding interaction is likely absent in the interaction of **1b** with the catalyst, leading to a lack of facial discrimination, and thus, low enantioenrichment. The reaction of N-Boc pyrrole **5**, which lacks sterically accessible hydrogen-bond acceptors, in the presence of **8**/$Cu(OTf)_2$ delivered **7** in only 52% yield and 46% ee, lending further evidence of the requirement for secondary interactions between the catalyst complex and the substrate to achieve high enantioenrichment under these conditions.



Scheme 1. *Copper-catalyzed enantioselective cyclopropanations of furans and pyrroles with carbenes formed from diazoacetates*

Davies and coworkers designed a more generalized system for cyclopropanations of furans and pyrroles that employed rhodium prolinate catalyst Rh_2(*S*-DOSP)$_4$ (Scheme 2).[6] This catalyst system did not require a chelating substituent on the ring and delivered both mono-and di- cyclopropanation products. Furan **9** reacted with donor-acceptor carbene precursor **10** to

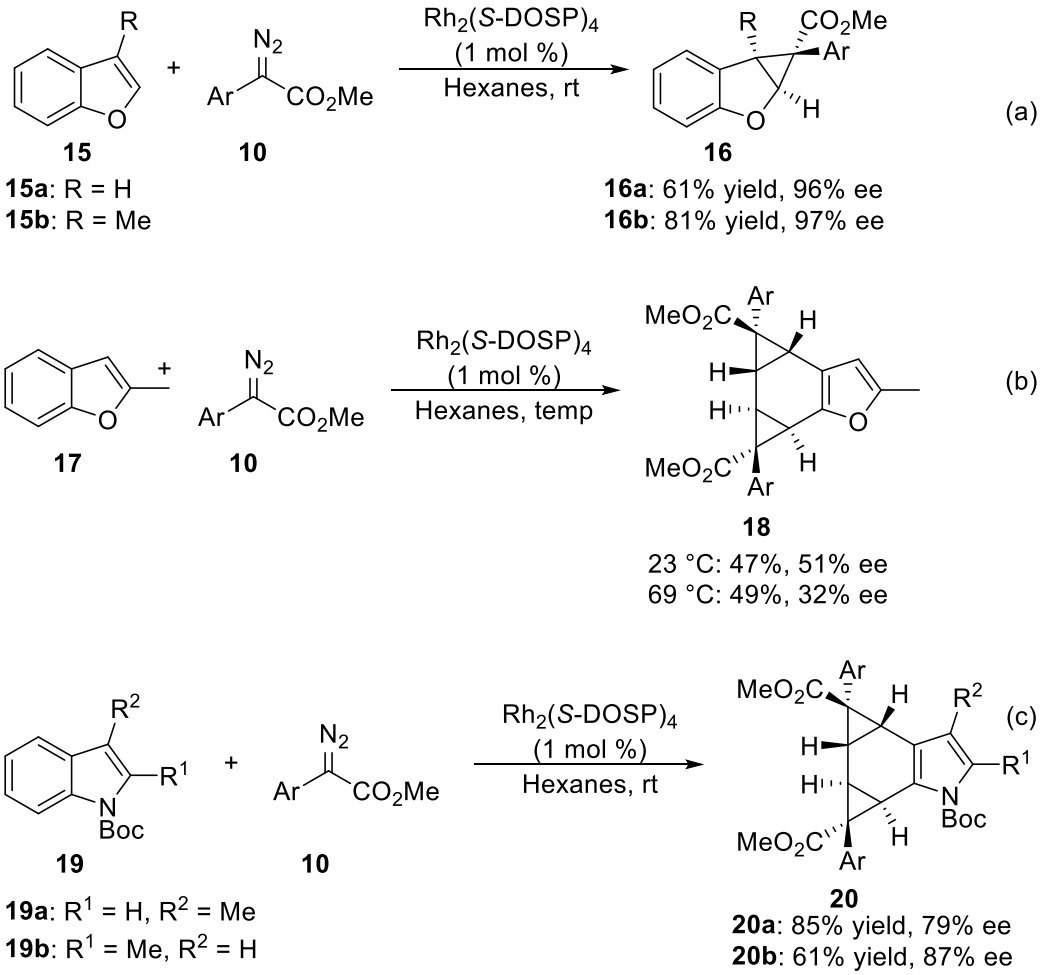
deliver monocyclopropanated furan **11** in 61% yield and 92% ee and di-cyclopropanated **12** in 8% yield and 93% ee (Scheme 2a). In the presence of excess carbene precursor **10**, **12** was the major product, isolated in 68% yield and 96% ee (Scheme 2a). The reaction of neat N-Boc pyrrole **5** delivered cyclopropane product **13** in 54% yield and 79% ee, and di-cyclopropanated **14** in 34% yield and 92% ee (Scheme 2b). Interestingly, the reactions yielded cyclopropanated furans **11** and **12** and cyclopropanated pyrroles **13** and **14** with opposite absolute stereochemistry, despite the reactions occurring in the presence of the same enantiomer of the catalyst.



Scheme 2. *Rhodium-catalyzed enantioselective cyclopropanations of furans and pyrroles with carbenes formed from diazo precursors*

When the authors extended this methodology to include benzofurans **15a** and **15b** as substrates, the system delivered cyclopropanation of the benzofuran C2-C3 with moderate-to-good yield and high enantioenrichment (Scheme 3). The reaction of **15a** with **10** furnished **16a** in 61% yield and 96% ee, while the reaction of **15b** with **10** delivered **16b** in 81% yield and 97% ee (Scheme 3a). However, the reaction of 2-methylbenzofuran **17** with **10** yielded product **18** with di-cyclopropanation of the benzenoid ring and no cyclopropanation of the C2-C3 bond (Scheme 3b). Not surprisingly, higher temperatures were detrimental to the enantioenrichment of the product, as the reaction delivered **18** as a single diastereomer in 47% yield and 51% ee at

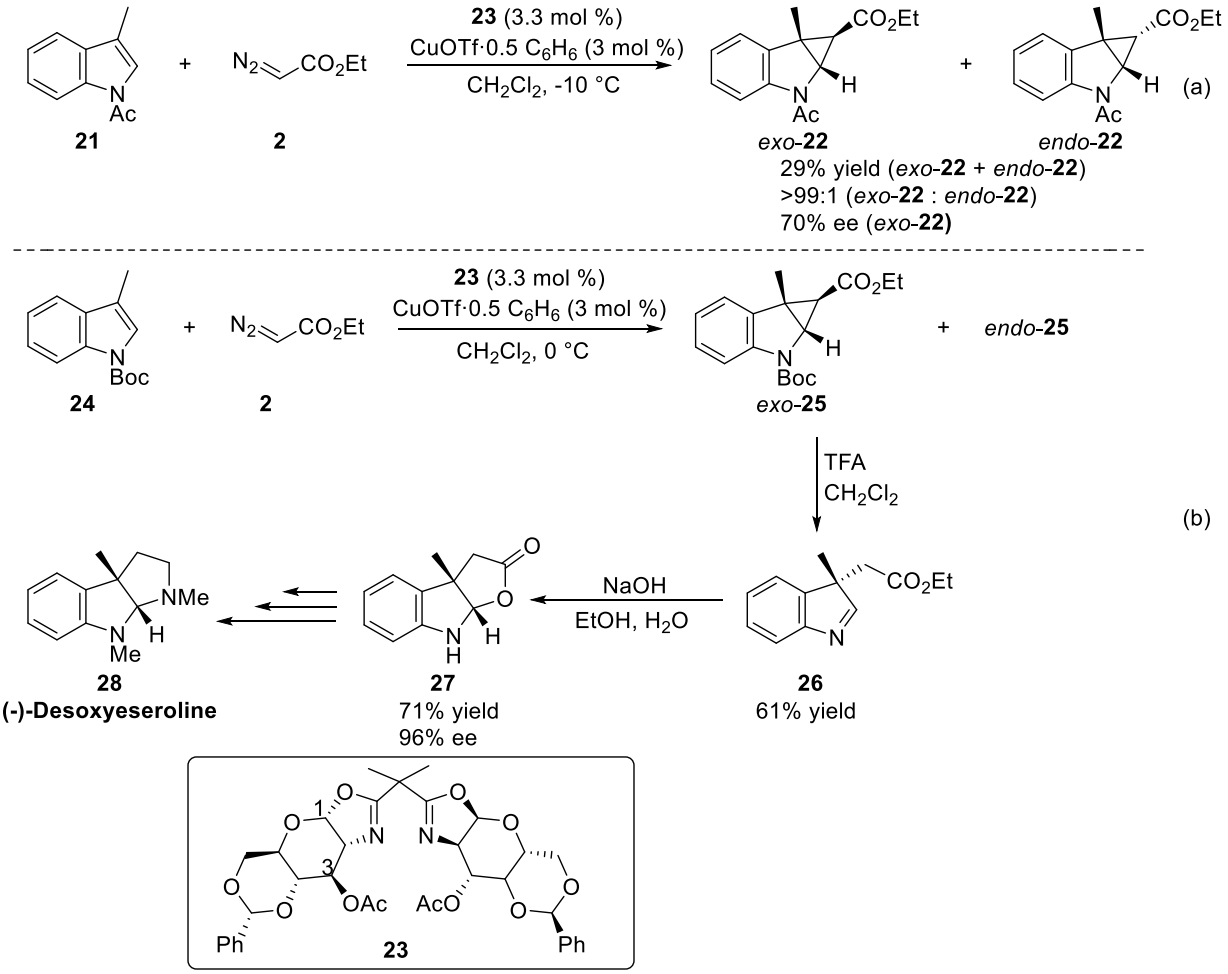
room temperature, and 49% yield and only 32% ee at 69 °C (Scheme 3b). Reactions of 2-methylindole **19a** and 3-methylindole **19b** also resulted in only benzenoid ring cyclopropanation products, although in higher enantioenrichment than the product from the reaction of benzofuran substrate **17** (Scheme 3c).



Scheme 3. *Reactions of benzofurans and indoles with carbene precursor* **10** *in the presence of* Rh_2*(S-DOSP)*$_4$

In 2012, the Boysen group reported catalytic, enantioselective cyclopropanations that selectively cyclopropanated the C2-C3 bonds of N-acylated indoles.[7] The transformation employed ethyldiazoacetate **2** as a carbene precursor and a copper (I) complex of 3-*O*-Ac *gluco*box ligand **23** as a catalyst. At -10 °C, N-acetyl-3-methylindole **21** reacted with **2** in the presence of the catalyst to deliver *exo*-**22** and *endo*-**22** in 29% combined yield, with >99:1

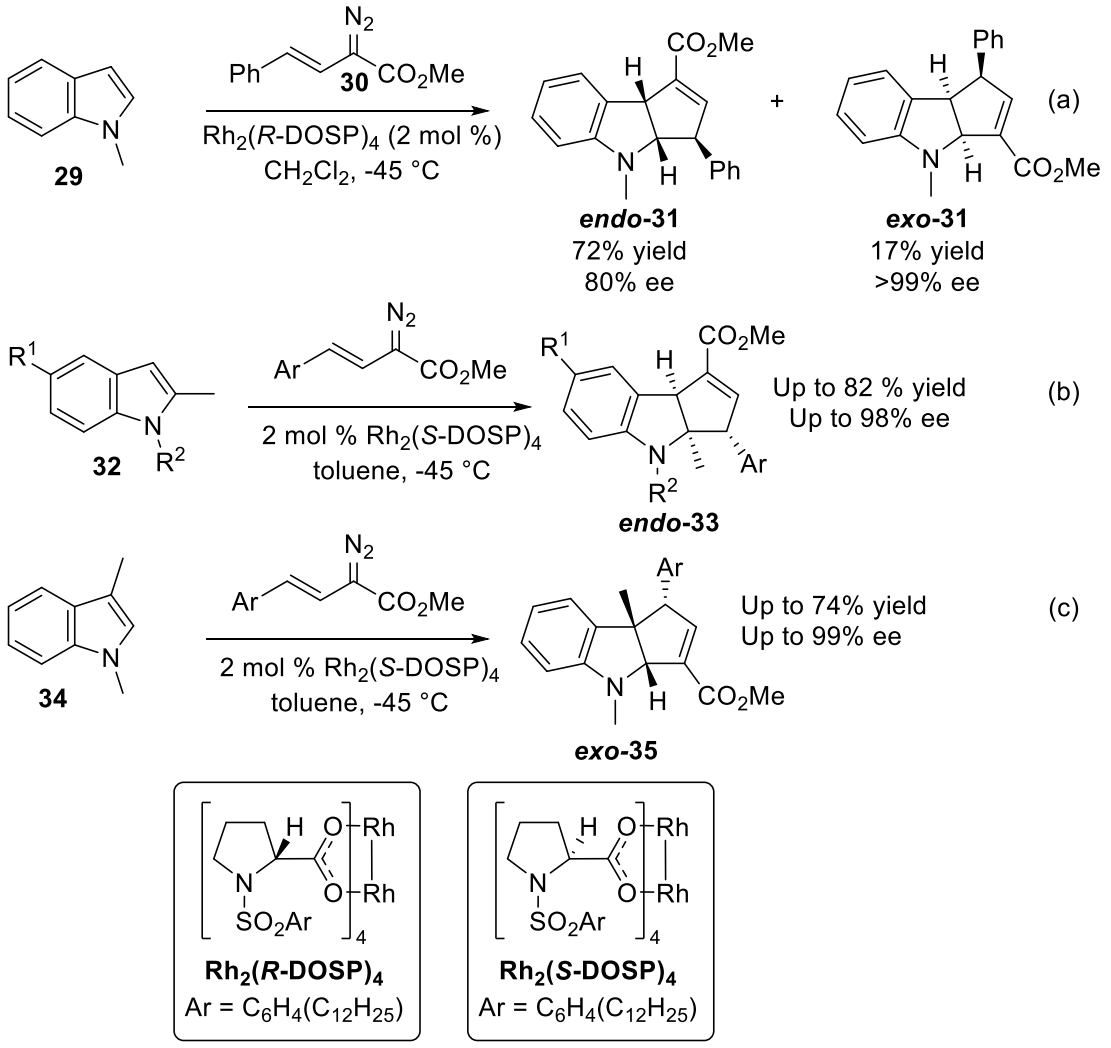
exo:*endo*-selectivity and 70% ee observed in *exo*-**22** (Scheme 4a). The reaction of N-Boc-3-methylindole **24** with **2** resulted in an increase in enantioenrichment to 96% ee, observed upon derivatization of cyclopropanated indole **25** to product **27** by Boc-deprotection and ring opening, followed by lactone formation (Scheme 4b). The enantioenrichment and diastereomeric ratio of products **25** could not be directly observed due to the presence of carbene homocoupling products. **27** was easily transformed to the natural product (-)-Desoxyeseroline **28** (Scheme 4b).



Scheme 4. *Reactions of N-acyl-3-methylindoles with* **2** *in the presence of a Cu(I)-3-O-Ac glucobox catalyst*

In 2010, Davies reported rhodium-catalyzed cyclopentannulations of N-methylindoles with phenylvinyldiazoacetates in the presence of Rh_2(*R*-DOSP)$_4$.[8] N-methylindole **29** reacted smoothly with (*E*)-phenylvinyldiazoacetate **30** in the presence of the rhodium catalyst to afford

regioisomeric *endo*-**31** and *exo*-**31** in a roughly 4:1 ratio (Scheme 5a). This formation of a mixture of regioisomers was unsurprising as vinylcarbenoids can be electrophilic at either the carbenoid or vinylogous sites.[9] In order to gain insight into the reaction mechanism, the authors carried out reactions of 1,2-disubstituted indoles **32** and 1,3-disubstituted indoles **34** with phenylvinyldiazoacetates in the presence of Rh_2(*S*-DOSP)$_4$. The [3+2]-cycloadditions of 1,2-

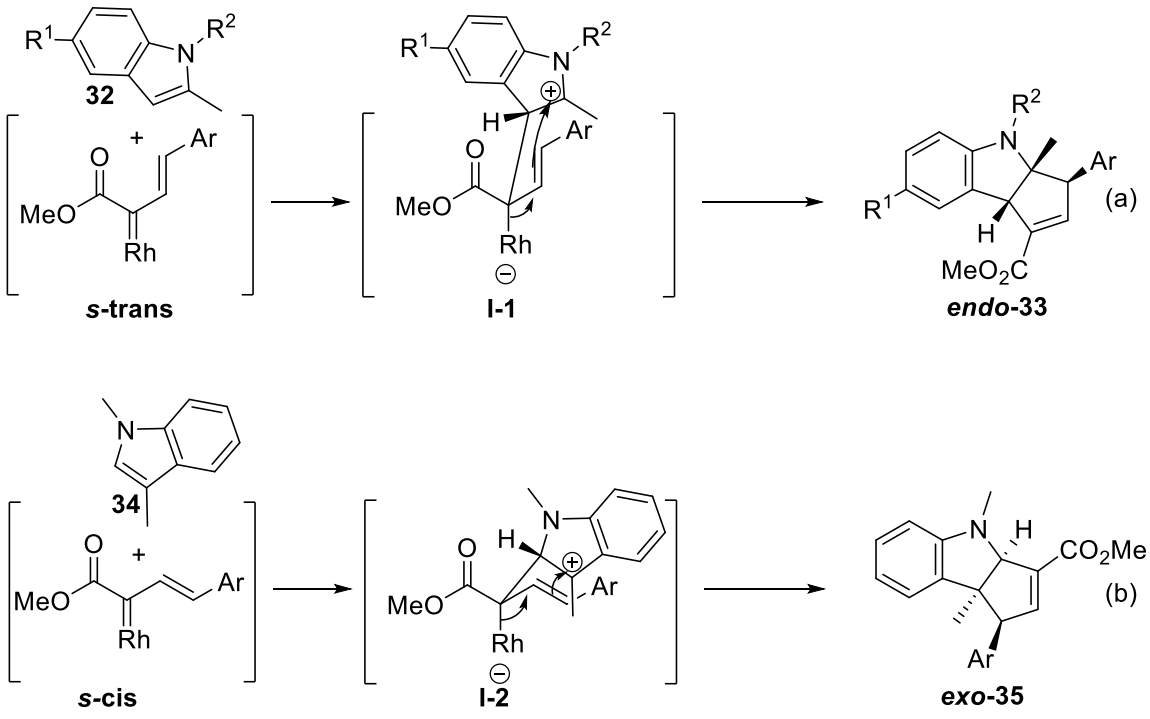


Scheme 5. *Cyclopentannulations of N-methylindoles with phenylvinyldiazoacetates in the presence of Rh_2(DOSP)$_4$*

disubstituted indoles **32** with phenylvinyldiazoacetates occurred with *endo*-diastereoselectivity and high enantioselectivity, and fusion of the indole C3-position to the ester terminus of the vinyl carbenoid (Scheme 5b). In contrast to the regioselectivity and diastereoselectivity observed with

1,2-disubstituted indoles, the reaction conditions applied to 1,3-dimethylindole **34** resulted in *exo*-selectivity and fusion of the indole C3 with the arene terminus of the vinyl carbenoid (Scheme 5c).

It is probable that the observed opposite regiochemical outcomes depending on the utilization of 1,2-disubstituted indoles **32** or 1,3-dimethylindole **34** arise from the approach of the indole to the carbenoid that places the C2- or C3- alkyl group of the indole distal to the prolinate ligand of the rhodium complex (Scheme 6). The diastereochemical outcome is likely to be dictated by the conformation of the vinyl carbenoid prior to ring closure: the reaction manifold to deliver *endo*-**33** likely involves an *s*-trans configured rhodium carbenoid species (Scheme 6a),

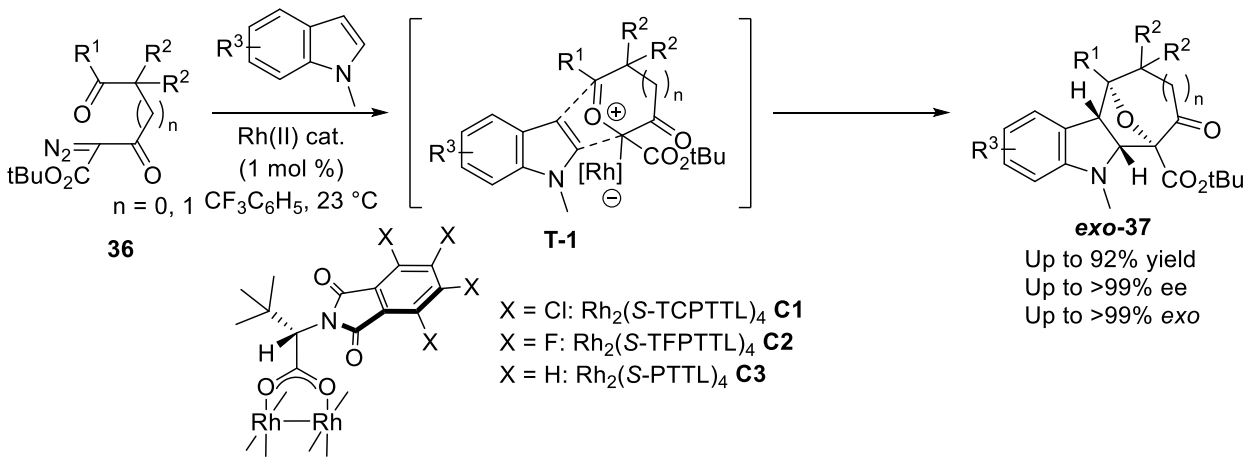


Scheme 6. *Proposed reaction mechanisms of indole cyclopentannulations with rhodium vinyl carbenoids in the presence of a rhodium catalyst*

while the pathway to *exo*-**35** likely involves an *s*-cis configured rhodium carbenoid species (Scheme 6b). It is well established that reactions of N-alkylindoles with rhodium carbenoids proceed via zwitterionic intermediates with the positive charge stabilized by the electron-rich

indole and the negative charge stabilized by the rhodium,[10] making it reasonable to propose **I-1** and **I-2** as intermediates in the reaction pathways that lead to *endo*-**33** and *exo*-**35**. It is also possible that the vinyl group orientation takes place in intermediates **I-1** and **I-2** prior to cyclization. Further mechanistic insight is required to determine at what point the rhodium vinyl carbenoid assumes the proper orientation to subsequently arrive at **I-1** or **I-2**.

Rhodium carbenoids are also useful intermediates in catalytic, enantioselective, dearomative cycloadditions of carbonyl ylides. A report from the Hashimoto group demonstrates the use of diazodiketoesters as cyclic carbonyl ylide precursors in rhodium-catalyzed enantioselective, dearomative cycloadditions with indole dipolarophiles.[11]

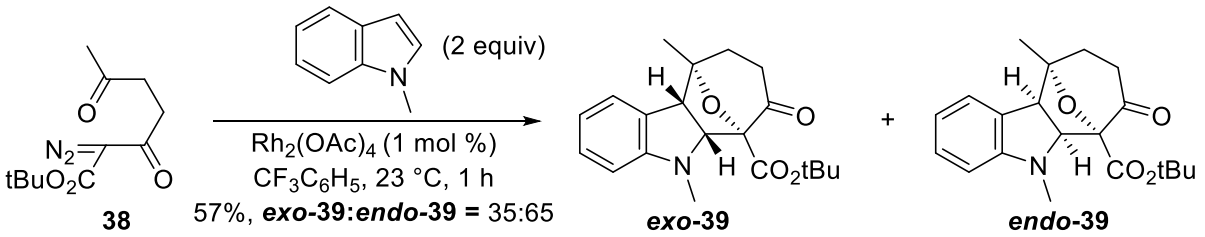


Scheme 7. *Rhodium-catalyzed carbonyl ylide cycloadditions with indole dipolarophiles*

Decomposition of the diazo moiety in **36** to a rhodium carbene, followed by nucleophilic attack of the carbene by the carbonyl oxygen results in a metallated cyclic carbonyl ylide (shown in **T-1**), which subsequently undergoes [3+2] cycloaddition with the indole C2-C3 bond (Scheme 7).

These transformations employed chiral rhodium catalysts **C1-C3** on the basis of previous work.[12] Reactions of carbonyl ylides derived from precursors **36** with indoles delivered cycloadducts *exo*-**37** with excellent enantioenrichment and diastereoselectivity (Scheme 7). Screening of catalysts revealed that the use of **C2** and **C3** as catalysts led to slightly diminished

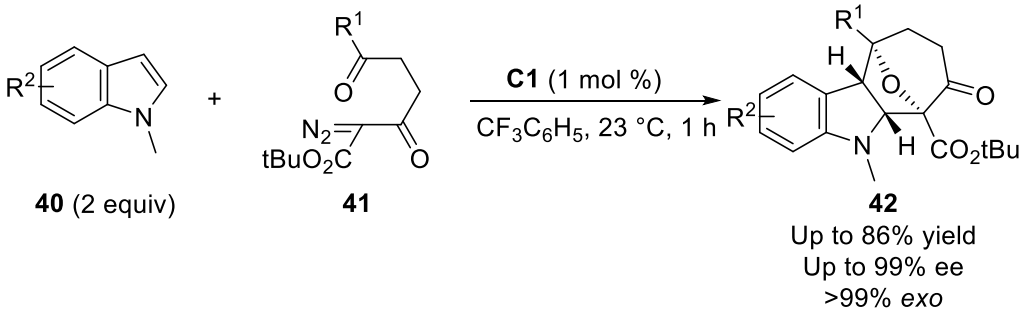
yields and enantioselectivities. The resulting mixture of *exo* and *endo* diastereomers **39** afforded by the reaction in the presence of an achiral rhodium catalyst highlights the necessity of a chiral rhodium catalyst for high diastereoselectivity (Scheme 8). Although the role of the phthalimido groups in the bridging ligands of the dirhodium (II) catalysts **C1-C3** in diastereselection is not entirely clear as of this writing, previous work demonstrates the importance of these groups in this context.[12-13]



Scheme 8. *Reaction of a 6-membered cyclic carbonyl ylide with N-methylindole in the presence of an achiral rhodium catalyst*

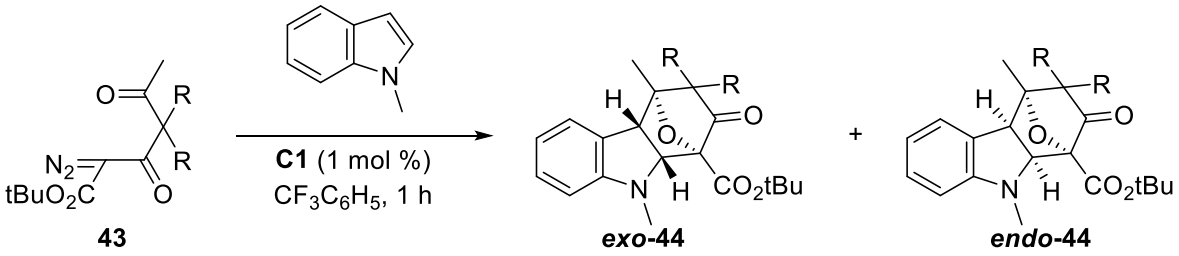
The established catalyst system was effective in cycloadditions of 6-membered cyclic carbonyl ylides. Reactions of indoles **40** with carbonyl ylides derived from precursor **41** in the presence of **C1** delivered indoline products **42** in up to 86% yield and 99% ee, with >99% *exo* selectivity (Scheme 9). The system did not perform as well, however, with 5-membered cyclic carbonyl ylides: reactions of N-methylindole with 5-membered cyclic carbonyl ylides derived from precursors **43** resulted in overall lower yields and enantioselectivities compared to reactions carried out with 6-membered cyclic carbonyl ylides. Reactions of carbonyl ylides derived from *gem*-dimethyl substituted precursors **43** with N-methylindole resulted in high *exo*:*endo* selectivity, but low enantioenrichment in products **44** (Table 1, entries 1-3). The reaction required a spirocyclopropane backbone on precursor **43**, as well as higher temperatures, in order to deliver synthetically useful diastereo- and enantioselectivity in the product mixture (entry 5)**.** These results suggest that 1) the rhodium catalyst is still bound to the carbonyl ylide at higher temperatures, since the carbonyl ylide detached from the catalyst would be achiral;[13d,14] and 2)

immediate trapping of the rhodium-bound carbonyl ylide by the indole is required for high yield, diastereoselectivity, and enantioselectivity.



Scheme 9. *Rhodium-catalyzed cycloadditions of 6-membered cyclic carbonyl ylides with N-methylindoles*

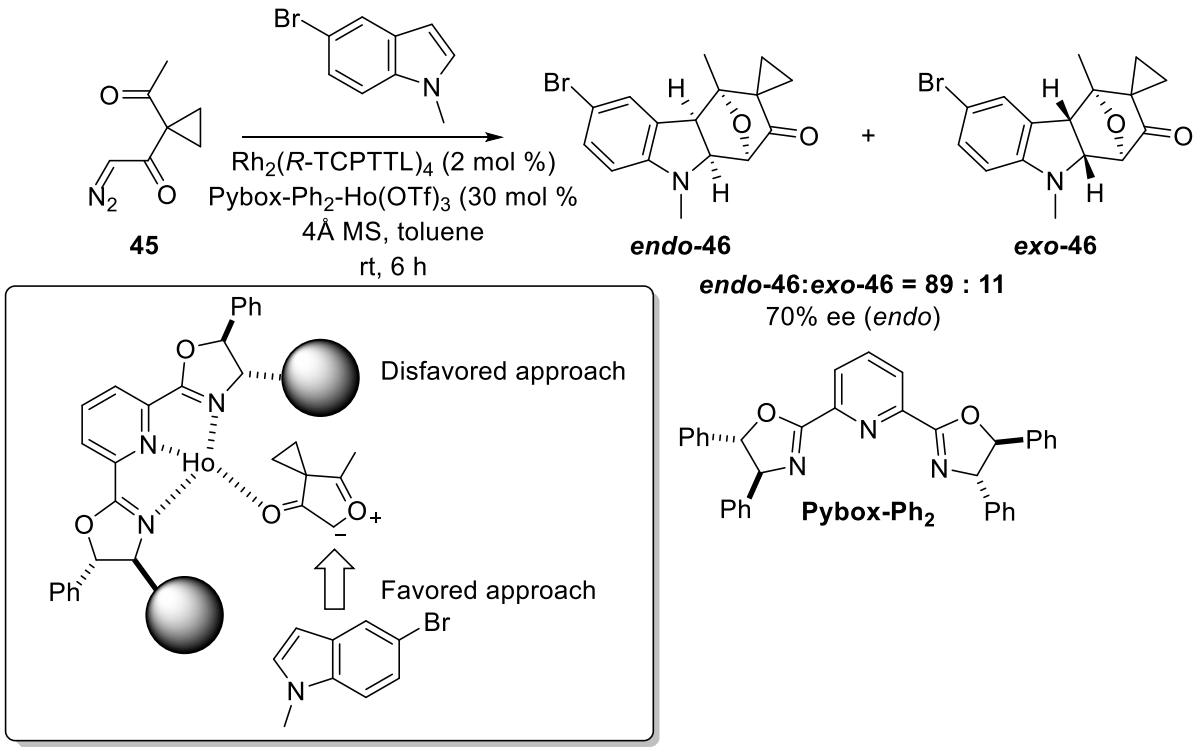
Table 1. *Rhodium-catalyzed cycloadditions of 5-membered cyclic carbonyl ylides with*



Entry	R	Temp (°C)	Yield (%)	*exo*:*endo*	ee *exo* (%)	ee *endo* (%)
1	Me	23	40	>99:1	50	
2	Me	60	84	>99:1	61	
3	Me	80	80	>99:1	59	
4	-CH_2CH_2-	23	69	87:13	82	2
5	-CH_2CH_2-	60	88	92:8	92	2

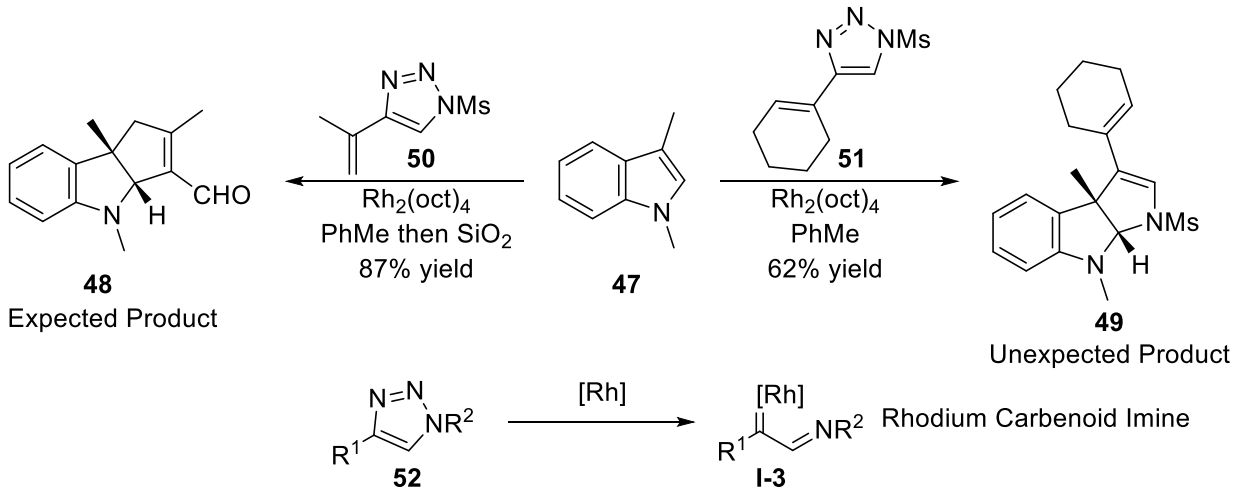
In a recent revisiting of rhodium catalyzed cycloadditions of cyclic carbonyl ylides with indole dipolarophiles, Suga and coworkers approached rhodium-catalyzed cycloadditions of cyclic carbonyl ylides with indoles from the standpoint of a Lewis acid/rhodium dual activation approach, where the rhodium catalyst drove the formation of the carbonyl ylide, and a chiral Lewis acid catalyst guided the approach of the indole dipolarophile to the dipole (Scheme 10).[15] Although this approach with 5-membered cyclic carbonyl ylides still did not deliver synthetically useful enantioenrichment, this catalyst system was notable in that it favored *endo*-**46** with the

proper choice of Lewis acid. This Lewis acid/rhodium dual activation approach thus complements the previous work by Hashimoto which favors *exo* selectivity in reactions of 5-membered cyclic carbonyl ylides with indoles.[11]



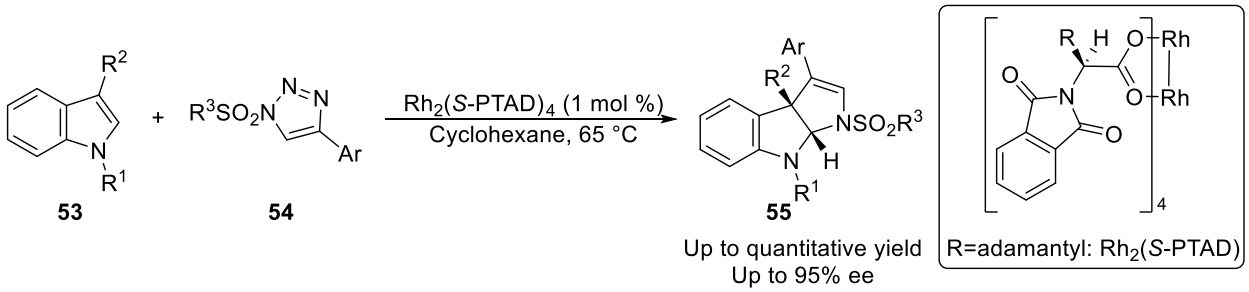
Scheme 10. *Lewis acid/rhodium dual activation strategy for cycloadditions of cyclic carbonyl ylides with indole dipolarophiles*

In 2013 the Davies group reported rhodium-catalyzed dearomative cycloadditions where 1,2,3-triazoles functioned as rhodium-carbenoid precursors.[16] A serendipitous discovery (Scheme 11) opened the door for the synthesis of pyrroloindolines via cycloadditions of N-alkylindoles with rhodium carbenoid imines.[16] 1,3-dimethylindole **47** reacted with triazole **50** in the presence of $Rh_2(oct)_4$ to yield aldehyde **48** as expected after hydrolysis of the resultant N-sulfonylimine. However, the corresponding reaction of **47** with triazole **51** yielded unexpected pyrrolo[2, 3*b*]indole **49**.

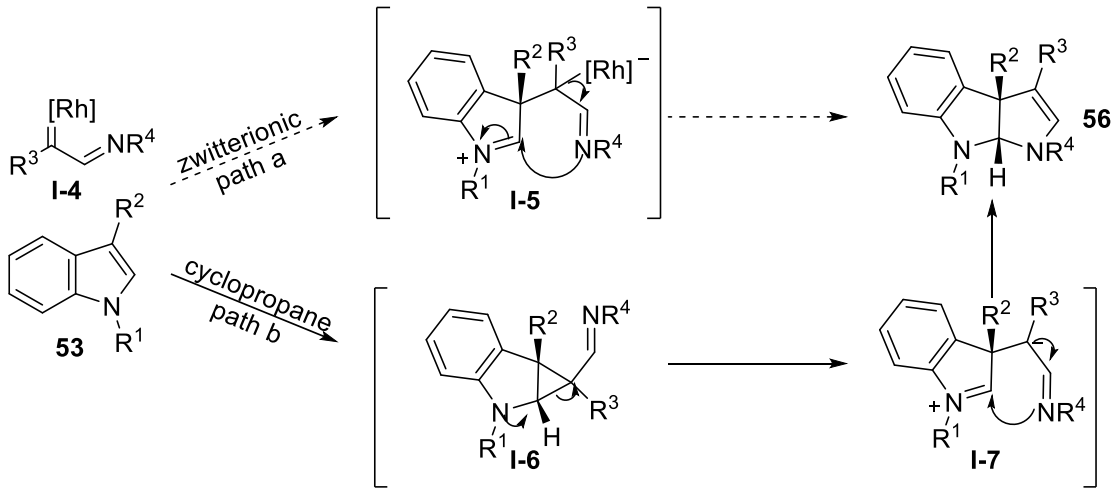


Scheme 11. *Serendipitous discovery of cycloadditions of indoles with rhodium carbenoid imines to deliver pyrroloindolines*

The formation of unexpected **49** led the authors to explore reactions of 4-arylsubstituted triazoles with indoles. 1,3-disubstituted indoles **53** reacted with triazoles **54** in the presence of Rh_2(*S*-PTAD)$_4$ to deliver products **55** in up to quantitative yield and 95% ee (Scheme 12). While the reaction tolerated of a wide range of functional groups on the aryl ring of the triazole and on the indole, it was intolerant of bulky groups (TBS, Bn) or electron-withdrawing groups (Ts, CO_2Me, Boc) on the indole nitrogen, as well as bulky substituents at the 1-position of the triazole. The formation of a pyrroloindoline product, coupled with the failure of the reaction in polar solvents, led the authors to propose a reaction mechanism that involved an initial cyclopropanation of the C2-C3 bond of the indole to form cyclopropane intermediate **I-6** followed by ring opening and recombination via intermediate **I-7** to form product **56** (Scheme 13).



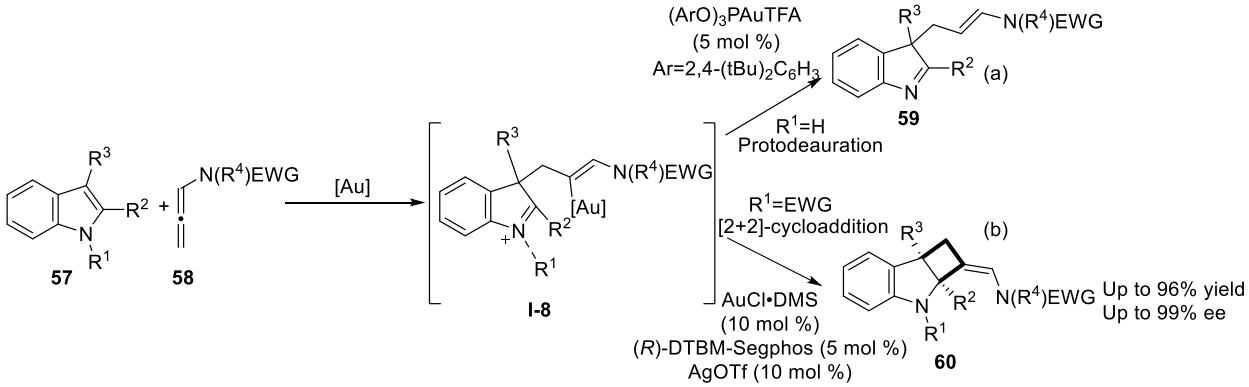
Scheme 12. *Formal cycloadditions of rhodium carbenoid imines with 1,3-dialkylindoles*



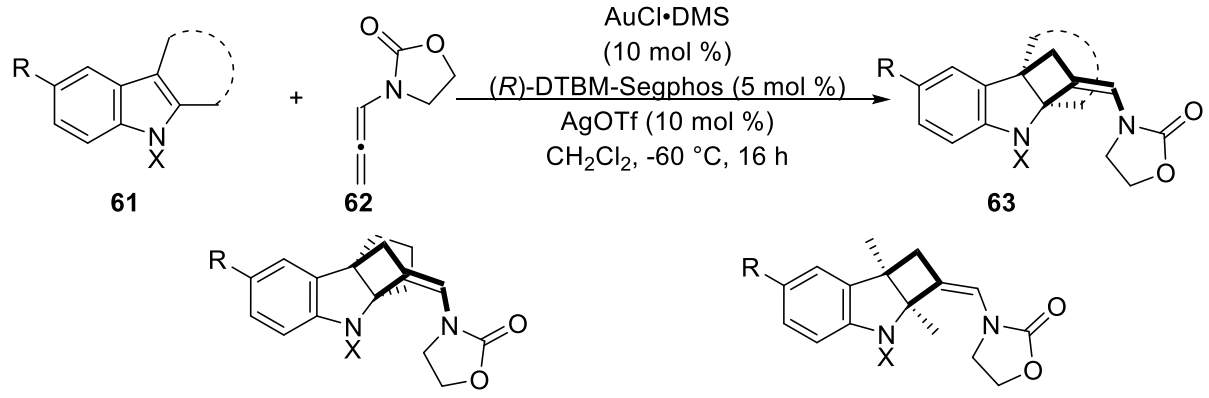
Scheme 13. *Proposed mechanistic pathways of pyrroloindoline formation in cycloadditions of rhodium carbenoid imines with indoles*

Recently, Bandini and coworkers[17] reported enantioselective gold-catalyzed [2+2] cycloadditions of alleneamides with indoles. Previous reactions of N-unsubstituted indoles with alleneamides delivered C-3 allylated products **59** (Scheme 14a) with no cycloadducts observed.[18] An electron-withdrawing group on the indole nitrogen rendered the indole C-2 position in **I-8** more electrophilic and an electron-rich phosphine made the gold center more nucleophilic, allowing for protodeauration to be outpaced by ring closure to deliver of indoline cyclobutanes **60** in good yields and high enantioselectivities (Scheme 14b). These reactions tolerated a wide range of substituents and occurred with perfect diastereoselectivity and *Z*-alkene selectivity. C2-C3 annulated indoles and 2,3-dialkylated indoles were effective dienophiles in these [2+2]-

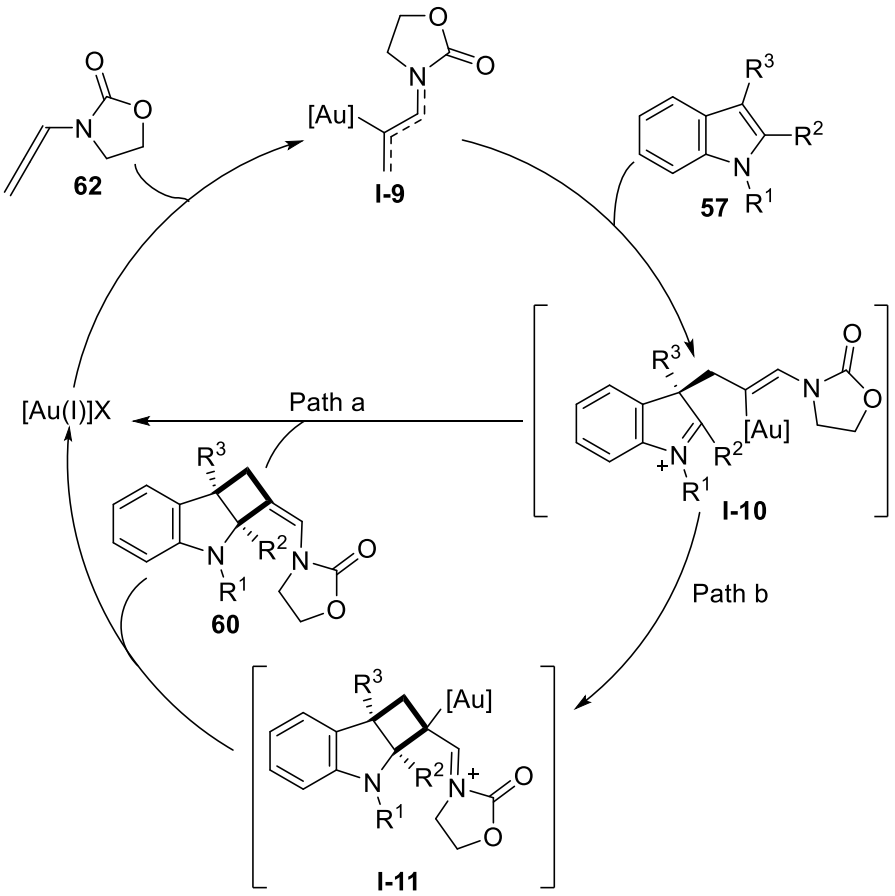
cycloadditions, with representative examples shown in Scheme 15. A 5-bromo substituent on the indole decreased the overall yield, but with no erosion in enantioselectivity (**63c**). Replacement of the indole N-Boc substituent with an N-CBz resulted in a lower but satisfactory yield (**63d**). Finally, the reaction carried out with an N-unsubstituted indole resulted in only 8% yield, highlighting the requirement for substitution at the indole nitrogen (**63e**). The exclusive *Z*-geometry of the alkene can likely be attributed to a ring closure that occurs simultaneously with deauration (Scheme 16, path a).



Scheme 14. *Gold-catalyzed reactions of indoles with allenamides to deliver C-3 allylated indoles and indoline-cyclobutanes*



Scheme 15. *Gold-catalyzed [2+2]-cycloadditions of indoles with alleneamides*



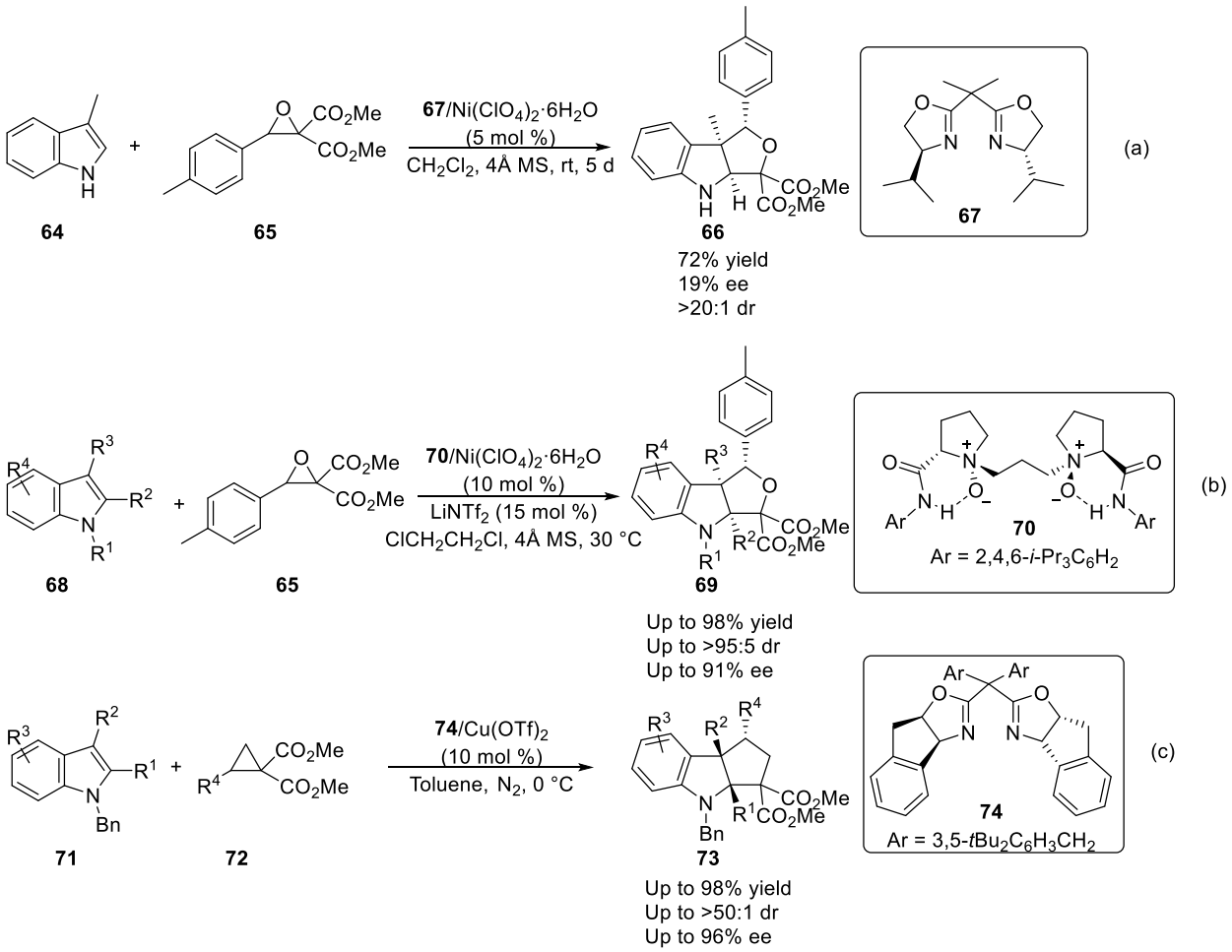
Scheme 16. *Proposed catalytic cycle for gold-catalyzed [2+2]-cycloadditions of indoles with alleneamides*

Enantioselective dearomative cycloadditions catalyzed by chiral Lewis acids

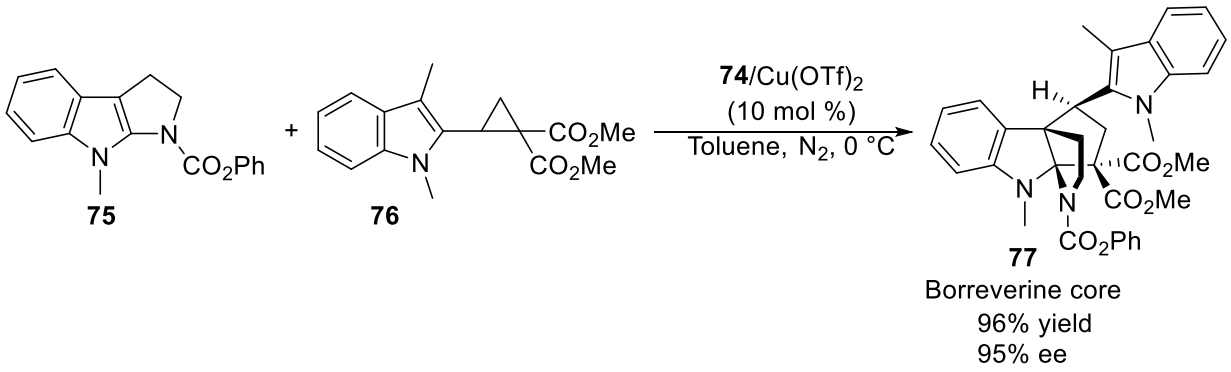
Chiral Lewis acid catalysts provide directional activation with the intention of favoring a certain stereochemical outcome as well as the advantage of a well-defined coordination environment around the metal center.[19] With these attributes in mind, they have been studied as catalysts in enantioselective, dearomative cycloadditions. Selected examples are reviewed herein where Lewis acids activate reagents to allow dearomative cycloadditions to occur with high enantioselectivity.

Donor-acceptor epoxides and donor-acceptor cyclopropanes have been used as annulation partners in dearomatizing cycloadditions with indoles. From the reaction of 3-methylindole **64** with oxiranyl dicarboxylate **65** in the presence of the complex generated from

$Ni(ClO_4)_2$ and bisoxazoline ligand **67**, Zhang and coworkers isolated furo[3, 4*b*]indole **66** in 72% yield with 19% ee and >20:1 dr (Scheme 17a).[20] Feng and coworkers created a more suitable catalyst for cycloadditions of oxiranyl dicarboxylate **65** with indoles **68** where a complex derived from $Ni(ClO_4)_2$ and chiral *N*, *N´*-dioxide ligand **70** was operative.[21] In this case, addition of $LiNTf_2$ to the reaction led to a more Lewis acidic nickel (II) species generated upon ion exchange.[22] The reaction carried out with 1,3-dialkylindoles **68** in the presence of the nickel catalyst furnished cycloadducts **69** in up to 98% yield, >95:5 dr, and up to 91% ee (Scheme 17b). Unsurprisingly, reactions of oxiranyl dicarboxylates bearing electron-neutral and electron-withdrawing aryl groups were not suitable carbonyl ylide precursors in this chemistry. The Tang group developed cycloadditions of donor acceptor cyclopropanes **72** with N-benzyl substituted indoles **71**, catalyzed by the complex of $Cu(OTf)_2$ and bisoxazoline ligand **74**, to deliver cyclopenta-fused indolines **73** in up to 98% yield, >50:1 dr, and 96% ee (Scheme 17c).[23] In the presence of this catalyst, fused tricyclic indole **75** underwent cycloaddition with donor-acceptor cyclopropane **76** to generate **77**, the core structure of Borreverine, in 96% yield and 95% ee as a single diastereomer (Scheme 18). In addition to the rhodium-catalyzed cyclopentannulations developed by Davies,[8] the cycloadditions developed by Tang provide another route for the enantioselective synthesis of cyclopenta-fused indolines.

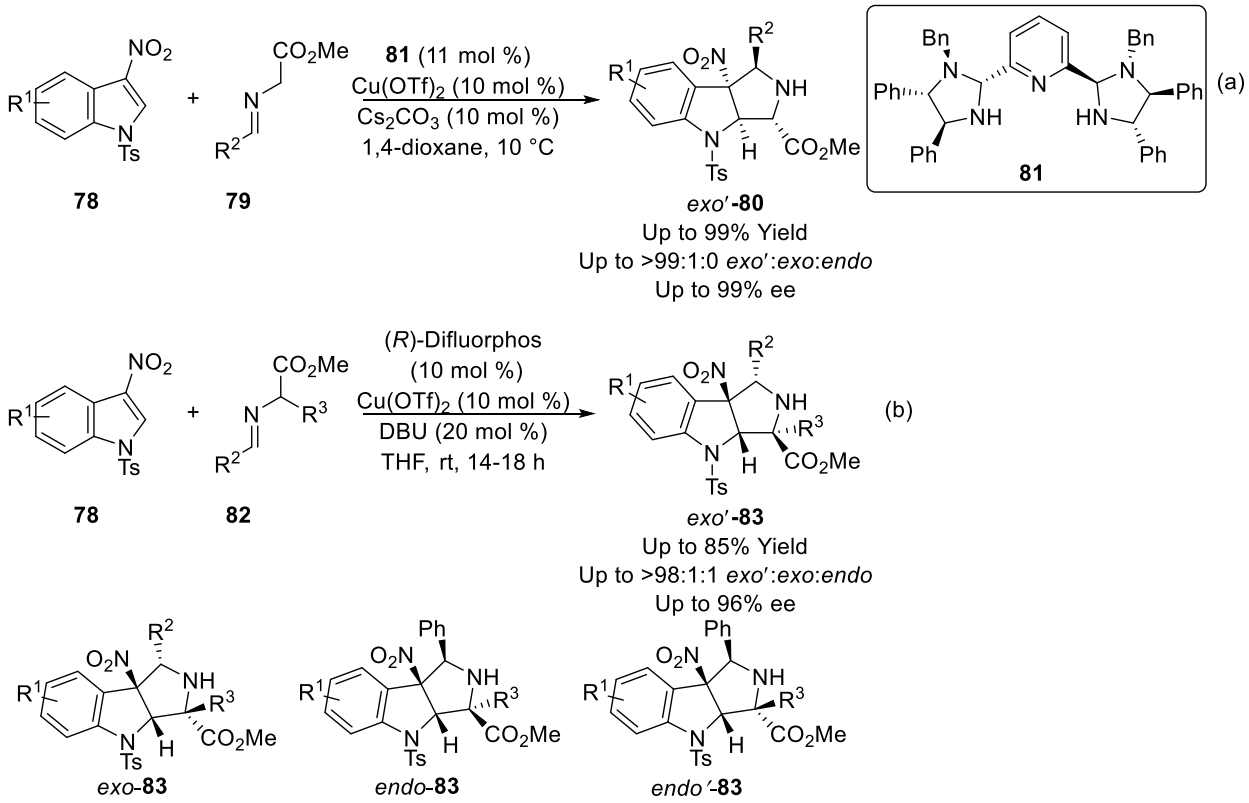


Scheme 17. *Lewis acid-catalyzed cycloadditions of indoles with donor-acceptor cyclopropanes*

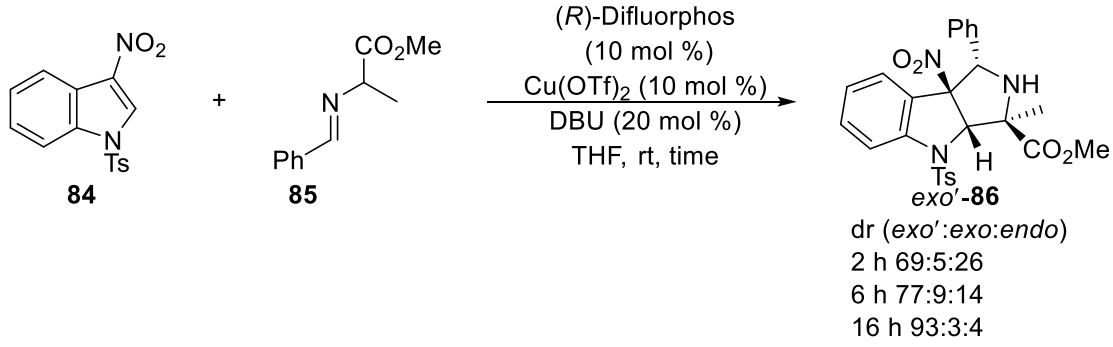


Scheme 18. *Application of Tang method[23] to the synthesis of Borreverine core*

Cycloadditions of azomethine ylides with aromatic dipolarophiles are another promising route to the rapid generation of polycyclic architectures.[24] Gribble and coworkers initially reported cycloadditions of highly reactive, unstabilized azomethine ylides with 2- and 3-nitroindoles to generate racemic pyrroloindolines.[25] More recently, Chataingner, Piettre and coworkers demonstrated that racemic cycloadditions of unstabilized azomethine ylides were possible with a broad scope of electron-deficient aromatic dipolarophiles.[26] In 2014, Arai and coworkers reported the first catalytic, enantioselective reactions of azomethine ylides with 3-nitroindoles to deliver pyrrolo[3, 4*b*]indoles.[27] Reactions of glycine-derived imino esters **79** with 3-nitroindoles **78** in the presence of the complex of $Cu(OTf)_2$ and PyBidine ligand **81** afforded pyrroloindolines *exo´*-**80** with high yield, diastereoselectivity, and enantioselectivity (Scheme 19a). Our group concurrently reported cycloadditions of azomethine ylides generated from α-substituted imino esters **82** with 3-nitroindoles **78**.[28] These reactions occurred in the presence of a $Cu(OTf)_2$/(*R*)-Difluorphos complex to deliver cycloadducts *exo´*-**83** in up to 85% yield, 98:1:1 *exo´*:*exo*:*endo* diastereoselectivity, and up to 96% ee (Scheme 19b). Interestingly, we observed in the cycloaddition of 3-nitro-N-tosylindole **84** with **85** in the presence of the copper catalyst the initial formation of a significant amount of *endo*-**85**, which epimerized to *exo´*-**85** as the reaction progressed. At two hours of reaction time, the observed *exo´*:*exo*:*endo* ratio was 69:5:26 (Scheme 20). After 6 hours, the ratio observed was 77:9:14, and at 16 hours it was 93:3:4 (Scheme 20). In the absence of the copper complex, the *exo´*:*exo*:*endo* remained approximately 60:10:30 throughout the entire course of the reaction, demonstrating that little epimerization occurs in the absence of the copper catalyst. The epimerization likely occurs via a *retro*-Mannich/Mannich reaction manifold.[29]



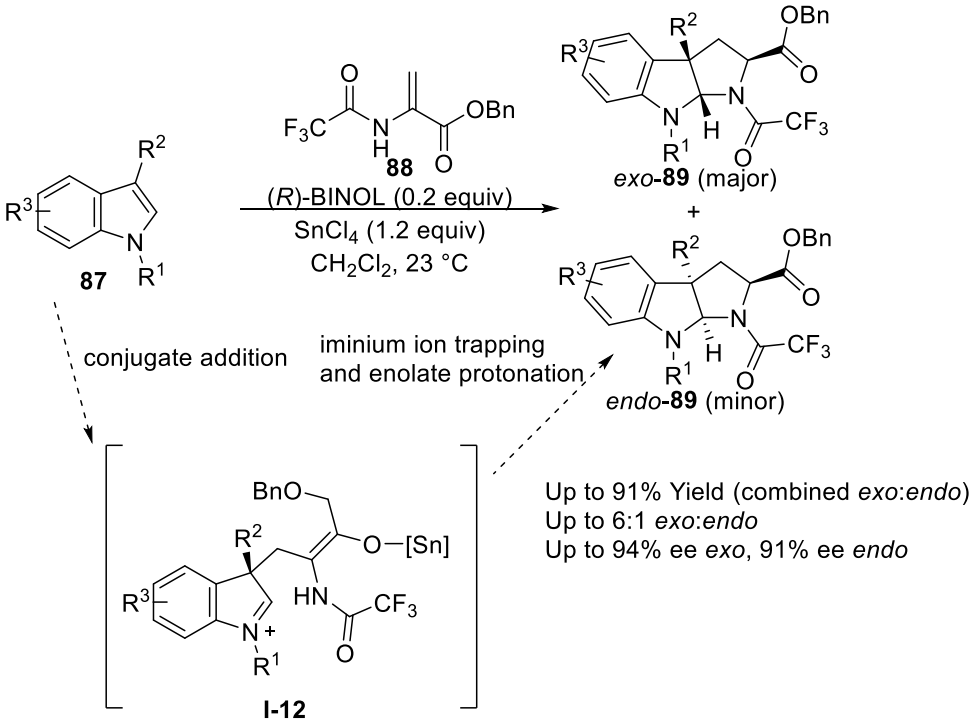
Scheme 19. *Copper-catalyzed azomethine ylide cycloadditions with 3-nitroindoles*



Scheme 20. *Evolution of diastereoselectivity over time in copper-catalyzed cycloadditions of azomethine ylides with 3-nitroindoles*

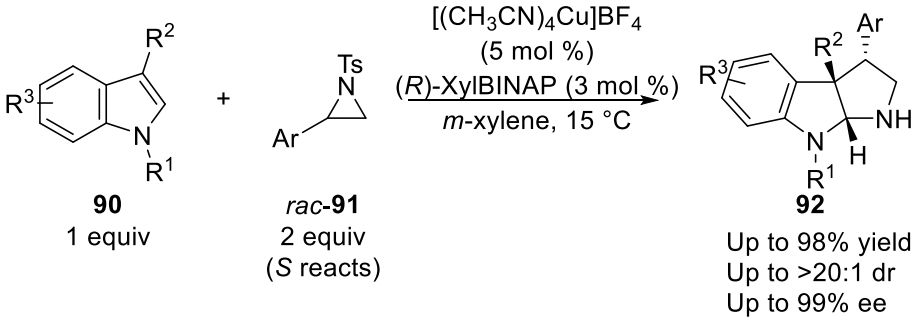
In 2010, the Reisman group reported catalytic, enantioselective, dearomative formal [3+2] cycloadditions of indoles **87** with 2-amidoacrylates **88** in the presence of a Sn/(*R*)-BINOL catalytic complex to deliver diastereomeric mixtures of pyrrolo[2, 3*b*]indoles *exo*-**89** and *endo*-**89** (Scheme 21).[30] The authors propose a stepwise reaction mechanism where a chiral Lewis acid activates the acrylate carbonyl toward conjugate addition by the indole, generating intermediate **I-12**. Iminium ion trapping and enolate protonation then deliver cycloadducts *exo*-

89 and *endo*-**89**, both with high enantioenrichment. Notably, the reaction pathways to form *exo*-**89** and *endo*-**89** operate on opposite faces of the indole, leading to opposite absolute stereochemistry at the carbons where the 5-membered rings are fused.



Scheme 21. *(R)-BINOL/$SnCl_4$ catalyzed formal cycloadditions of 2-amidoacrylates with indoles*

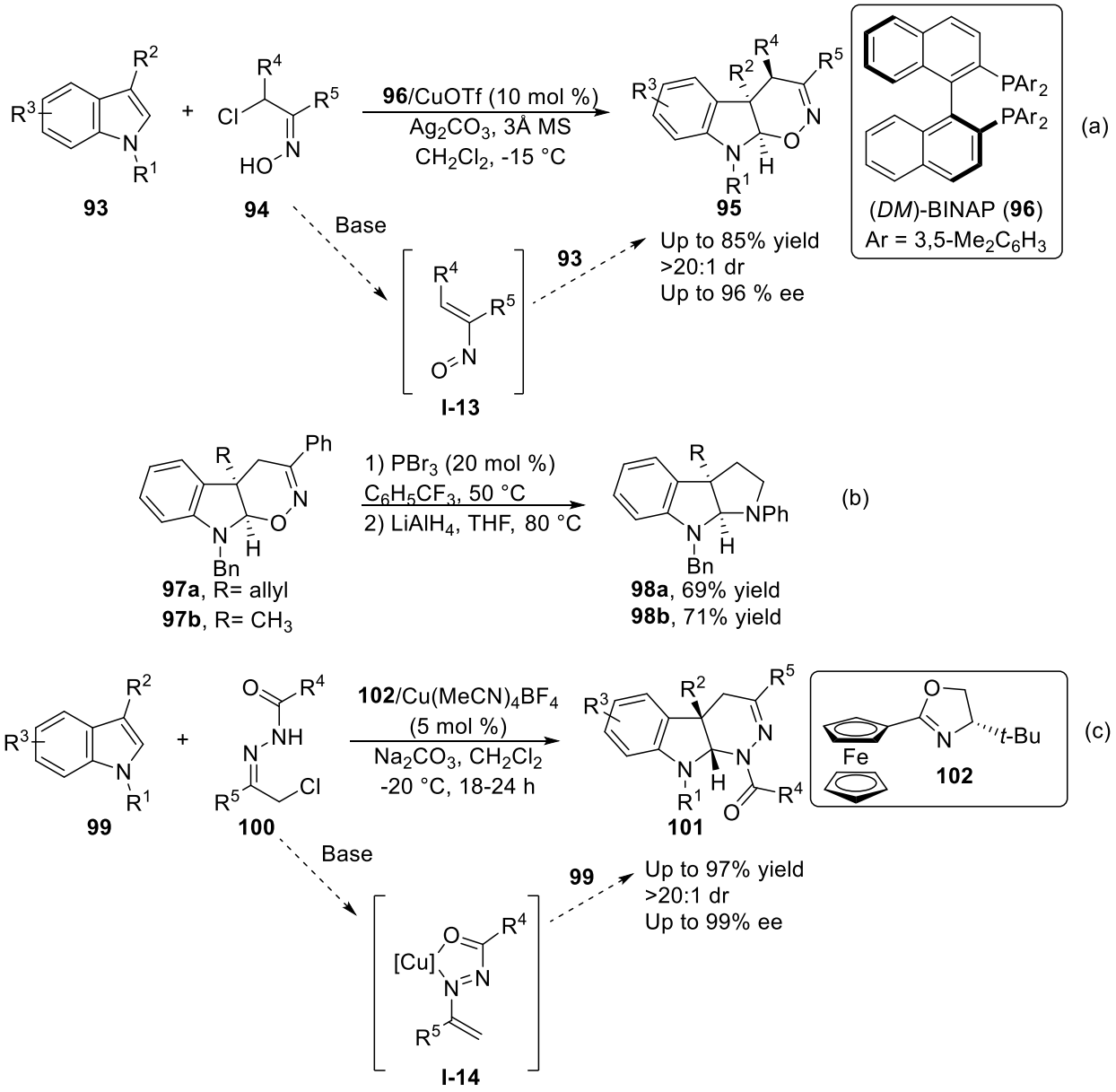
A report from Chai discloses copper-catalyzed enantioselective cycloadditions of 2-aryl-N-tosyl aziridines with indoles via kinetic resolutions of 2-aryl-N-tosylaziridines, generating enantioenriched pyrrolo[2, 3*b*]indoles.[31] Copper(I) complexes of (*R*)-XylBINAP preferentially catalyzed the reaction of *S*-**91** with indoles **90** to deliver pyrrolo[2, 3*b*]indoles **92** in up to 98% yield with >20:1 dr and up to 99% ee (Scheme 22). The reaction scope encompassed a broad array of aziridines, and it was notable that aziridines with electron-deficient aryl groups reacted sluggishly to give low yields of cycloadducts.



Scheme 22. *Catalytic, enantioselective cycloadditions of N-tosylaziridines with indoles via kinetic resolution*

Recent work demonstrates that chiral Lewis acids are effective as enantioselective catalysts in dearomative Diels-Alder reactions where arenes function as dienophiles. Reports from the groups of Larianov[32] and Wang[33] disclose inverse electron-demand Diels-Alder reactions where heterodienes are generated *in situ* via dehydrohalogenation of heterodiene precursors. Chiral Lewis acids control the approach of the aromatic dienophiles to the dienes, resulting in highly enantioenriched products (Scheme 23). Larianov reported enantioselective Diels-Alder reactions between 1,3-dialkylsubstituted indoles **93** and transient nitrosoalkene species **I-13**, generated *in situ* from chlorooxime **94** (Scheme 23a).[32] The reactions occurred in the presence of a complex generated from CuOTf and (*DM*)-BINAP **96** to afford cycloadducts **95** in up to 85% yield, >20:1 dr, and up to 96% ee. The authors report that the catalyst is very sensitive to the presence of chloride ions, necessitating the use of silver carbonate, which functions as a base and a sequestering agent for chloride ions generated by the dehydrohalogenation process. A PBr_3-catalyzed Beckman rearrangement of oxazine products **97a** and **97b** proceeded smoothly to deliver pyrrolo[2, 3*b*]indoles **98a** and **98b** (Scheme 23b), providing an additional route to pyrroloindoline scaffolds. Wang's group demonstrated that azadienes **I-14**, generated *in situ* from hydrazones **100**, reacted smoothly with 1,3-dialkyl substituted indoles **99** in the presence of Cu(I) and Phosferrox ligand **102** to deliver

terahydropyridazine products **102** in high yields with good enantio- and diastereoselectivity (Scheme 23c).[33]

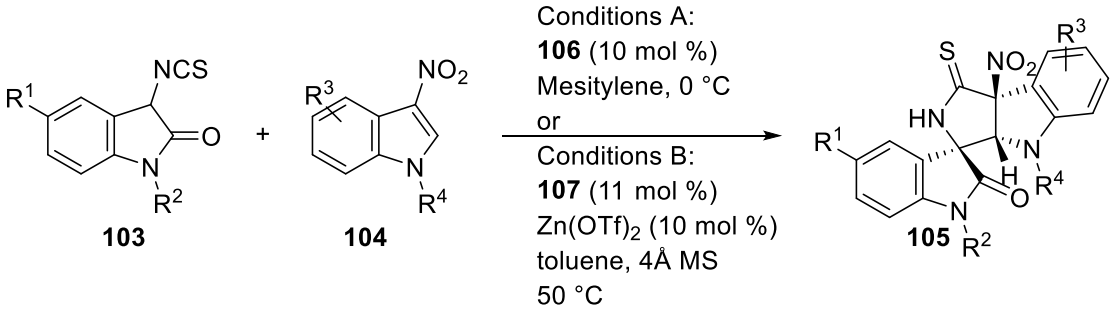


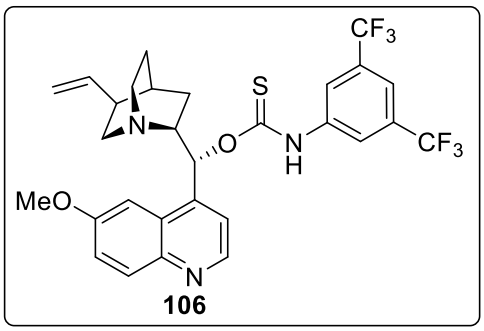
Scheme 23. *Lewis acid-catalyzed enantioselective dearomative Diels-Alder reactions with indole dienophiles*

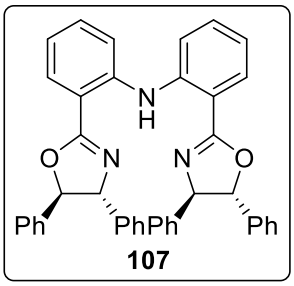
Yuan and coworkers recently reported organocatalyzed[34] and chiral Lewis acid-catalyzed[35] cycloadditions of 3-isothiocyanatooxindoles **103** with 3-nitroindoles **104** to generate enantioenriched polycyclic spirooxindoles **105** (Table 2). Organocatalyzed reactions of **103** with **104** occurred in the presence of chiral bifunctional organocatalyst **106**. The authors propose that

the substrate-catalyst diastereomeric transition state that delivers enantioenrichment is achieved via a hydrogen bonding interaction between the thioamide N-H of **106** and the nitro-group of **104**. This hydrogen-bonding interaction also activates the indole for the Michael addition of the enolate of **103** to the C2 position of the indole, which is followed by cyclization. As shown in Table 2, the organocatalyzed process was extremely sensitive to the nature of the N-protecting groups of **103** and **104**. Reactions of **103** and **104** in the presence of $Zn(OTf)_2$ and diphenylamine-linked-bisoxazoline ligand **107** were much less sensitive to the nature of the N-protecting groups of **103** and **104**, as this catalyst could deliver high diastereo- and enatnioselectivity with a broader array of substrates (Table 2).

Table 2. *Comparison of organocatalyzed and Lewis-acid catalyzed cycloadditions of 3-isothiocyanato oxindoles with 3-nitroindoles*



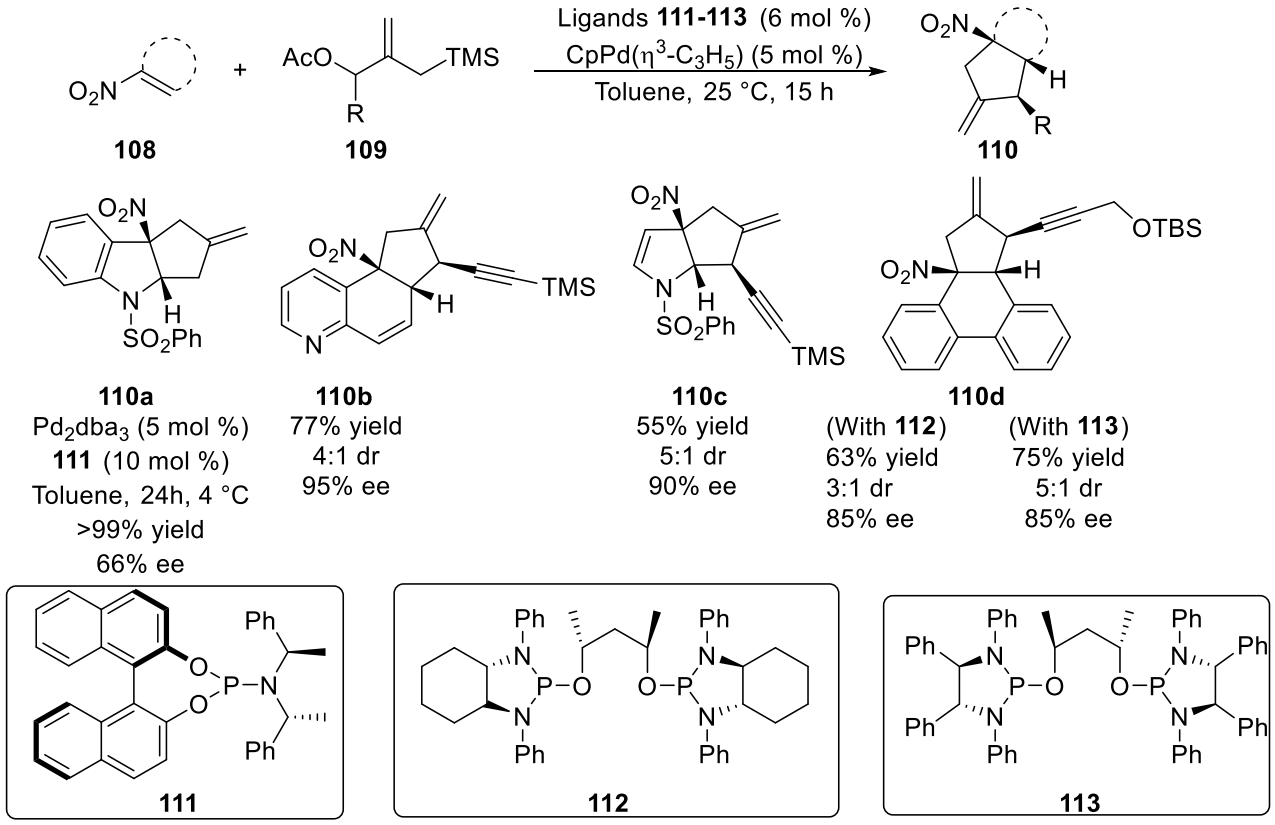




R^4, R^2	Conditions A	Conditions B
R^4 = Ts, Bs; R^2 = Me	82:18->99:1 dr, 59-96% ee	93:7-99:1 dr, 91-99% ee
R^4 = Ms, Ns, CBz, Boc, CO_2Et,; R^2 = Me	50:50-91:9 dr, 31-83% ee	>99:1 dr, 98-99% ee
R^4 = Ts; R^2 = Et, Bn, Ph	79:21-86:14 dr, 36-40% ee	85:15->99:1 dr, 92-98% ee

Enantioselective dearomative cycloadditions via cascade reactions involving allylic substitution

Dearomative cycloadditions via cascade reactions involving allylic substitution rely on the *in situ* formation of a species that contains an electrophilic metal-allyl functionality and a nucleophilic moiety. This species can react with a 2π-electron reaction partner in an asynchronous process.[36] In 2014, the Trost group reported palladium-catalyzed trimethylenemethane (TMM) cycloadditions with nitroarenes (Scheme 24).[37] Under the

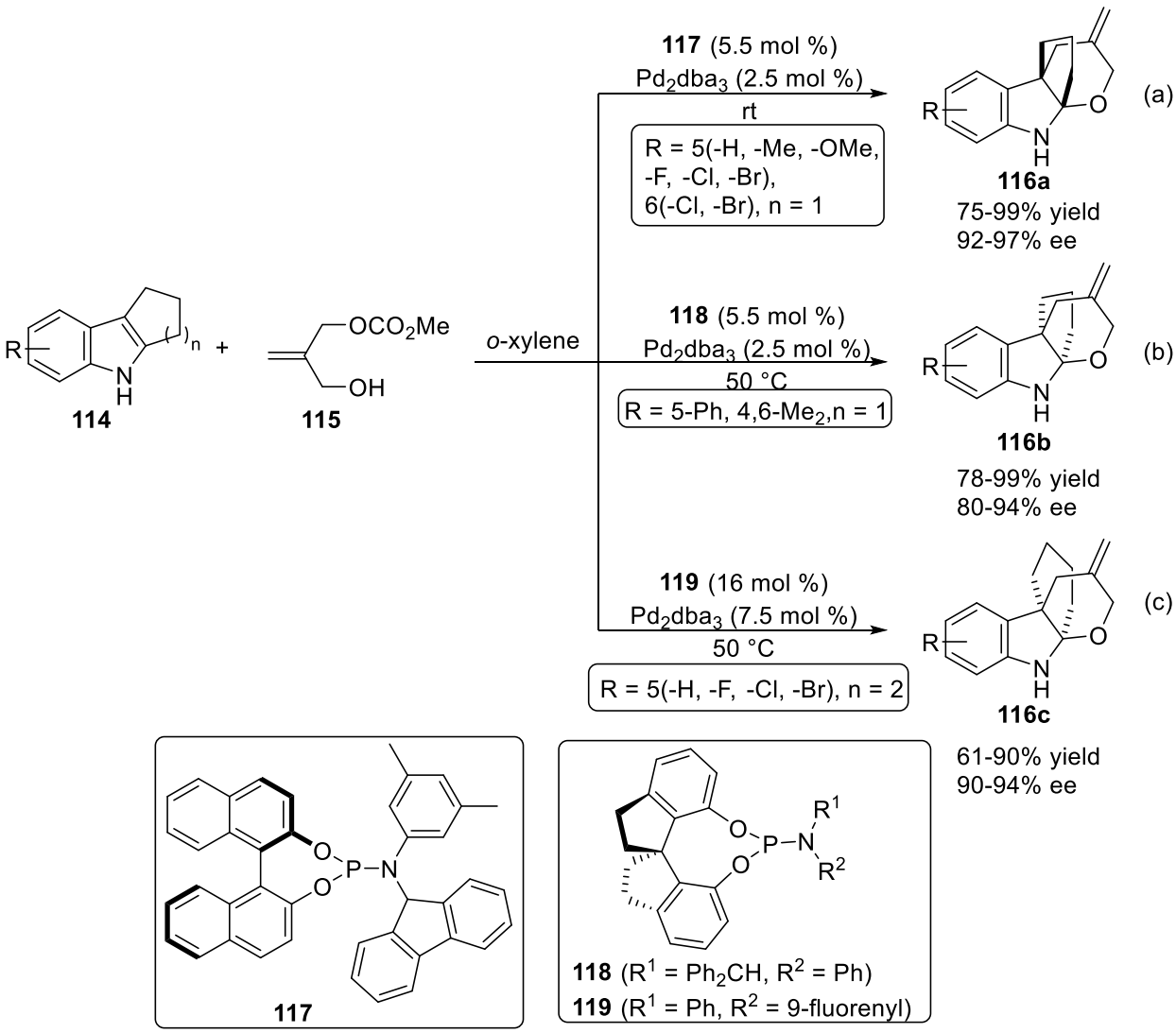


Scheme 24. *Palladium-catalyzed trimethylenemethane cycloadditions with arenes*

palladium-catalyzed conditions, the TMM unit generated *in situ* from silyl acetate **109** includes an electrophilic palladium allyl complex and a negatively charged nucleophilic site.[36] Phosphoramidite ligands **111-113** were suitable ligands for this transformation. This method is notable in that it not only provides another means for catalytic, enantioselective dearomative

cyclopentannulations of indoles, it also overcomes the problem of rearomatization by the extrusion of nitrous acid, observed previously in TMM cycloadditions with nitroarenes.[38]

The You lab recently reported a dearomative cycloaddition cascade reaction involving the attack of cycloalkyl-fused indoles **114** on a palladium-allyl species generated from 2-



Scheme 25. *Palladium-catalyzed cycloadditions of 2-(hydroxymethyl)allyl methyl carbonates with indoles*

(hydroxymethyl)allyl methyl carbonate **115** to form tetracyclic products **116** (Scheme 25).[39] Indoles with fused cyclopentane rings reacted smoothly at room temperature in the presence of a Pd^0 catalyst and ligand **117** to yield tetracyclic products **116a** in 75-99% yield and 92-97% ee

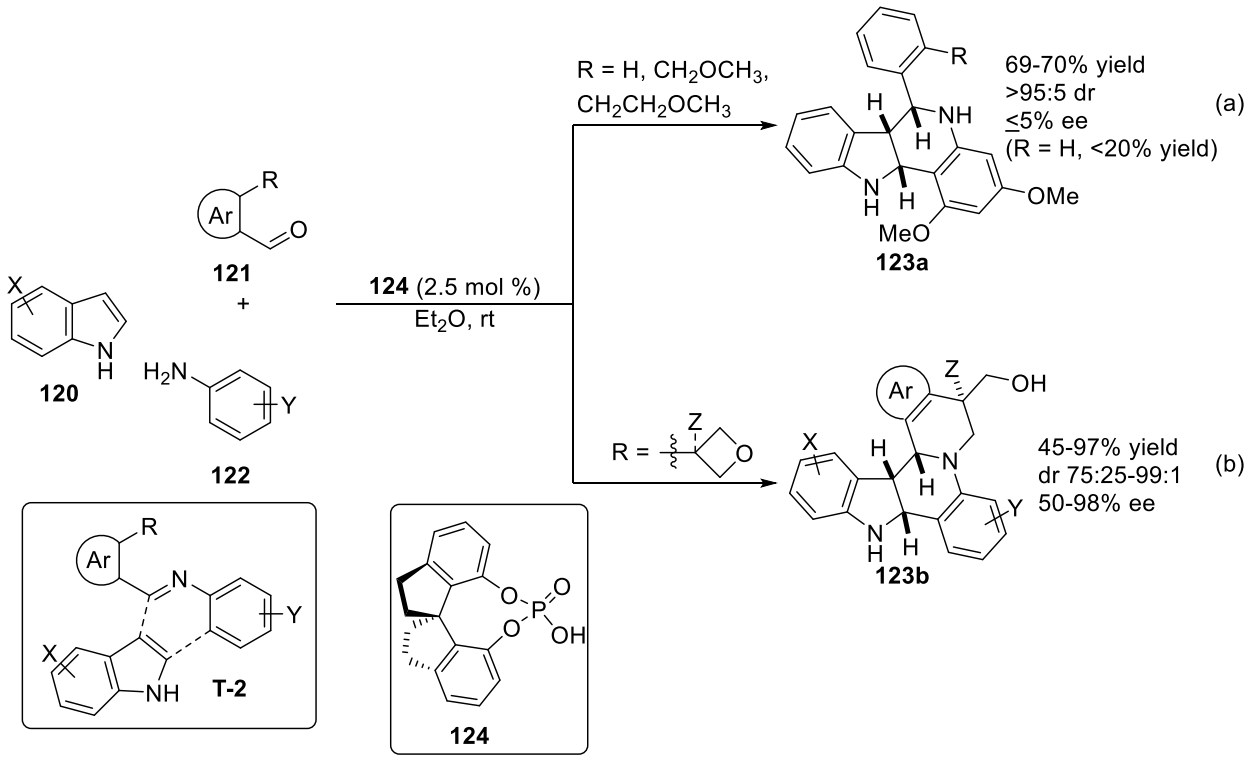
(Scheme 25a). Reactions of 5-Ph substituted and 4,6-Me_2-substituted indoles **114** required higher temperatures and less sterically congested ligand **118** to deliver acceptable yields and enantioselectivities in products **116b** (Scheme 25b). In addition to higher temperatures, the reactions of indoles **114** bearing fused cyclohexane rings required higher catalyst loading to deliver products **116c** (Scheme 25c).

Enantioselective dearomative cycloadditions catalyzed by chiral phosphoric acids

Chiral phosphoric acids have the advantages of stability in the presence of oxygen and water, long term stability, and convenience due to the fact that they are single component catalysts.[40] In addition, most chiral phosphoric acids have pK_a values between 2 and 4,[41] allowing facile protonation of substrates and the formation of tight ion pairs with substrates. These advantages make them promising as catalysts in enantioselective dearomative cycloadditions.

In 2013 Zhu and Sun reported catalytic, asymmetric, multi-component aza-Diels Alder reactions with indole dienophiles in the presence of a chiral phosphoric acid catalyst to deliver complex polycyclic indoles (Scheme 26).[42] Aryl aldehydes **121** and anilines **122** condensed to form arylidenealdehydes that functioned as aza-dienes in Diels-Alder reactions with indoles **120** (see **T-2** in Scheme 26) in the presence of chiral phosphoric acid **124**. Given the good performance of ethers as directing groups in previously reported enantioselective chiral phosphoric acid-catalyzed reactions,[43] the authors placed various ethers at the *ortho*-position of arenes **121**. Simple alkyl ethers allowed the reaction to take place efficiently to deliver products **123a** in high yields but with low enantioenrichment (Scheme 26a). However, an oxetane group in the *ortho*-position led to the formation of products **123b** with good-to-excellent enantioselectivities through a pathway that included oxetane desymmetrization. In addition, the

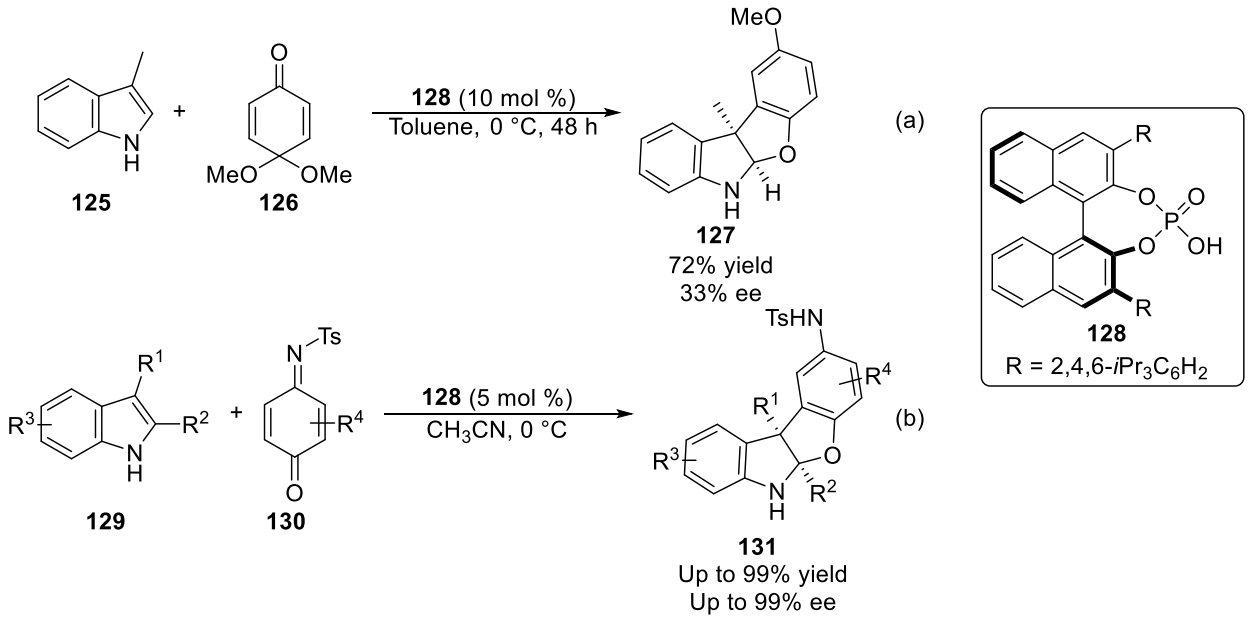
importance of the free indole N-H was clear: when the reaction was run with a protected indole nitrogen, the yield was less than 20%. This reaction is notable in that it sets four stereocenters with high enantioenrichment.



Scheme 26. *Chiral phosphoric acid-catalyzed multi-component dearomative aza-Diels-Alder reactions with indole dienophiles*

Zhang and coworkers reported enantioselective [3+2] couplings of quinone monoacetals and quinone monoimines with indoles in the presence of chiral phosphoric acid catalysts.[44] After initial attempts with Lewis acids delivered low yields and no enantioselectivity, they discovered that chiral phosphoric acid **128** catalyzed the coupling of 3-methylindole **125** with quinone monoacetal **126** to furnish benzofuro[2, 3*b*]indole **127** in 72% yield and 33% ee (Scheme 27a).[44a] Reactions of quinone monimines **130** with indoles **129** in the presence of the catalyst delivered annulated indole products **131** with yields and enantioselectivities of up to 99% (Scheme 27b).[44b] It should be noted that a methyl group *ortho* to the imine moiety in monoimine **130** resulted in no reaction in the presence of the catalyst, and the reaction carried out with N-Boc or N-Cbz

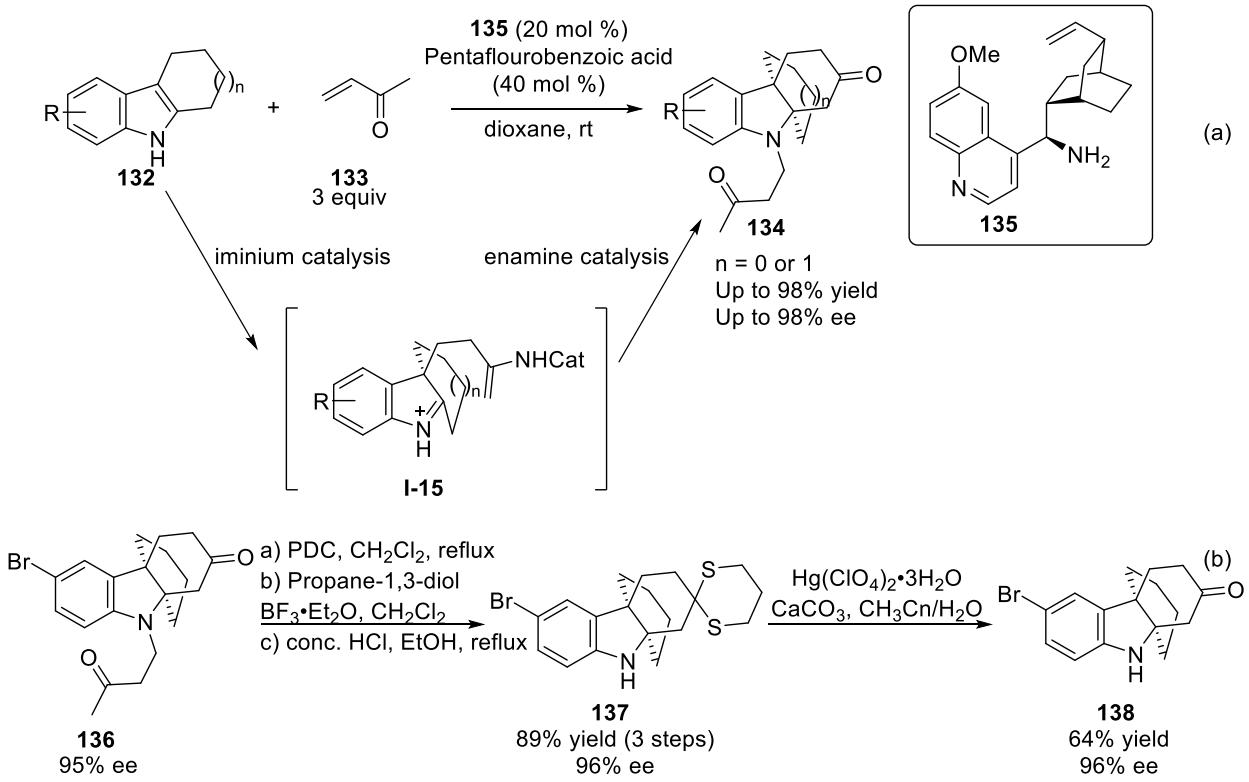
substituted imines led only to decomposition of the imines and no desired reaction, leaving areas for further development of this chemistry.



Scheme 27. *Chiral phosphoric acid-catalyzed cyclizations of quinone monoacetals and quinone monoimines with indoles*

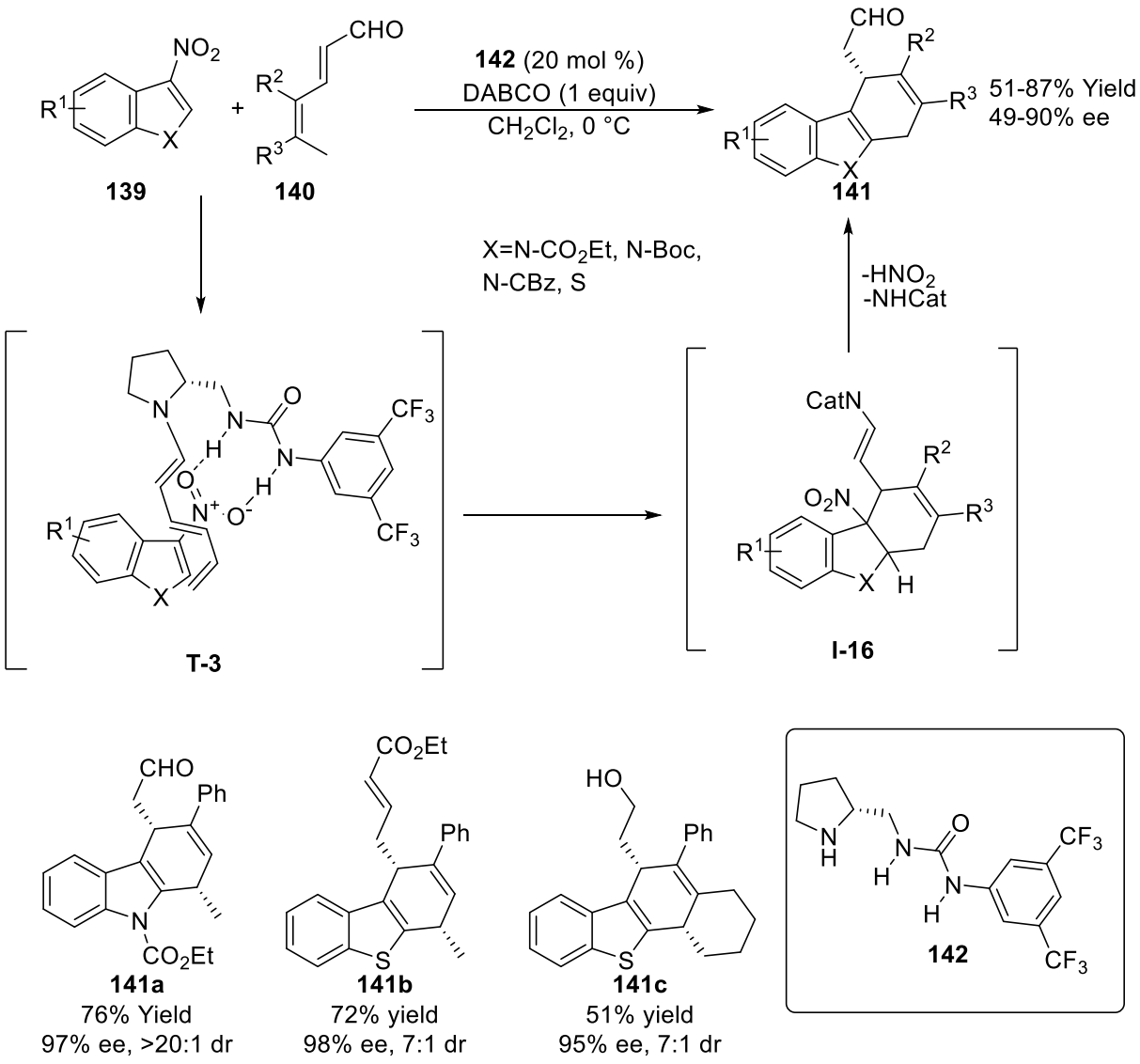
Enantioselective dearomative cycloadditions via iminium ion catalysis

Catalysts bearing chiral amine moieties are ubiquitous as alternatives to metal catalysts in enantioselective transformations.[45] You and coworkers developed asymmetric, dearomative formal [4+2] cycloadditions of 2,3-disubstituted indoles with methyl vinyl ketone catalyzed by a quinine-based primary amine catalyst (Scheme 28).[46] Methyl vinyl ketone **133** interacts with amine catalyst **135** to form an α,β-unsaturated iminum ion, which is attacked from the 3-position of indoles **132**, forming cationic intermediate **I-15** (Scheme 28a). The enamine formed undergoes ring closure, followed by hydrolysis. After conjugate addition of a second equivalent of methyl vinyl ketone **133** by the indoline N-H, the reaction affords products **134** in up to 98% yield and 98% ee (Scheme 28a). Oxidation with PDC to the amide, followed by dithiol protection of the carbonyls, hydrolysis and global deprotection provided free indole N-H product **138** with perfect enantioretention (Scheme 28b).



Scheme 28. *Organocatalytic enantioselective formal [4+2] cycloaddition of 2,3-disubstituted indoles with methyl vinyl ketone*

Jørgensen and coworkers recently reported enantioselective formal [4+2] cycloadditions via enamine catalysis.[47] Dienals **140** condense with the pyrrolidine N-H of catalyst **142** to form trienamine species that react with nitroarenes **139** as shown in transition state **T-3** (Scheme 29). Transition state **T-3** leads to intermediate **I-16**, which undergoes base-promoted denitration, followed by hydrolysis to deliver products **141** in 51-87% yield and 49-90% ee. Notably, reactions of 6-substituted dienals with arenes under these conditions result in very high enantioenrichment (Scheme 29, bottom). The authors propose that the catalyst plays three roles in the reaction: 1) hydrogen bonding with the nitro group to lower the LUMO of the indole C2-C3; 2) control of facial selectivity, and 3) assisting in the base-promoted dinitration process. The reaction with 3-nitrobenzothiophene dienophiles under these conditions is exceptional, as dienophiles of this type have previously required temperatures of up to 180 °C in order to react.[48]



Scheme 29. *Catalytic, enantioselective, Diels-Alder reactions with indole dipolarophiles via trienamine catalysis*

Enantioselective dearomative cycloadditions: conclusions and outlook

Although many robust methods for catalytic, enantioselective dearomative cycloadditions have been reported, this region of chemical space remains open for further exploration. Currently, most arenes employed as 2 π-electron partners in catalytic, enantioselective dearomative cycloadditions are heteroarenes, which have lower aromatic stabilization energies

relative to benzene.[49] Cycloadditions involving non-heteroarenes as 2 π-electron partners remain a challenge.

Another problem that remains to be solved is that currently, there exists no catalytic system in the realm of catalytic, dearomative cycloadditions that encompasses an arene scope containing both electron-poor and electron-rich 2 π-electron aromatic partners. Currently, every reported method either employs 2 π-electron partners with solely electron-donating groups or solely electron-withdrawing groups. Additionally, although there are reports of racemic dearomative cycloadditions betaine dipoles with arenes,[50] there exist no reports of catalytic, enantioselective reactions of these highly reactive dipoles with arenes.

To date, the field of catalytic, enantioselective cycloadditions with arenes as 2 π-electron partners is still in its infancy. Catalytic, enantioselective, dearomative cycloadditions offer the potential to construct polycyclic systems in a streamlined and elegant fashion, and thus, these reactions will continue to attract much investigation in the years to come.

Thesis Organization

This thesis is comprised of 5 chapters. Chapter 1 is a review of catalytic, enantioselective, dearomative cycloadditions where arenes and heteroarenes are 2 π-electron partners. Chapter 2 is a modification of an article published in *Organic Chemistry Frontiers* in 2016. It discloses the first example of catalytic, enantioselective, dearomative cycloadditions of stabilized α-substituted azomethine ylides (derived from imino esters of α-substituted amino acids) with 3-nitroindoles to furnish pyrrolo[3, 4*b*] indoles in high yield, enantioselectivity, and diastereoselectivity. Dr. Arkady Ellern, crystallographer in the Iowa State University Department of Chemistry, collected the data for the crystal structure reported. The author of this thesis was responsible for the remainder of the research discussed. Chapter 3 is a modification

of an article published in *Organic and Biomolecular Chemistry* in 2013. In this manuscript, catalytic, enantioselective cycloadditions of nitrile imines with methyleneindolinines are explored. These reactions were catalyzed by a magnesium-bisoxazoline complex and delivered spiro[pyrazolin-3,3′-oxindoles] in high yield and enantioenrichment. Kelsie Pugh, an undergraduate in the Stanley lab at the time, was responsible for a portion of the synthesis of methyleneindolinones and the purification of a portion of the spiro[pyrazolin-3,3′-oxindoles]. Dr. Michael Slade, a postdoctoral fellow in the Stanley lab at the time, was responsible for the synthesis of dipoles and the testing of these dipoles in the reaction, as well as the dipole competition reactions. Dr. Arkady Ellern, crystallographer in the Iowa State University Department of Chemistry, collected the data for the crystal structure reported. The author of this thesis was responsible for methyleneindolinone synthesis, ligand synthesis, screening of conditions, the dipolarophile scope, and the dipolarophile competition reactions. Chapter 4 is a manuscript that has been submitted for publication in *Tetrahedron Letters*. It discusses the first example of palladium-catalyzed conjugate additions of arylboronic acids to 2-substituted chromones. The reaction described occurs in aqueous medium overcomes competing protodeboronation and biaryl forming reactions to deliver substituted flavanones in up to 90% yield. The author of this thesis was responsible for the entirety of the research disclosed. Chapter 5 is a summary of the key conclusions drawn from each of the other chapters.

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CHAPTER 2

ENANTIOSELECTIVE DEAROMATIVE [3+2] CYCLOADDITIONS OF INDOLES WITH AZOMETHINE YLIDES DERIVED FROM ALANINE IMINO ESTERS

Modified from a paper published in *Organic Chemistry Frontiers*[a]

Anthony L. Gerten and Levi M. Stanley[*]

Abstract

Catalytic, enantioselective [3 + 2] cycloadditions of azomethine ylides derived from alanine imino esters with 3-nitroindoles are reported. The dearomative cycloaddition reactions occur in the presence of a catalyst generated *in situ* from $Cu(OTf)_2$ and (*R*)-Difluorphos to form *exo′*-pyrroloindoline cycloadducts and establish four contiguous stereogenic centers, two of which are fully substituted. The *exo′*-pyrroloindoline products are formed in moderate-to-good yields (39–85%) with high diastereoselectivities (up to 98 : 1 : 1 dr) and enantioselectivities (up to 96% ee).

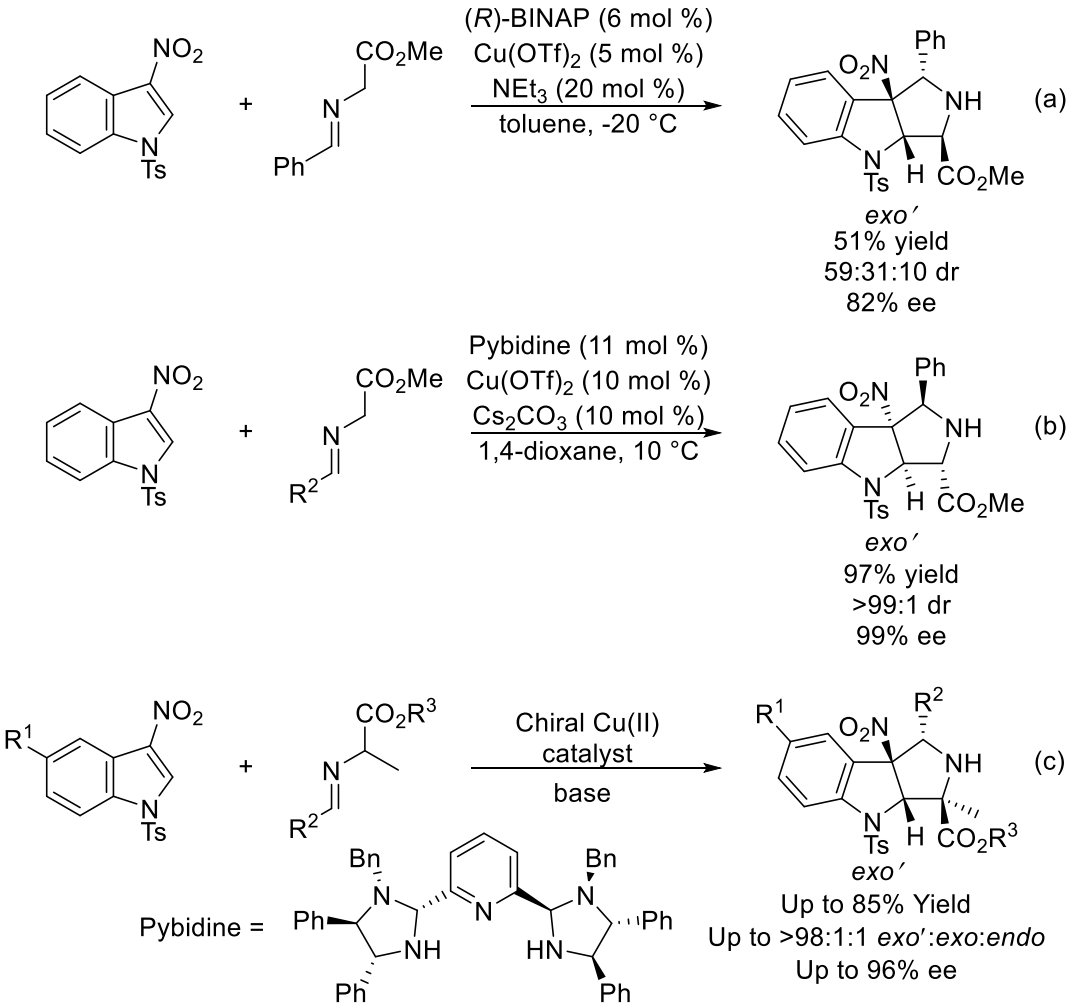
Introduction

The development of dearomatization reactions offers the potential to rapidly generate molecular complexity and new molecular frameworks.[1] In recent years, [2+2],[2] [3+2],[3] [4+2],[4] and [5+2][5] dearomative cycloadditions have emerged as promising strategies to construct polycyclic carbocycles and heterocycles from arenes and heteroarenes. Despite the steady development of new dearomative cycloaddition reactions, examples of catalytic, enantioselective dearomative cycloadditions are rare.[2b,3b,3c,3f,3i]

Among the promising classes of dearomative cycloadditions for further development are intermolecular [3+2] cycloadditions of nitrogen-containing 1,3-dipoles with arenes and heteroarenes. In particular, cycloadditions of azomethine ylides with arenes and heteroarenes

have emerged as a viable approach to generate polycyclic nitrogen heterocycles.[6] Gribble and co-workers initially reported cycloadditions of unstabilized azomethine ylides with 2- and 3-nitroindoles to form racemic pyrroloindolines.[7] More recently, Chatainger, Piettre, and co-workers showed that cycloadditions of unstabilized azomethine ylides with electron-deficient arenes and heteroarenes form a wide variety of racemic, polycyclic cycloadducts in good-to-excellent yields.[8]

We initially discovered reactivity with glycine-derived iminoesters (Scheme 1a). However, during the course of our studies, Awata and Arai reported the first catalytic,



Scheme 1. *Enantioselective cycloadditions of glycine and alanine-derived azomethine ylides with 3-nitroindoles*

enantioselective dearomative cycloadditions of stabilized azomethine ylides with 3-nitroindoles

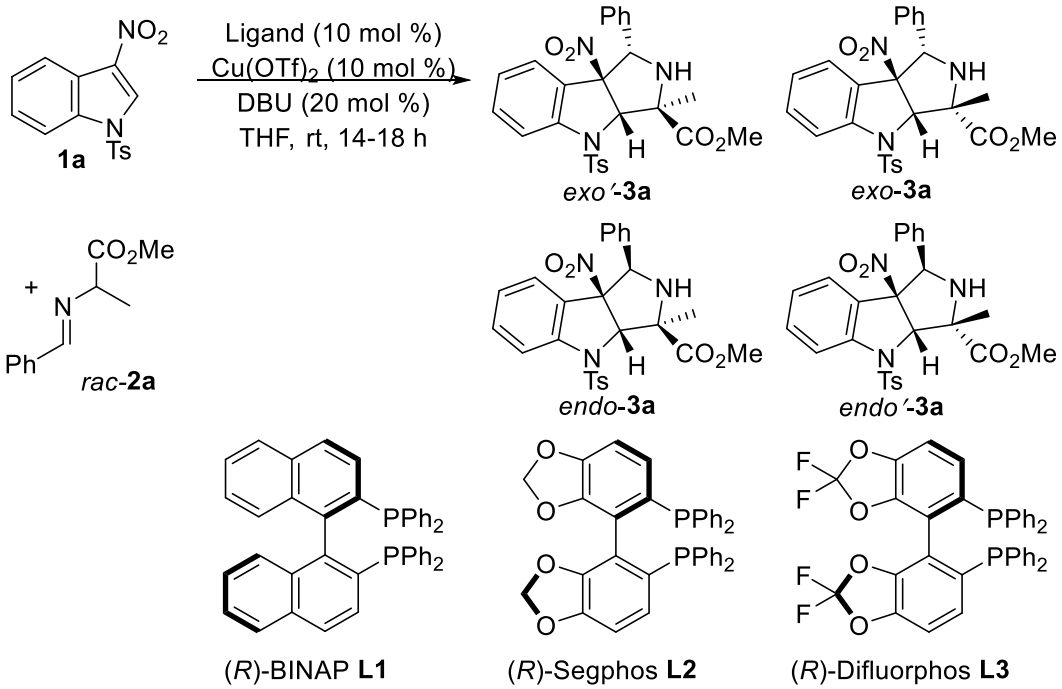
(Scheme 1b).[9] Cycloadditions of a wide range of azomethine ylides derived from glycine imino esters occur with excellent enantioselectivity and nearly perfect *exo´*-selectivity when reactions are run in the presence of a complex prepared from $Cu(OTf)_2$ and a chiral PyBidine ligand. However, catalytic, enantioselective dearomative cycloadditions of azomethine ylides derived from alanine iminoesters have not been reported. Herein, we report the first examples of diastereo- and enantioselective dearomative cycloadditions of alanine-derived azomethine ylides with 3-nitroindoles. These reactions generate pyrroloindolines with four contiguous stereogenic centers, two of which are fully substituted (Scheme 1c).

Enantioselective dearomative [3+2] cycloadditions of indoles with azomethine ylides derived from alanine imino esters: identification of reaction conditions

To identify a diastereo- and enantioselective catalyst for dearomative cycloadditions of alanine-derived azomethine ylides, we evaluated the model reaction of N-tosyl-3-nitroindole **1a** with racemic **2a** (Table 1). Initially, we found that Lewis acid complexes of chiral bisphosphine ligands (*R*)-BINAP, (*R*)-Segphos, (*R*)-Difluorphos (10 mol%) catalyzed the cycloadditions of **1a** with **2a**. These reactions formed a diastereomeric mixture of cycloadducts **3a** with *exo´*-**3a** generated as the major diastereomer (entries 1-4). The reaction of **1a** with **2a** occurred with the highest diastereoselectivity (93 : 3 : 4 *exo´*-**3a** : *exo*-**3a** : *endo*-**3a**) with the copper(II) triflate complex of (*R*)-Difluorphos as catalyst (entry 4).[10] The cycloadduct *exo´*-**3a** was isolated in 73% yield with 86% ee. The high enantioselectivity and diastereoselectivity observed for the model reaction led us to explore additional reaction parameters using the combination of $Cu(OTf)_2$ and (*R*)-Difluorphos as catalyst.

By lowering the reaction temperature to 0 °C and -20 °C, we observed higher enantioselectivity for *exo´*-**3a** (92-93% ee) with lower diastereoselectivity (entries 5 and 6). For

Table 1. *Identification of catalysts and reaction conditions for the cycloaddition of* **1a** *and* **2a**.



Entry	Ligand	Temp (°C)	Equiv. 2a	dr (*exo´:exo:endo*)	Yield (*exo´*-3a) (%)	ee (*exo´*-3a) (%)
1[a]	**L1**	rt	1.0	52:9:39	37	29
2	**L1**	rt	1.0	66:13:21	39	64
3	**L2**	rt	1.0	79:9:12	60	82
4	**L3**	rt	1.0	93:3:4	73	86
5	**L3**	0	1.0	73:9:18	51	92
6	**L3**	-20	1.0	41:15:44	34	93
7	**L3**	rt	1.0	71:11:18	58	76
8	**L3**	rt	1.2	93:3:4	75	89
9	**L3**	rt	1.5	92:3:5	78	88
10	**L3**	rt	2.0	92:3:5	72	90

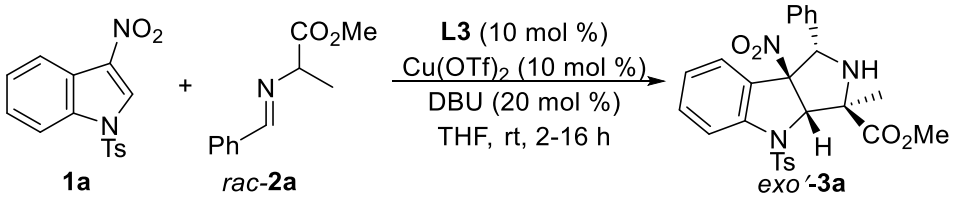
[a]$AgClO_4$ used instead of $Cu(OTf)_2$, and NEt_3 used as base instead of DBU.

example, the reaction of **1a** with **2a** forms a 41 : 15 : 44 mixture of *exo´*: *exo* : *endo* diastereomers when the reaction is carried out at -20°C. The *endo* selectivity of the reaction carried out at -20 °C led us to postulate that the model cycloaddition is *endo*-selective, but epimerization of *endo*-**3a** to *exo´*-**3a** occurs at higher temperatures through a *retro*-Mannich/Mannich addition pathway and leads to the observed *exo´*-selectivity.[11]

Lowering the loading of the copper catalyst also proved detrimental to the diastereo- and enantioselectivity of the model reaction. The reaction of **1a** with **2a** in the presence of 5 mol% of the copper catalyst formed **3a** as a 71 : 11 : 18 mixture of *exo´*: *exo* : *endo* diastereomers with *exo´*-**3a** isolated in 76% ee (entry 7). The decrease in enantioselectivity and diastereoselectivity observed at lower catalyst loading suggests: (1) the rate of uncatalyzed background reaction is likely competitive with the rate of the catalyzed process; and (2) the copper complex may catalyze the epimerization of *endo*-**3a** to *exo´*-**3a**.

Varying the concentration of iminoester **2a** has minimal impact on the yield and selectivity of the model reaction (compare entries 4 and 8-10). The diastereoselectivity remains essentially unchanged when varying the amounts of imino ester **2a** from 1.0-2.0 equivalents. However, a slight excess (1.2 equivalents, entry 8) of **2a** leads to a modest increase in enantioselectivity, but this trend does not hold when the concentration of **2a** is further increased (entries 9 and 10).

To develop a better understanding of the rates of the catalyzed reaction and the uncatalyzed reaction and the evolution of diastereoselectivity over time, we conducted cycloadditions of **1a** and **2a** in the presence and absence of copper catalyst and monitored the yield and diastereoselectivity over time (Table 2). The catalyzed reaction of **1a** with **2a** occurs to approximately 90% conversion after 2 h (entry 1) and is complete after 6 h (entry 3), while the uncatalyzed reaction occurs to approximately 50% and 80% conversion over the same time periods (entries 2 and 4). Although the uncatalyzed background reaction is slower than the catalyzed process, this data shows that the rate of uncatalyzed cycloaddition is sufficient to negativiely impact the enantioselectivity of the cycloadditions and likely explains the poor enantioselectivity observed when the catalyst loading is lowered.



Entry	Cu(II) catalyst	Time (h)	dr (*exo´*:*exo*:*endo*)	NMR Yield (%)[a]	ee (*exo´*-3b) (%)
1	Yes	2	69:5:26	84 (91)	87
2	No	2	59:6:35	49 (52)	--
3	Yes	6	77:9:14	99 (99)	90
4	No	6	60:10:30	78 (82)	--
5	Yes	16	93:3:4	99 (99)	89

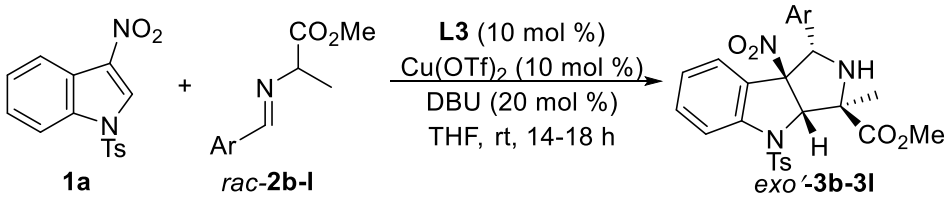
Table 2. *Evolution of Stereoselectivity in Catalyzed versus Uncatalyzed Reactions of 1a with 2b*
[a]Determined by ^{1}H NMR spectroscopy of the crude reaction mixture using dibromomethane as the internal standard. Conversion of **1a** is listed in parentheses.

The evolution of diastereoselectivity over time is greatly influenced by the presence or absence of the copper catalyst. The uncatalyzed model reaction forms a 59 : 6 : 35 ratio of *exo´*: *exo* : *endo* diastereomers after 2 h, and this ratio does not change significantly over an additional 4 h (Table 2, entries 2 and 4). In contrast, the diastereoselectivity of the copper-catalyzed cycloaddition changes markedly with reaction time. The catalyzed reaction forms a 69 : 5 : 26 ratio of *exo´*: *exo* : *endo* diastereomers after 2 h (entry 1); a ratio that is similar to that observed in the uncatalyzed reaction. However, the diastereomeric ratio improves to 77 : 9 : 14 (entry 3) after 6 h and to 93 : 3 : 4 (entry 5) after 16 h. The dramatic decrease in the amount of *endo*-**3a** and increase in the amount of *exo´*-**3a** indicates that the complex generated from $Cu(OTf)_2$ and **L3** catalyzes the epimerization of *endo*-**3a** to *exo´*-**3a** which leads to high *exo´* selectivity of the cycloaddition reaction.

Enantioselective dearomative [3+2] cycloadditions of indoles with azomethine ylides derived from alanine imino esters: scope of alanine-derived imino esters

With a practical set of reaction conditions and a diastereoselective and enantioselective catalyst identified, we evaluated cycloadditions of *N*-tosyl-3-nitroindole **1a** with a variety of iminoesters **2b**-**2l** derived from alanine methyl ester and an array of aromatic aldehydes. Results of these reactions are summarized in Table 3. In general, cycloadditions of **1a** with imino esters containing 4-substitutued aryl groups occur to form *exo´*-**3** in >70% yield with >90% ee and greater than 90 : 7 : 3 *exo´*: *exo* : *endo* diastereoselectivity (entries 1-5). The notable exceptions to these typical yields and selectivities include the reactions of imino esters **2b** (Ar = 4-$F_3CC_6H_4$) and **2c** (Ar = 4-ClC_6H_4). The cycloaddition of **2b** with **1a** occurs in high yield with excellent diastereoselectivity (entry 1). However, *exo´*-**3b** is isolated with 80% ee, possibly due to a faster rate of uncatalyzed background reaction with an azomethine ylide containing an electron-withdrawing 4-trifluoromethyl group on the arene moiety. This hypothesis is supported by a positive correlation between enantioselectivity of the reaction and increasing electron-donating ability of the substituents at the 4-position on the aryl ring of the dipoles. The cycloaddition of **2c** with **1a** forms *exo´*-**3c** in 70% yield with 88% ee, but the reaction occurs with modest diastereoselectivity (entry 2). Notably, the reaction of electron-rich imino ester **2g**, containing a 3,4,5-trimethoxyphenyl moiety, with **1a** affords **3g** in only 32% ee (entry 6). This result suggests that the azomethine ylide generated from imino ester **2g** binds very tightly to the copper catalyst. A tightly bound copper catalyst slows catalytic turnover and allows the racemic background reaction to become more competitive with the catalyzed process.

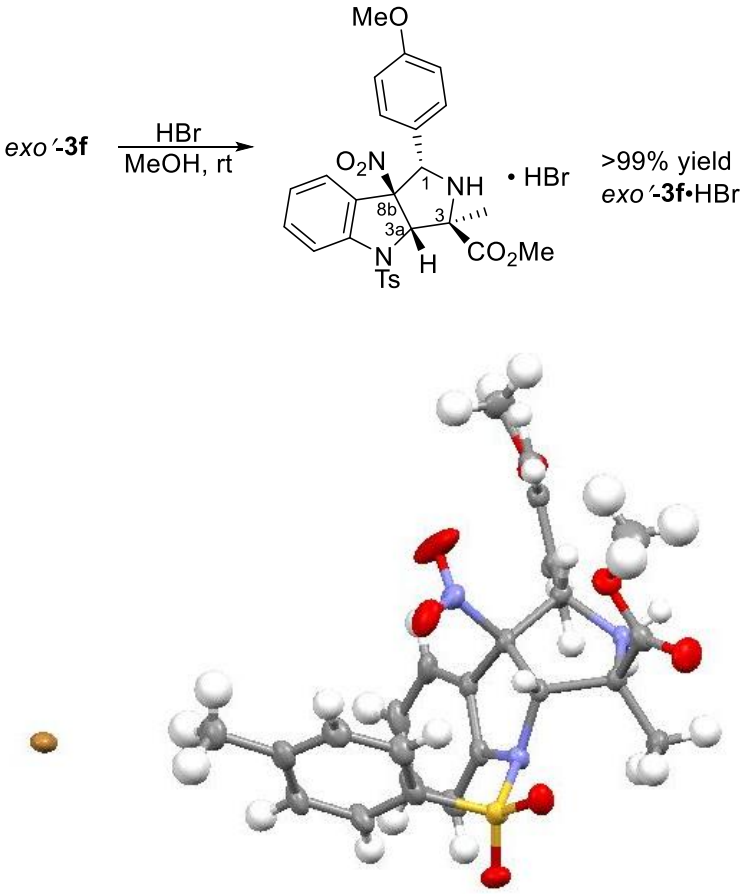
Table 3. *Scope of dearomative cycloadditions of indole* **1a** *with iminoesters* **2b-l**



Entry	*rac*-2 (Ar)	*exo´*-3	dr (*exo´:exo:endo*)	Yield *exo´*-3 (%)	ee *exo´*-3 (%)
1	**2b** (4-$F_3CC_6H_4$)	**3b**	>98:1:1	83	80
2	**2c** (4-ClC_6H_4)	**3c**	78:5:17	70	88
3	**2d** (4-BrC_6H_4)	**3d**	95:4:1	78	90
4	**2e** (4-H_3CC6H4)	**3e**	90:7:3	76	91
5	**2f** (4-$MeOC_6H_4$)	**3f**	95:4:1	71	96
6	**2g** (3,4,5-$MeOC_6H_4$)	**3g**	65:13:22	39	32
7	**2h** (3-$MeOC_6H_4$)	**3h**	89:8:3	72	89
8	**2i** (3-BrC_6H_4)	**3i**	69:8:23	40	80
9	**2j** (2-$MeOC_6H_4$)	**3j**	74:7:19	39	82
10	**2k** (2-FC_6H_4)	**3k**	67:5:27	51	87
11	**2l** (2-ClC_6H_4)	**3l**	88:8:4	85	79

Cycloadditions of imino esters **2h**-**2l** containing 2- and 3-substituted aryl groups with **1a** generally occur with slightly lower yields and selectivities (entries 7-11) than imino esters **2b**-**2f**. While the cycloaddition of 3-MeO-substituted imino ester **2h** occurs to form *exo´*-**3h** in high yield with high diastereo- and enantioselectivity (entry 7), the cycloaddition of 3-Br-substituted imino ester **2i** formed *exo´*-**3i** in only 40% yield with modest diastereoselectivity, likely due to a relatively slow epimerization of *endo*-**3i** to *exo´*-**3i**, and slightly lower enantioselectivity (entry 8). Cycloadditions of 2-MeO-, 2-F, and 2-Cl-substituted imino esters **2j-l** formed *exo´*-**3j-l** in 39-85% yield with 79-87% ee and with diastereoselectivities ranging from 67 : 5 : 27 to 88 : 8 : 4 *exo´*: *exo* : *endo* (entries 9-11).

The absolute configuration of *exo´*-**3f** was determined after treatment with HBr to form *exo´*-**3f**·HBr in >99% yield (Scheme 2). The absolute configuration of *exo´*-**3f**·HBr was determined to be (1*S*, 3*R*, 3a*S*, 8b*S*) by X-ray crystallographic analysis.



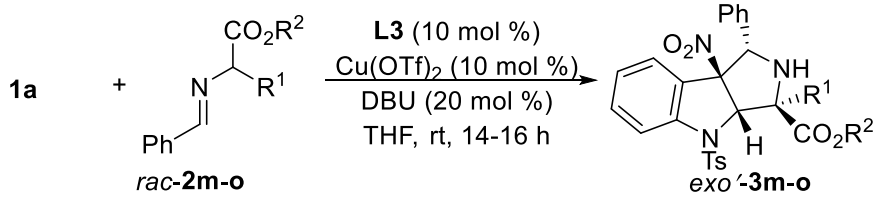
Scheme 2. *Determination of the absolute stereochemistry of exo´-***3f**.

Enantioselective dearomative [3+2] cycloadditions of indoles with azomethine ylides derived from alanine imino esters: additional substrate scope

Although our studies focused on reactions of *N*-tosyl-3-nitroindole **1a** with imino esters derived from alanine methyl ester, we have also demonstrated that cycloadditions involving an imino ester derived from alanine isopropyl ester and *N*-tosyl-5-bromo-3-nitroindole occur in high yields with excellent stereoselectivity (Table 4, entry 1, Scheme 3). For example, the reaction of N-tosyl-3-nitroindole **1a** with imino ester **2m** derived from alanine isopropyl ester occurs with 93 : 7 *exo´*: *exo* diastereoselectivity and forms pyrroloindoline *exo´-***3m** in 71% yield with 94% ee (Table 4, entry 1). The *endo* diastereomer was not observed after the 18 h reaction time. However, reactions of phenylalanine-derived **2n** and leucine-derived **2o** with **1a** in the presence

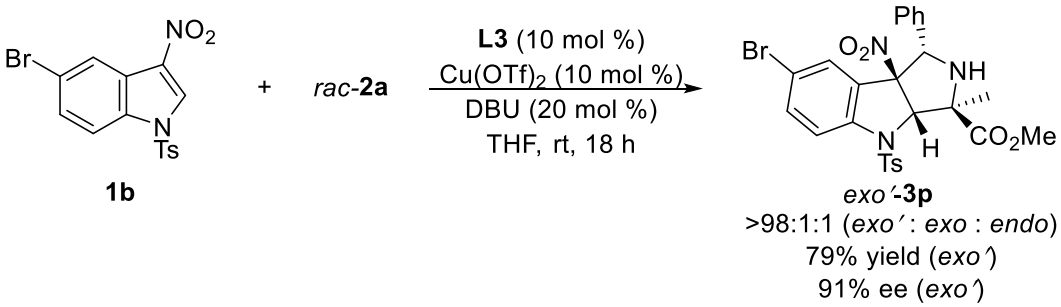
of the catalyst resulted in lower enantio- and diastereoselectivity. These reactions delivered *exo´*-**3n** in 67% yield, 48 : 25 : 27 *exo´* : *exo* : *endo* diastereomeric ratio and 36% ee, and *exo´*-**3o** in 71% yield, 72 : 19 : 9 *exo´* : *exo* : *endo* diastereomeric ratio and 30% ee (entries 2-3). In these cases, it is likely that increased steric bulk lowers the binding constant of the catalyst to the imino ester, allowing for a competitive racemic background reaction. The cycloaddition of imino ester **2a** with *N*-tosyl-5-bromo-3-nitroindole **1b** occurs with nearly perfect *exo´* selectivity (>98 : 1 : 1 *exo´* : *exo* : *endo*, Scheme 3). Pyrroloindoline *exo´*-**3p** was isolated in 79% yield and 91% ee.

Table 2. *Dearomative cycloadditions of* **1a** *with imino esters* **2m-o**



Entry	*rac*-2 (R^1, R^2)	*exo´*-3	dr (*exo´:exo:endo*)	Yield *exo´*-3 (%)	ee *exo´*-3 (%)
1	**2m** (R^1=Me, R^2=*i*-Pr)	**3m**	93:7:0	71	94
2	**2n** (R^1=Bn, R^2=Me)	**3n**	48:25:27	67[a]	36
3	**2o** (R^1=*i*-Bu, R^2=Me)	**3o**	72:19:9	71[b]	30

[a] Isolated in 46 : 24 : 30 *exo´*: *exo* : *endo* diastereomeric ratio. [b] Isolated in 75 : 20 : 0 *exo´*: *exo* : *endo* ratio.



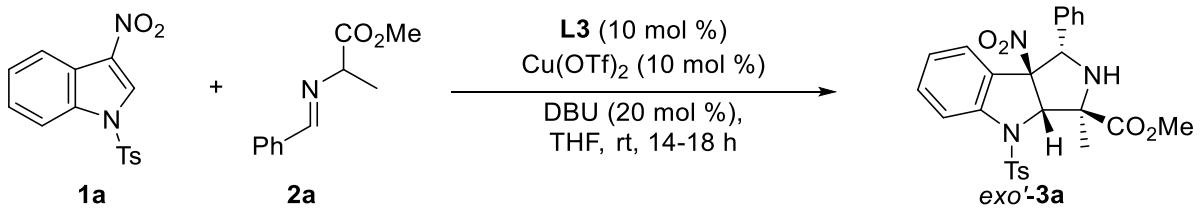
Scheme 3. *Reaction of* **1b** *with rac*-**2a**

Enantioselective dearomative [3+2] cycloadditions of indoles with azomethine ylides derived from alanine imino esters: effects of single enantiomer dipoles on reaction outcomes

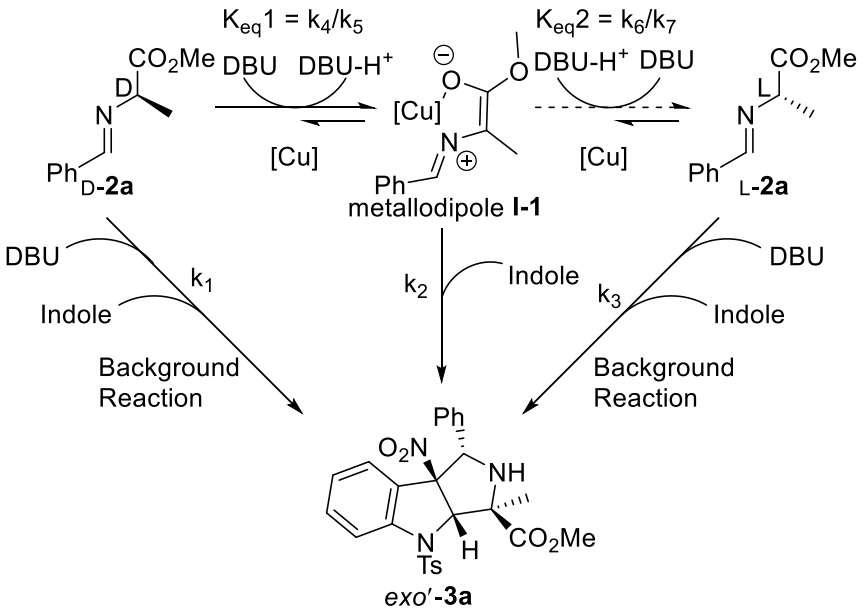
To our knowledge, no experiment has been carried out to determine whether or not single enantiomer α-substituted imino esters with opposite absolute stereochemistry react differently with dipolarophiles in the presence of the same single enantiomer catalyst in azomethine ylide cycloadditions. The dearth of information available on this topic prompted us to subject single enantiomer imino esters to our reaction conditions to determine whether or not the starting absolute stereochemistry of the imino ester impacts the yield, enantioselectivity, and diastereoselectivity of the reaction. Interestingly, D-**2a** and DL-**2a** reacted similarly with **1a** in the presence of the copper catalyst to deliver *exo´*-**3a** with high yield, diastereoselectivity, and enantioselectivity (Table 5, entries 2-3). However, the reaction of L-**2a** with **1a** in the presence of the catalyst afforded *exo´*-**3a** with 93:3:4 *exo´*: *exo* : *endo* selectivity and 80% yield, but only 58% ee (entry 1). The differences in enantioselectivity depending on the absolute stereochemistry of the dipole may arise from differences in equilibrium between each enantiomer of the iminoester and metallodipole **I-1** (Scheme 4). When iminoester D-**2a** is subjected to the reaction conditions, it is likely that the equilibrium between the iminoester and metallodipole **I-1** lies in favor of the metallodipole, and the majority of the iminoester thus moves through the catalyzed pathway, resulting in high enantioenrichment in *exo'*-**3a**. In the case of L-**2a**, the equilibrium between the iminoester and metallodipole **I-1** lies in favor of the iminoester, and the racemic background reaction thus becomes competitive with the catalyzed process, leading to lower enantioselectivity in *exo'*-**3a**. The high enantioselectivity in the reaction of DL-**2a** with **1a**

could be the result of a positive nonlinear effect or the involvement of already formed enantioenriched product as part of the active catalytic species.[12]

Table 5. *Effects of Dipole* **2a** *Stereochemistry on Reaction Outcomes*



Entry	2a Configuration	dr (*exo′*:*exo*:*endo*)	Yield (%)	% ee (*exo′*)
1	L	93:3:4	80	58
2	D	94:4:1	72	82
3	DL	93:3:4	75	89



Scheme 4. *Possible pathways for formation of exo´-***3a** *from* D**-2a** *and* L**-2a**

Enantioselective dearomative [3+2] cycloadditions of indoles with azomethine ylides derived from alanine imino esters: conclusion

In summary, we have developed the first catalytic, enantioselective dearomative cycloadditions of alanine-derived imino esters with 3-nitroindoles. These *exo´*-selective

dearomative cycloadditions form a variety of highly enantioenriched pyrroloindolines with four contiguous stereogenic centers, two of which are fully substituted, when the reactions are conducted in the presence of a catalyst generated from $Cu(OTf)_2$ and (*R*)-Difluorphos. The high diastereoselectivities observed favoring the formation of the *exo´*-cycloadduct result from a $Cu(OTf)_2$/(*R*)-Difluorphos-catalyzed epimerization of the *endo*-cycloadduct to the *exo´*-cycloadduct during the course of the reaction. Studies to develop new catalytic, enantioselective dearomative cycloadditions with additional classes of aromatic and heterearomatic dipolarophiles are ongoing in our laboratory.

Experimental details

General experimental details

All air-sensitive procedures were conducted under inert atmosphere in a nitrogen-filled dry box or by standard Schlenk techniques. All reactions were performed under an atmosphere of nitrogen unless otherwise stated. All glassware for moisture sensitive reactions was dried at 140 °C in an oven. THF and CH_2Cl_2 were degassed by purging with argon for 45 minutes and dried with a solvent purification system by passing through a one-meter column of activated alumina. Flash column chromatography was performed on Fisher brand silica gel 60 (230-400 mesh) or Silicylce Siala-P silica gel or on a Teledyne Isco CombiFlash Rf automated chromatography system with RediSep Rf Gold normal-phase silica columns. Products of reactions were visualized on TLC plates under UV light.

HRMS (ESI) analysis was performed at the Iowa State University Chemical Instrumentation Facility on an Agilent 6540 QTOF spectrometer. Optical rotations were measured on an Atago AP-300 automatic polarimeter. HPLC analyses were carried out on a Water Alliance HPLC system with an e2695 Separations Module and a 2489 (UV/Vis) dual

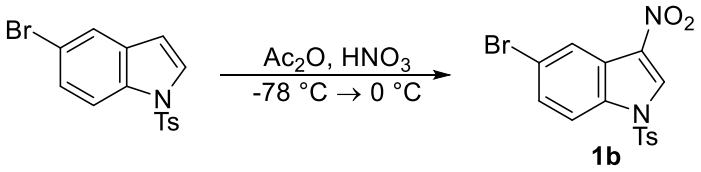
wavelength detector. NMR spectra were acquired on Varian MR-400 and Bruker Avance III 600 spectrometers at the Iowa State University Chemical Instrumentation Facility. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to residual $CHCl_3$ in $CDCl_3$ (7.26 ppm for ^{1}H and 77.23 ppm for ^{13}C). ^{19}F NMR shifts are reported in ppm relative to trifluoroacetic acid as an external standard (F_3CCO_2H = -76.55 ppm).

Materials

Benzaldehyde, 4-chlorobenzaldehyde, 4-methylbenzaldehyde, 4-methoxybenzaldehyde, 3-methoxybenzaldehyde, 2-methoxybenzaldehyde, 2-chlorobenzaldehyde, 3,4,5-trimethoxybenzaldehyde and DL-phenylalanine were purchased from Sigma-Aldrich and used without further purification. 4-Trifluoromethylbenzaldehyde, 4-bromobenzaldehyde, 3-bromobenzaldehyde, and 2-fluorobenzaldehyde were purchased from Oakwood Chemical Company and used without further purification. DL-alanine, D-alanine methyl ester hydrochloride, L-alanine methyl ester hydrochloride, and DL-leucine were purchased from AK Scientific and used without further purification. Amino acid methyl ester hydrochlorides were prepared by bubbling HCl gas through a methanolic solution of the amino acid followed by removal of the volatiles under reduced pressure to furnish the amine hydrochloride. DL-alanine isopropyl ester hydrochloride was prepared by bubbling HCl gas through a solution of DL-alanine in isopropanol followed by removal of the volatiles under reduced pressure to furnish the required amine hydrochloride. Tosyl chloride and indole were purchased from Sigma-Aldrich and used without further purification. 5-bromoindole was purchased from Frontier Scientific and used without further purification. 5-Bromo-*N*-tosylindole was prepared according to a literature procedure.[13] 3-Nitro-*N*-tosylindole **1a** was prepared according to a literature procedure.[14] $Cu(OTf)_2$, *rac*-BINAP, (*R*)-BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthalene), (*R*)-segphos ((*R*)-(+)-

5,5´-Bis(diphenylphosphino)-4,4´ -bi-1,3-benzodioxole), and (*R*)-Difluorphos ((*R*)-(-)-5,5'-Bis(diphenylphosphino)-2,2,2´,2´-tetrafluoro-4,4´-bi-1,3-benzodioxole) were purchased from Strem Chemicals and used without further purification.

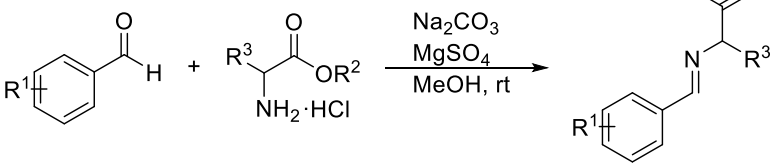
Synthesis of 5-bromo-3-nitro-N-tosylindole 1b[9,15]



1b

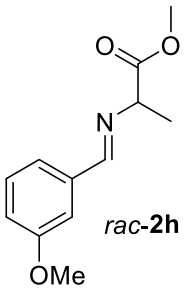
5-Bromo-*N*-tosylindole (2.30 g, 6.57 mmol, 1.00 equiv) was added to a round bottom flask and suspended in 32 ml of acetic anhydride. A solution of 1.3 mL of 70% nitric acid and 13 mL of acetic anhydride was added dropwise over 30 minutes to the suspension of 5-bromo-3-nitroindole at -78 °C. The solution was warmed to 0 °C and maintained at this temperature for 4 h. The reaction was quenched with water and extracted with dichloromethane (3x). The combined organic layer was washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield crude 5-bromo-3-nitro-*N*-tosylindole **1b**. Crude **1b** was recrystallized fr om 1:1 hexane:dichloromethane to yield 5-bromo-3-nitro-1-tosylindole **1b** (1.35 g, 3.41 mmol, 52%). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 2.41 (s, 3H), 7.34(d, *J* = 8.0 Hz, 2H), 7.57 (dd, *J* = 9.0, 1.4 Hz, 1H), 7.83-7.90 (m, 3H), 8.40 (d, *J* = 1.4 Hz, 1H), 8.54 (s, 1H) **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 22.0, 115.3, 120.1, 123.5, 124.2, 127.66, 127.67, 128.8, 130.2, 130.9, 132.5, 133.8, 147.3.

General procedure for synthesis of imino esters *rac*-2a-f, *rac*-2h-o



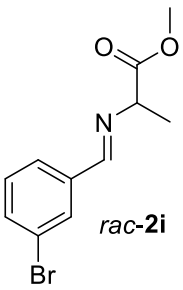
rac-**2a**: R^1 = H, R^2 = Me, R^3 = Me
rac-**2b**: R^1 = 4-CF_3, R^2 = Me, R^3 = Me
rac-**2c**: R^1 = 4-Cl, R^2 = Me, R^3 = Me
rac-**2d**: R^1 = 4-Br, R^2 = Me, R^3 = Me
rac-**2e**: R^1 = 4-Me, R^2 = Me, R^3 = Me
rac-**2f**: R^1 = 4-MeO, R^2 = Me, R^3 = Me
rac-**2h**: R^1 = 3-MeO, R^2 = Me, R^3 = Me
rac-**2i**: R^1 = 3-Br, R^2 = Me, R^3 = Me
rac-**2j**: R^1 = 2-MeO, R^2 = Me, R^3 = Me
rac-**2k**: R^1 = 2-F, R^2 = Me, R^3 = Me
rac-**2l**: R^1 = 2-Cl, R^2 = Me, R^3 = Me
rac-**2m**: R^1 = H, R^2 = *i*-Pr, R^3 = Me
rac-**2n**: R^1 = H, R^2 = Me, R^3 = Bn
rac-**2o**: R^1 = H, R^2 = Me, R^3 = *i*-Bu

To a suspension of DL-amino acid methyl ester hydrochloride or DL-alanine isopropyl ester hydrochloride (1.2 equiv), sodium carbonate (1.5 equiv), and a small amount of magnesium sulfate in methanol (0.36 M solution with respect to the amine hydrochloride) was added the appropriate aldehyde (1 equiv). The reaction mixture was stirred for 12 h at room temperature. The reaction mixture was then filtered through celite into a separatory funnel. The mixture was extracted into diethyl ether. The ether layer was washed with water (2x) and brine (2x). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford imino esters *rac*-**2a**-**2o**, which were used without further purification. NMR spectra match reported NMR data for known imino esters **2a**,[16] **2b**,[17] **2c**,[16] **2d**,[17] **2e**,[17] **2f**,[17] **2j**,[18] **2k**,[17] **2l**,[19] **2m**,[19-20] **2n**,[16] and **2o**.[16]



Methyl (*E*)-2-((3-methoxybenzylidene)amino)propanoate (*rac*-2h): Prepared according to the general procedure from DL-alanine methyl ester hydrochloride (1.00 g, 7.17 mmol) and 3-methoxybenzaldehyde (0.72 mL, 5.9 mmol) to yield *rac*-**2h** as a yellow oil in 87% yield (1.13 g, 5.12 mmol). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.52 (d, *J* = 6.8 Hz, 3H), 3.72 (s, 3H), 3.81 (s, 3H), 4.14 (q, *J* = 6.8 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 7.24-7.33 (m, 2H), 7.37 (s, 1H), 8.26 (s, 1H)

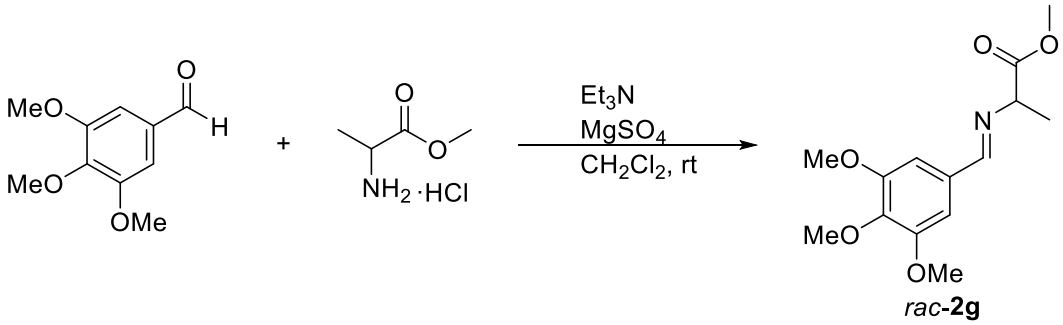
^{13}C NMR ($CDCl_3$, 151 MHz) δ 19.4, 52.1, 55.3, 67.9, 111.9, 117.9, 121.8, 129.5, 137.2, 159.9, 162.9, 172.9. **HRMS** (ESI) calcd. for $C_{12}H_{16}NO_3^+$ $[M+H]^+$ 222.1125, found 222.1130.



rac-**2i**

Methyl (*E*)-2-((3-bromobenzylidene)amino)propanoate (*rac*-2i): Prepared according to the general procedure from DL-alanine methyl ester hydrochloride (1.00 g, 7.17 mmol) and 3-bromobenzaldehyde (0.70 mL, 6.0 mmol) to yield *rac*-**2i** as a yellow oil in 91% yield (1.46 g, 5.40 mmol). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.56 (d, *J* = 6.8 Hz, 3H), 3.78 (s, 3H), 4.20 (q, *J* = 6.8 Hz, 1H), 7.31 (dd, *J* = 7.6, 7.2 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.2 Hz, 1H), 8.00 (s, 1H), 8.28 (s, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 19.6, 52.5, 68.0, 123.1, 127.5, 130.3, 131.1, 134.2, 137.8, 161.6, 172.9. **HRMS** (ESI) calcd. for $C_{11}H_{13}BrNO_2^+$ $[M+H]^+$ 270.0124, found 270.0126.

Synthesis of Methyl (E)-2-((3,4,5-trimethoxybenzylidene)amino)propanoate *rac*-2g

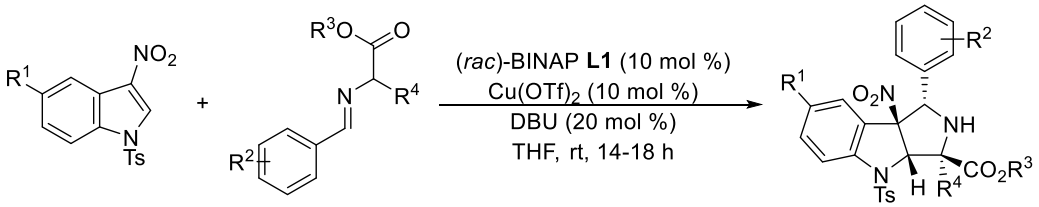


rac-**2g**

To a suspension of 3,4,5-trimethoxybenzaldehyde (1.00 g, 5.09 mmol, 1 equiv) and DL-alanine methyl ester hydrochloride (0.854 g, 6.12 mmol, 1.2 equiv) in CH_2Cl_2 (10.75 ml) was added triethylamine (0.853 ml, 6.12 mmol, 1.2 equiv) and a small amount of magnesium sulfate. The reaction mixture was stirred at room temperature until judged by TLC to be complete. The reaction mixture was then filtered through celite into and concentrated. The reaction mixture was then extracted into diethyl ether. The ether layer was washed with water (2x) and brine (1x). The organic layer was filtered and concentrated under reduced pressure to furnish *rac*-**2g** as a

yellow oil in 74% yield (1.06 g, 3.76 mmol). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.49 (d, *J* = 6.8 Hz, 3H), 3.71 (s, 3H), 3.84 (s, 3H), 3.87 (q, *J* = 6.8 Hz), 6.98 (s, 2H), 8.18 (s, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 19.5, 52.3, 56.4, 61.0, 67.9, 105.6, 131.4, 140.8, 153.5, 162.7, 173.1.

General procedure for synthesis of racemic pyrroloindolines *exo*′-3a-p



1a: R^1 = H
1b: R^1 = Br

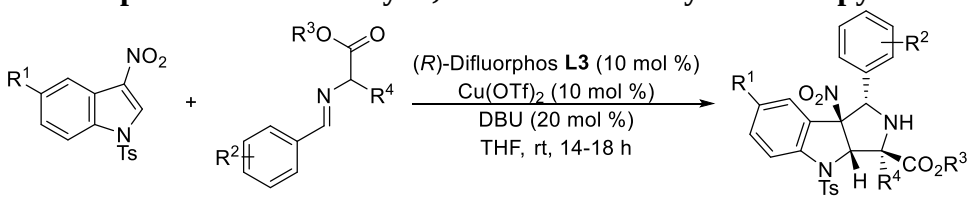
rac-**2a**: R^2 = H, R^3 = Me, R^4 = Me
rac-**2b**: R^2 = 4-CF_3, R^3 = Me, R^4 = Me
rac-**2c**: R^2 = 4-Cl, R^3 = Me, R^4 = Me
rac-**2d**: R^2 = 4-Br, R^3 = Me, R^4 = Me
rac-**2e**: R^2 = 4-Me, R^3 = Me, R^4 = Me
rac-**2f**: R^2 = 4-MeO, R^3 = Me, R^4 = Me
rac-**2g**: R^2 = 3,4,5-MeO, R^3 = Me, R^4 = Me
rac-**2h**: R^2 = 3-MeO, R^3 = Me, R^4 = Me
rac-**2i**: R^2 = 3-Br, R^3 = Me, R^4 = Me
rac-**2j**: R^2 = 2-OMe, R^3 = Me, R^4 = Me
rac-**2k**: R^2 = 2-F, R^3 = Me, R^4 = Me
rac-**2l**: R^2 = 2-Cl, R^3 = Me, R^4 = Me
rac-**2m**: R^2 = H, R^3 = *i*-Pr, R^4 = Me
rac-**2n**: R^2 = H, R^3 = Me, R^4 = Bn
rac-**2o**: R^2 = H, R^3 = Me, R^4 = *i*-Bu

exo′-**3a**: R^1 = H, R^2 = H, R^3 = Me, R^4 = Me
exo′-**3b**: R^1 = H, R^2 = 4-CF_3, R^3 = Me, R^4 = Me
exo′-**3c**: R^1 = H, R^2 = 4-Cl, R^3 = Me, R^4 = Me
exo′-**3d**: R^1 = H, R^2 = 4-Br, R^3 = Me, R^4 = Me
exo′-**3e**: R^1 = H, R^2 = 4-Me, R^3 = Me, R^4 = Me
exo′-**3f**: R^1 = H, R^2 = 4-MeO, R^3 = Me, R^4 = Me
exo′-**3g**: R^1 = H, R^2 = 3,4,5-MeO, R^3 = Me, R^4 = Me
exo′-**3h**: R^1 = H, R^2 = 3-MeO, R^3 = Me, R^4 = Me
exo′-**3i**: R^1 = H, R^2 = 3-Br, R^3 = Me, R^4 = Me
exo′-**3j**: R^1 = H, R^2 = 2-OMe, R^3 = Me, R^4 = Me
exo′-**3k**: R^1 = H, R^2 = 2-F, R^3 = Me, R^4 = Me
exo′-**3l**: R^1 = H, R^2 = 2-Cl, R^3 = Me, R^4 = Me
exo′-**3m**: R^1 = H, R^2 = H, R^3 = *i*-Pr, R^4 = Me
exo′-**3n**: R^1 = H, R^2 = H, R^3 = Me, R^4 = Bn
exo′-**3o**: R^1 = H, R^2 = H, R^3 = Me, R^4 = *i*-Bu
exo′-**3p**: R^1 = Br, R^2 = H, R^3 = Me, R^4 = Me

In a nitrogen-filled dry-box, $Cu(OTf)_2$ (7.2 mg, 0.020 mmol, 0.10 equiv), (*rac*)-BINAP (12.5 mg, 0.0200 mmol, 0.100 equiv), and the appropriate indole **1a** or **1b** (0.200 mmol, 1.00 equiv) were added to a 1-dram vial. In a second 1-dram vial, a 0.48 M solution of the appropriate imino ester *rac*-**2a**-**2o** in THF was prepared. Both vials were sealed with a PTFE/silicone-lined septum cap and removed from the dry-box. The mixture of $Cu(OTf)_2$, *R*-BINAP, and the indole was suspended in THF (0.5 mL) and allowed to stir for 1 h at room temperature. DBU (40 μL of a 1 M solution in THF, 0.040 mmol, 0.20 equiv) and the appropriate iminoester (0.50 mL of a 0.48M solution in THF, 0.24 mmol, 1.2 equiv) were then

added to the vial containing the mixture of Lewis acid and dipolarophile. The reaction mixture was allowed to stir overnight at room temperature and was monitored by TLC. Once the reaction was judged to be complete, the reaction mixture was filtered through a pad of silica (eluting with EtOAc). The crude reaction mixture was then concentrated under reduced pressure. $CDCl_3$ (2 ml) was added to dissolve the crude reaction mixture, and the diastereomeric ratio was determined by ^1H NMR spectroscopy using dibromomethane as the internal standard. The crude reaction mixture was purified by flash column silica gel chromatography (hexanes:EtOAc) to yield racemic pyrroloindolines *exo*′-**3a-p**.

General procedure for catalytic, enantioselective synthesis of pyrroloindolines *exo*′-3a-p



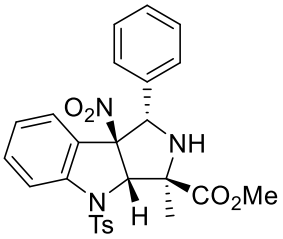
1a: R^1 = H
1b: R^1 = Br

rac-**2a**: R^2 = H, R^3 = Me, R^4 = Me
rac-**2b**: R^2 = 4-CF_3, R^3 = Me, R^4 = Me
rac-**2c**: R^2 = 4-Cl, R^3 = Me, R^4 = Me
rac-**2d**: R^2 = 4-Br, R^3 = Me, R^4 = Me
rac-**2e**: R^2 = 4-Me, R^3 = Me, R^4 = Me
rac-**2f**: R^2 = 4-MeO, R^3 = Me, R^4 = Me
rac-**2g**: R^2 = 3,4,5-MeO, R^3 = Me, R^4 = Me
rac-**2h**: R^2 = 3-MeO, R^3 = Me, R^4 = Me
rac-**2i**: R^2 = 3-Br, R^3 = Me, R^4 = Me
rac-**2j**: R^2 = 2-OMe, R^3 = Me, R^4 = Me
rac-**2k**: R^2 = 2-F, R^3 = Me, R^4 = Me
rac-**2l**: R^2 = 2-Cl, R^3 = Me, R^4 = Me
rac-**2m**: R^2 = H, R^3 = *i*-Pr, R^4 = Me
rac-**2n**: R^2 = H, R^3 = Me, R^4 = Bn
rac-**2o**: R^2 = H, R^3 = Me, R^4 = *i*-Bu

exo′-**3a**: R^1 = H, R^2 = H, R^3 = Me, R^4 = Me
exo′-**3b**: R^1 = H, R^2 = 4-CF_3, R^3 = Me, R^4 = Me
exo′-**3c**: R^1 = H, R^2 = 4-Cl, R^3 = Me, R^4 = Me
exo′-**3d**: R^1 = H, R^2 = 4-Br, R^3 = Me, R^4 = Me
exo′-**3e**: R^1 = H, R^2 = 4-Me, R^3 = Me, R^4 = Me
exo′-**3f**: R^1 = H, R^2 = 4-MeO, R^3 = Me, R^4 = Me
exo′-**3g**: R^1 = H, R^2 = 3,4,5-MeO, R^3 = Me, R^4 = Me
exo′-**3h**: R^1 = H, R^2 = 3-MeO, R^3 = Me, R^4 = Me
exo′-**3i**: R^1 = H, R^2 = 3-Br, R^3 = Me, R^4 = Me
exo′-**3j**: R^1 = H, R^2 = 2-OMe, R^3 = Me, R^4 = Me
exo′-**3k**: R^1 = H, R^2 = 2-F, R^3 = Me, R^4 = Me
exo′-**3l**: R^1 = H, R^2 = 2-Cl, R^3 = Me, R^4 = Me
exo′-**3m**: R^1 = H, R^2 = H, R^3 = *i*-Pr, R^4 = Me
exo′-**3n**: R^1 = H, R^2 = H, R^3 = Me, R^4 = Bn
exo′-**3o**: R^1 = H, R^2 = H, R^3 = Me, R^4 = *i*-Bu
exo′-**3p**: R^1 = Br, R^2 = H, R^3 = Me, R^4 = Me

In a nitrogen-filled dry-box, $Cu(OTf)_2$ (7.2 mg, 0.020 mmol, 0.10 equiv), *R*-Difluorphos (15.3 mg, 0.0200 mmol, 0.100 equiv), and the appropriate indole **1a** or **1b** (0.200 mmol, 1.00 equiv) were added to a 1-dram vial. In a second 1-dram vial, a 0.48 M solution of the appropriate imino ester *rac*-**2a**-**2o** in THF was prepared. Both vials were sealed with a PTFE/silicone-lined septum cap and removed from the dry-box. The mixture of $Cu(OTf)_2$, *R*-

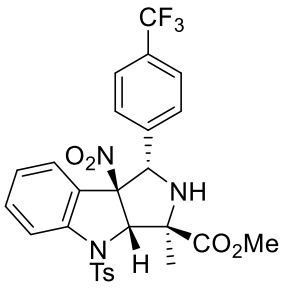
BINAP, and the indole was suspended in THF (0.5 mL) and allowed to stir for 1 h at room temperature. DBU (40 μL of a 1 M solution in THF, 0.040 mmol, 0.20 equiv) and the appropriate iminoester (0.50 mL of a 0.48M solution in THF, 0.24 mmol, 1.2 equiv) were then added to the vial containing the mixture of Lewis acid and dipolarophile. The reaction mixture was allowed to stir overnight at room temperature and was monitored by TLC. Once the reaction was judged to be complete, the reaction mixture was filtered through a pad of silica (eluting with EtOAc). The crude reaction mixture was then concentrated under reduced pressure. $CDCl_3$ (2 ml) was added to dissolve the crude reaction mixture, and the diastereomeric ratio was determined by ^1H NMR spectroscopy using dibromomethane as the internal standard. The crude reaction mixture was purified by flash column silica gel chromatography (hexanes:EtOAc) to yield pyrroloindolines *exo*′-**3a-p**.



exo′-**3a**

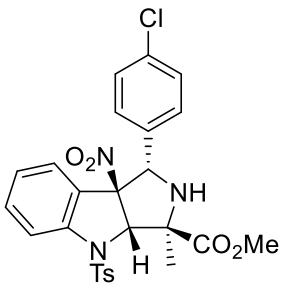
Methyl (1*S*,3*R*,3a*S*,8b*S*)-3-methyl-8b-nitro-1-phenyl-4-tosyl 1,2,3,3a,4,8b-hexahydropyrrolo[3,4-b]indole-3-carboxylate (*exo*′-3a): Prepared according to the general procedure from **1a** (63.2 mg, 0.200 mmol) and **2a** (45.9 mg, 0.240 mmol) to yield a 93:3:4 mixture of *exo*′:*exo*:*endo* diastereomers. The mixture was purified by flash column chromatography (90:10 hexanes:EtOAc) to yield *exo*′-**3a** (76.0 mg, 0.150 mmol, 75%) as a white foam with >95:5 diastereomeric ratio. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 5.9 min (major); t_R 11.5 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 80:20, 1.0 mL/min] to be 89% ee. $[\alpha]_D^{24}$ = -55.8° (c 0.50, $CHCl_3$).**^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.73 (s, 3H), 2.31 (s, 3H), 2.45-2.91 (br s, 1H), 3.96 (s, 3H), 4.76 (s, 1H), 5.82 (dd, *J* = 7.8, 0.8 Hz, 1H), 5.88 (s, 1H), 6.72 (ddd, *J* = 8.4, 7.8, 0.8 Hz,

1H), 7.01 (d, *J* = 7.2 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 7.22 (appt, *J* = 7.6 Hz, 2H), 7.29-7.38 (m, 2H), 7.45 (d, *J* = 8.1 Hz, 2H) , 7.77 (d, *J* = 8.4 Hz, 1H) **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 21.8, 22.2, 53.6, 69.0, 69.1, 74.5, 101.5, 117.0, 124.1, 124.4, 127.7, 128.2, 128.7, 129.0, 129.3, 129.88, 131.6, 132.8, 135.2, 144.7, 145.1, 175.8. **HRMS** (ESI) calcd. for $C_{26}H_{26}N_3O_6S$+ [M+H]+ 508.1537, found 508.1538.



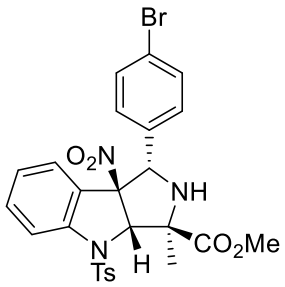
exo′-**3b**

Methyl (1*S*,3*R*,3a*S*,8b*S*)-3-methyl-8b-nitro-4-tosyl-1-(4-(trifluoromethyl)phenyl)-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-b]indole-3-carboxylate (*exo′*-3b): Prepared according to the general procedure from **1a** (63.2 mg, 0.200 mmol) and **2b** (62.2 mg, 0.240 mmol) to yield a >98:1:1 mixture of *exo′*:*exo*:*endo* diastereomers. The mixture was purified by flash column chromatography (100:0 to 80:20 hexanes:EtOAc) to yield *exo′*-**3b** (96.0 mg, 0.167 mmol, 83%) as a white foam with >95:5 diastereomeric ratio. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 6.3 min (major); t_R 34.1 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 80:20, 1.0 mL/min] to be 81% ee. $[\alpha]_D^{25}$ = -69.3° (c 0.55, $CHCl_3$).**^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.75 (s, 1H), 2.31 (s, 3H), 2.48-2.94 (br s, 1H), 3.96 (s, 3H), 4.81 (s, 1H), 5.82 (d, *J* = 8.0 Hz, 1H), 5.89 (s, 1H), 6.73 (dd, 8.2, 7.6 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 2H), 7.17 (d, *J* = 6.6 Hz, 2H), 7.36 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.43-7.54 (m, 4H), 7.79 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR** ^{13}C NMR ($CDCl_3$, 151 MHz) δ 21.7, 22.0, 53.6, 68.2, 68.9, 74.2, 101.2, 117.0, 124.06 (q, *J* = 272.3 Hz), 124.07, 124.1, 124.9 (q, *J* = 3.7 Hz), 127.8, 128.1, 129.4, 129.8, 131.4 (q, *J* = 32.5 Hz), 131.9, 132.6, 139.5, 144.7, 145.2, 175.5. **^{19}F NMR** ($CDCl_3$, 565 MHz) δ -63.27. **HRMS** (ESI) calcd. for $C_{27}H_{25}F_3N_3O_6S$+ [M+H]+ 576.1411, found 576.1415.



exo′-**3c**

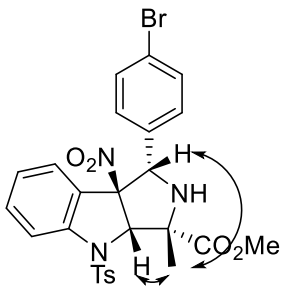
Methyl (1*S*,3*R*,3a*S*,8b*S*)-1-(4-chlorophenyl)-3-methyl-8b-nitro-4-tosyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-b]indole-3-carboxylate (*exo′*-3c): Prepared according to the general procedure from **1a** (63.2 mg, 0.200 mmol) and **2c** (54.2 mg, 0.240 mmol) to yield a 78:5:17 mixture of *exo′*:*exo*:*endo* diastereomers. The mixture was purified by flash column chromatography (100:0 to 80:20 hexanes:EtOAc) to yield *exo′*-**3c** (76.0 mg, 0.140 mmol, 70%) as a white foam with >95:5 diastereomeric ratio. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 7.1 min (major); t_R 25.8 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 80:20, 1.0 mL/min] to be 88% ee. $[\alpha]_D^{23}$ = -39.5° (c 0.51, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.72 (s, 3H), 2.30 (s, 3H), 2.62-2.73 (br s, 1H), 3.95 (s, 3H), 4.71 (d, *J* = 3.5 Hz, 1H) 5.87 (d, *J* = 1.2 Hz, 1H), 5.91 (dd, *J* = 7.6, 0.8 Hz, 1H), 6.77 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H) 7.20 (d, *J* = 8.0 Hz, 2H), 7.36 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 1H) **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 21.8, 22.1, 53.6, 68.2, 68.9, 74.2, 101.2, 117.0, 124.2, 127.8, 128.3, 128.5, 129.9 (2C), 130.2, 131.8, 132.7, 133.8, 135.1, 144.7, 145.2, 175.7. **HRMS** (ESI) calcd. for $C_{26}H_{25}ClN_3O_6S$+ [M+H]+ 542.1147, found 542.1152.



exo′-**3d**

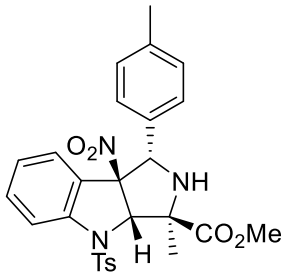
Methyl (1*S*,3*R*,3a*S*,8b*S*)-1-(4-bromophenyl)-3-methyl-8b-nitro-4-tosyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-b]indole-3-carboxylate (*exo′*-3d): Prepared according to the general procedure from **1a** (63.2 mg, 0.200 mmol) and **2d** (64.8 mg, 0.240 mmol) to yield a 95:4:1 mixture of *exo′*:*exo*:*endo* diastereomers. The mixture was purified by flash column chromatography (100:0 to 80:20 hexanes:EtOAc) to yield *exo′*-**3d** (92.0 mg, 0.157 mmol, 78%) as a white foam with >95:5 diastereomeric ratio. The enantiomeric excess was

determined by HPLC analysis (254 nm, 25 °C) t_R 7.7 min (major); t_R 31.4 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 80:20, 1.0 mL/min] to be 90% ee. $[\alpha]_D^{23}$ = -252.1° (c 0.48, $CHCl_3$). **^{1}H NMR** ($(CD_3)_2CO$, 400 MHz) δ 1.70 (s, 3H), 2.32 (s, 3H), 3.47-3.57 (br s, 1H), 3.89 (s, 3H), 4.86 (d, *J* = 3.6 Hz), 5.89-6.01 (m, 2H), 6.83 (ddd, *J* = 8.2, 7.4, 0.7 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.40-7.49 (m, 3H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 1H) **^{13}C NMR** ($(CD_3)_2CO$, 101 MHz) δ 21.4, 21.9, 53.4, 68.6, 69.2, 75.2, 102.0, 117.2, 123.2, 124.7, 125.4, 128.6, 128.8, 130.6, 131.6, 131.7, 132.6, 133.8, 136.1, 145.5, 146.0, 175.5. **HRMS** (ESI) calcd. for $C_{26}H_{25}BrN_3O_6S$+ [M+H]+ 586.0642, found 586.0643.



exo-**3d**

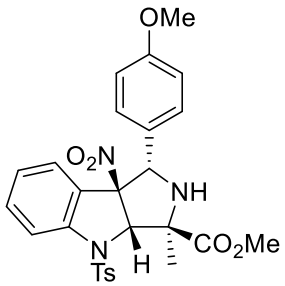
Methyl (1*S*,3*S*,3a*S*,8b*S*)-1-(4-bromophenyl)-3-methyl-8b-nitro-4-tosyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-b]indole-3-carboxylate (*exo*-3d): An analytical sample of *exo*-**3d** was isolated from the reaction of **1a** and **2d**. The relative stereochemistry was assigned by NOE analysis. **^{1}H NMR** ($(CD_3)_2CO$, 400 MHz) δ 1.87 (s, 3H), 2.29 (s, 3H), 3.32 (d, *J* = 12.0 Hz, 1H), 3.87 (s, 3H), 5.23 (d, *J* = 12.0 Hz, 1H), 5.39 (s, 1H), 5.96 (dd, *J* = 7.9, 0.6 Hz, 1H), 6.93 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.47 (dd, *J* = 7.9, 7.6 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 1H). **HRMS** (ESI) calcd. for $C_{26}H_{25}BrN_3O_6S$+ [M+H]+ 586.0642, found 586.0655.



exo′-**3e**

Methyl (1*S*,3*R*,3a*S*,8b*S*)-3-methyl-8b-nitro-1-(p-tolyl)-4-tosyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-b]indole-3-carboxylate (*exo′*-3e): Prepared according to the general procedure from **1a** (63.2 mg, 0.200 mmol) and **2e** (49.3 mg, 0.240 mmol) to yield a 90:7:3 mixture of

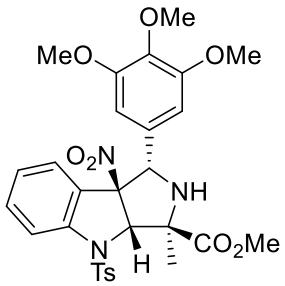
exo′:*exo*:*endo* diastereomers. The mixture was purified by flash column chromatography (100:0 to 80:20 hexanes:EtOAc) to yield *exo*′-**3e** (79.0 mg, 0.151 mmol, 76%) as a white foam with >95:5 diastereomeric ratio. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 6.6 min (major); t_R 22.4 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 80:20, 1.0 mL/min] to be 91% ee. $[\alpha]_D^{25}$ = -312.5° (c 0.51, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.72 (s, 3H), 2.30 (s, 3H), 2.33 (s, 3H), 2.55-2.78 (br s, 1H), 3.95 (s, 3H), 4.72 (s, 1H), 5.83-5.94 (m, 2H), 6.75 (dd, *J* = 8.2, 7.8 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 2H), 7.03 (d, *J* = 7.6 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.34 (appt, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 1H) **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 21.4, 21.8, 22.2, 53.6, 68.9, 69.0, 74.4, 101.4, 116.9, 124.1, 124.4, 127.7, 128.5, 128.8, 129.1, 129.9, 131.6, 132.0, 132.8, 139.1, 144.6, 145.1, 175.9. **HRMS** (ESI) calcd. for $C_{27}H_{28}N_3O_6S$+ [M+H]+ 522.1693, found 522.1695.



exo′-**3f**

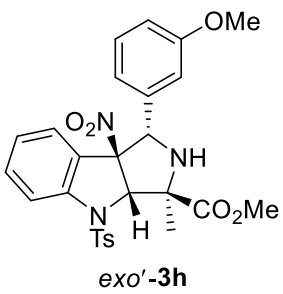
Methyl (1*S*,3*R*,3a*S*,8b*S*)-1-(4-methoxyphenyl)-3-methyl-8b-nitro-4-tosyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-b]indole-3-carboxylate (*exo*′-3f): Prepared according to the general procedure from **1a** (64.4 mg, 0.204 mmol) and **2f** (53.1 mg, 0.240 mmol) to yield a 95:4:1 mixture of *exo*′:*exo*:*endo* diastereomers. The mixture was purified by flash column chromatography (100:0 to 70:30 hexanes:EtOAc) to yield *exo*′-**3f** (78.0 mg, 0.145 mmol, 71%) as a white foam with >95:5 diastereomeric ratio. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 9.2 min (major); t_R 37.6 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 80:20, 1.0 mL/min] to be 96% ee. $[\alpha]_D^{25}$ = -141.2° (c 0.51, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.72 (s, 3H), 2.30

(s, 3H), 2.59-2.73 (bs, 1H), 3.79 (s, 3H), 3.95 (s, 3H), 4.69 (s, 1H), 5.88 (s, 1H), 5.93 (d, *J* = 7.8 Hz, 1H), 6.69-6.82 (m, 3H), 6.91 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 1H) **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 21.8, 22.2, 53.6, 55.5, 68.79, 68.84, 74.3, 101.4, 113.4, 116.9, 124.1, 124.4, 127.1, 127.7, 129.1, 129.86, 129.90, 131.6, 132.7, 144.6, 145.1, 160.3, 175.9 **HRMS** (ESI) calcd. for $C_{27}H_{28}N_3O_7S$+ [M+H]+ 538.1642, found 538.1642.



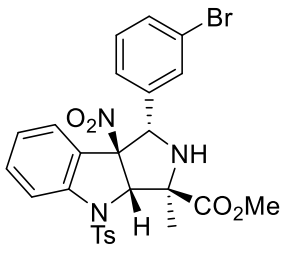
exo′-**3g**

Methyl (1*S*,3*R*,3a*S*,8b*S*)-3-methyl-8b-nitro-4-tosyl-1-(3,4,5-trimethoxyphenyl)-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-b]indole-3-carboxylate (*exo′*-3g): Prepared according to the general procedure from **1a** (63.2 mg, 0.200 mmol) and **2g** (67.5 mg, 0.240 mmol) to yield a 65:13:22 mixture of *exo′*:*exo*:*endo* diastereomers. The mixture was purified by flash column chromatography (100:0 to 60:40 hexanes:EtOAc) to yield *exo′*-**3g** (47.0 mg, 0.078 mmol, 39%) as a yellow foam with >95:5 diastereomeric ratio. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 44.4 min (major); t_R 51.2 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 95:5, 1.0 mL/min] to be 32% ee. $[\alpha]_D^{24}$ = +18.4° (c .434, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.73 (s, 3H), 2.30 (s, 3H), 2.69 (s, 1H), 3.63 (s, 6H), 3.82 (s, 3H), 3.96 (s, 3H), 4.67 (s, 1H), 5.83 (s, 1H), 5.97 (d, *J* = 7.8 Hz, 1H), 6.20 (s, 2H), 6.78 (dd, *J* = 8.2, 7.6 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.35 (dd, *J* = 7.8, 7.6 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 21.8, 22.2, 53.6, 56.2, 61.2, 68.9, 69.3, 74.3, 101.4, 110.2, 117.0, 124.0, 124.4, 127.7, 129.1, 129.9, 130.7, 131.6, 132.6, 138.6, 144.6, 145.2, 152.9, 175.8. **HRMS** (ESI) calcd. for $C_{29}H_{32}N_3O_9S$+ [M+H]+ 598.1854, found 598.1855.



exo′-**3h**

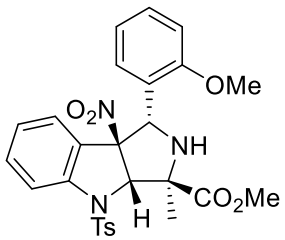
Methyl (1*S*,3*R*,3a*S*,8b*S*)-1-(3-methoxyphenyl)-3-methyl-8b-nitro-4-tosyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-b]indole-3-carboxylate (*exo′*-3h): Prepared according to the general procedure from **1a** (63.2 mg, 0.200 mmol) and **2h** (53.1 mg, 0.240 mmol) to yield a 89:8:3 mixture of *exo′*:*exo*:*endo* diastereomers. The mixture was purified by flash column chromatography (100:0 to 70:30 hexanes:EtOAc) to yield *exo′*-**3h** (77.0 mg, 0.143 mmol, 72%) as a white foam with >95:5 diastereomeric ratio. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 7.7 min (major); t_R 12.7 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 80:20, 1.0 mL/min] to be 89% ee. $[\alpha]_D^{25}$ = -69.1° (c 0.55, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.73 (s, 3H), 2.30 (s, 3H), 2.41-2.93 (bs, 1H), 3.63 (s, 3H), 3.96 (s, 3H), 4.76 (s, 1H), 5.86 (s, 1H), 5.91 (d, *J* = 7.6 Hz, 1H), 6.51 (s, 1H), 6.62 (d, *J* = 6.4 Hz, 1H), 6.75 (dd, *J* = 8.2, 7.8 Hz, 1H), 6.86 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.14 (dd, *J* = 8.2, 6.4 Hz, 1H), 7.34 (ddd, *J* = 7.8, 7.6, 0.8 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 1H) **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 21.7, 22.1, 53.5, 55.4, 68.92, 68.99, 74.5, 101.4, 113.5, 115.5, 116.9, 120.96, 120.99, 124.0, 124.3, 127.7, 129.0, 129.2, 129.8, 131.6, 132.7, 144.6, 145.1, 159.4, 175.8. **HRMS** (ESI) calcd. for $C_{27}H_{28}N_3O_7S$+ [M+H]+ 538.1642, found 538.1646.



exo′-**3i**

Methyl (1*S*,3*R*,3a*S*,8b*S*)-1-(3-bromophenyl)-3-methyl-8b-nitro-4-tosyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-b]indole-3-carboxylate (*exo′*-3i): Prepared according to the general procedure from **1a** (63.2 mg, 0.200 mmol) and **2i** (64.8 mg, 0.240 mmol) to yield a 69:8:23 mixture of

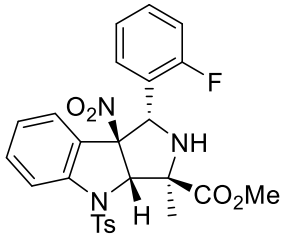
exo′:*exo*:*endo* diastereomers. The mixture was purified by flash column chromatography (100:0 to 80:20 hexanes:EtOAc) to yield *exo′*-**3i** (47.0 mg, 0.080 mmol, 40%) as a white foam with >95:5 diastereomeric ratio. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 7.6 min (major); t_R 12.3 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 80:20, 1.0 mL/min] to be 80% ee. $[\alpha]_D^{24}$ = -846.2° (c 0.56, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.73 (s, 3H), 2.31 (s, 3H), 2.64-2.74 (br s, 1H), 3.95 (s, 3H), 4.72(s, 1H), 5.82-5.92 (m, 2H), 6.79 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.98 (d, *J* = 6.6 Hz, 1H), 7.06-7.17 (m, 4H), 7.37 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.42-7.50 (m, 3H), 7.79 (d, *J* = 8.0 Hz, 1H) **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 21.8, 22.1, 53.7, 68.2, 69.0, 74.2, 101.3, 117.1, 122.3, 124.10, 124.11, 127.6, 127.8, 128.5, 129.7, 129.9, 131.85, 131.91, 132.4, 132.6, 137.7, 144.7, 145.2, 175.6. **HRMS** (ESI) calcd. for $C_{26}H_{25}BrN_3O_6S$+ [M+H]+ 586.0642, found 586.0646.



exo′-**3j**

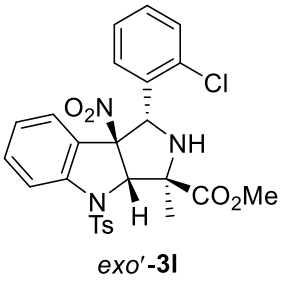
Methyl (1*S*,3*R*,3a*S*,8b*S*)-1-(2-methoxyphenyl)-3-methyl-8b-nitro-4-tosyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-b]indole-3-carboxylate(*exo′*-3j): Prepared according to the general procedure from **1a** (63.2 mg, 0.200 mmol) and **2j** (53.1 mg, 0.240 mmol) to yield a 74:7:19 mixture of *exo′*:*exo*:*endo* diastereomers. The mixture was purified by flash column chromatography (100:0 to 80:20 hexanes:EtOAc) to yield *exo′*-**3j** (42.0 mg, 0.078 mmol, 39%) as a white foam with >95:5 diastereomeric ratio. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 7.0 min (major); t_R 16.5 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 80:20, 1.0 mL/min] to be 82% ee. $[\alpha]_D^{25}$ = +42.4° (c 0.24, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.71 (s, 3H), 2.30 (s, 3H), 2.55-2.81 (br s, 1H), 3.60 (s, 3H), 4.00 (s, 3H), 5.24 (s, 1H), 5.76 (s, 1H), 5.93 (d, *J* = 8.0 Hz, 1H),

6.72-6.78 (m, 2H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.20-7.43 (m, 4H), 7.76 (d, *J* = 8.0 Hz, 1H) **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 21.8, 22.4, 53.6, 54.9, 64.3, 69.1, 76.1, 100.4, 109.8, 117.3, 120.4, 123.9, 124.2, 124.4, 127.4, 128.6, 129.5, 129.8, 129.9, 131.2, 132.5, 144.6, 145.1, 157.5, 176.1. **HRMS** (ESI) calcd. for $C_{27}H_{28}N_3O_7S$+ [M+H]+ 538.1642, found 538.1646.



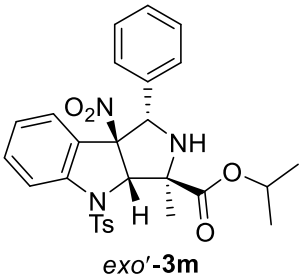
exo′-**3k**

Methyl (1*S*,3*R*,3a*S*,8b*S*)-1-(2-fluorophenyl)-3-methyl-8b-nitro-4-tosyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-b]indole-3-carboxylate (*exo′*-3k): Prepared according to the general procedure from **1a** (64.8 mg, 0.205 mmol) and **2k** (50.2 mg, 0.240 mmol) to yield a 67:5:27 mixture of *exo′*:*exo*:*endo* diastereomers. The mixture was purified by flash column chromatography (100:0 to 80:20 hexanes:EtOAc) to yield *exo′*-**3k** (55.0 mg, 0.104 mmol, 51%) as a white foam with >95:5 diastereomeric ratio. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 5.9 min (major); t_R 15.3 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 80:20, 1.0 mL/min] to be 87% ee. $[\alpha]_D^{25}$ = -24.3° (c 0.41, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.71 (s, 3H), 2.29 (s, 3H), 2.43-2.94 (br s, 1H), 3.98 (s, 3H) 5.14 (s, 1H), 5.85 (s, 1H), 6.01 (d, *J* = 7.8 Hz, 1H), 6.78 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.88-6.98 (m, 2H), 7.02 (appt, *J* = 9.0 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.27-7.43 (m, 4H), 7.78 (d, *J* = 8.0 Hz, 1H) **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 21.7, 22.3, 53.7, 62.9, 69.1, 74.9, 100.6, 115.3 (d, *J* = 21.4 Hz), 117.2, 122.5 (d, *J* = 12.2 Hz), 123.8 (d, *J* = 3.3 Hz), 123.9, 124.3, 127.5, 129.2, 129.88, 129.92 (d, *J* = 3.5 Hz), 130.6 (d, *J* = 8.5 Hz) 131.6, 132.4, 144.7, 145.2, 161.1 (d, *J* = 248.1 Hz), 175.7. **^{19}F NMR** ($CDCl_3$, 565 MHz) δ -117.22. **HRMS** (ESI) calcd. for $C_{26}H_{25}FN_3O_6S$+ [M+H]+ 526.1443, found 526.1455.



exo′-**3l**

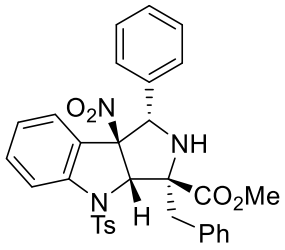
Methyl (1*S*,3*R*,3a*S*,8b*S*)-1-(2-chlorophenyl)-3-methyl-8b-nitro-4-tosyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-b]indole-3-carboxylate (*exo′*-3l): Prepared according to the general procedure from **1a** (63.2 mg, 0.200 mmol) and **2l** (54.2 mg, 0.240 mmol) to yield a 88:8:4 mixture of *exo′*:*exo*:*endo* diastereomers. The mixture was purified by flash column chromatography (100:0 to 80:20 hexanes:EtOAc) to yield *exo′*-**3l** (92.0 mg, 0.170 mmol, 85%) as a white foam with >95:5 diastereomeric ratio. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 5.4 min (major); t_R 7.5 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 80:20, 1.0 mL/min] to be 79% ee. $[\alpha]_D^{25}$ = -35.3° (c 0.62, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.72 (s, 3H), 2.30 (s, 3H), 2.59-2.82 (br s, 1H), 4.02 (s, 3H), 5.35 (s, 1H), 5.78 (s, 1H), 6.03 (d, *J* = 7.8 Hz, 1H), 6.78 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 7.00 (dd, *J* = 7.6, 7.4 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.22 (ddd, *J* = 8.0, 7.6, 1.4 Hz, 1H), 7.32-7.41 (m, 4H), 7.79 (d, *J* = 8.0 Hz, 1H) **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 21.7, 22.4, 53.7, 65.5, 68.9, 75.4, 100.3, 117.3, 123.8, 124.1, 126.3, 127.5, 129.6, 129.9, 130.0, 130.1, 131.0, 131.6, 132.2, 133.3, 134.5, 144.7, 145.3, 175.9. **HRMS** (ESI) calcd. for $C_{26}H_{25}ClN_3O_6S$+ [M+H]+ 542.1147, found 542.1152.



exo′-**3m**

Isopropyl (1*S*,3*R*,3a*S*,8b*S*)-3-methyl-8b-nitro-1-phenyl-4-tosyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-b]indole-3-carboxylate (*exo′*-3m): Prepared according to the general procedure from **1a** (63.2 mg, 0.200 mmol) and **2m** (52.6 mg, 0.240 mmol) to yield a 93:7 mixture of *exo′*:*exo* diastereomers. The mixture was purified by flash column chromatography (100:0 to

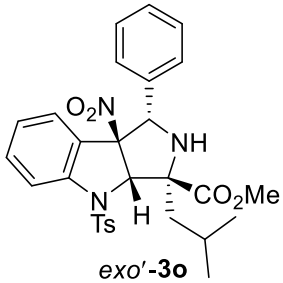
80:20 hexanes:EtOAc) to yield *exo′*-**3m** (76.0 mg, 0.142 mmol, 71%) as a white foam with >95:5 diastereomeric ratio. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 4.6 min (major); t_R 6.7 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 80:20, 1.0 mL/min] to be 94% ee. $[\alpha]_D^{25}$ = -45.3° (c 0.53, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.41 (d, *J* = 6.0 Hz, 3H), 1.46 (d, *J* = 6.0 Hz, 3H), 1.71 (s, 3H), 2.31 (s, 3H), 2.43-3.12 (br s, 1H), 4.76 (s, 1H), 5.24 (septet, *J* = 6.0 Hz, 1H), 5.74-5.93 (m, 2H), 6.73 (dd, *J* = 8.2, 7.6 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.22 (appt, *J* = 7.2 Hz, 2H), 7.29-7.38 (m, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 8.2 Hz, 1H) **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 21.7, 21.95, 22.04, 22.1, 68.9, 69.3, 70.3, 74.4, 101.6, 117.1, 124.1, 124.4, 127.7, 128.2, 128.7, 129.0, 129.3, 129.8, 131.6, 132.6, 135.4, 144.8, 145.1, 174.9. **HRMS** (ESI) calcd. for $C_{28}H_{30}N_3O_6S$+ [M+H]+ 536.1850, found 536.1851.



exo′-**3n**

Methyl (1*S*,3*R*,3a*S*,8b*S*)-3-benzyl-8b-nitro-1-phenyl-4-tosyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-b]indole-3-carboxylate (*exo′*-3n): Prepared according to the general procedure from **1a** (64.8 mg, 0.205 mmol) and **2n** (64.2 mg, 0.240 mmol) to yield a 48:25:27 mixture of *exo′*:*exo*:*endo* diastereomers. The mixture was purified by flash column chromatography (95:5 to 90:10 hexanes:EtOAc) to yield *exo′*-**3n** (80.0 mg, 0.137 mmol, 68%) as a yellow foam with 46:24:30 *exo′*:*exo*:*endo* diastereomeric ratio. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 57.2 min (major); t_R 72.6 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 98:2, 1.0 mL/min] to be 36% ee. $[\alpha]_D^{25}$ = -327.3° (c 0.22, $CHCl_3$). ^{1}H NMR and ^{13}C NMR data are reported for the major diastereomer: **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 2.31 (s, 3H), 3.27 (d, *J* = 13.5 Hz, 1H), 3.77 (d, *J*

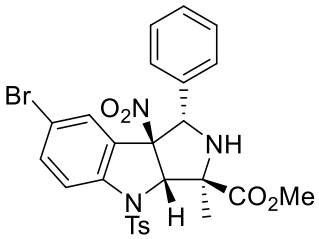
= 13.5 Hz, 1H), 3.89 (s, 3H), 3.95 (s, 1H), 4.74 (s, 1H), 5.84-5.88 (m, 2H), 6.78 (dd, *J* = 8.2 Hz, 7.6 Hz, 1H), 7.02 (d, *J* = 7.4 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 6.9 Hz, 2H), 7.19-7.23 (m, 3H), 7.27-7.35 (m, 3H), 7.40 (dd, *J* = 7.8, 7.6 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.83 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 21.8, 42.3, 53.2, 69.4, 72.8, 75.5, 101.5, 117.4, 124.3, 124.4, 127.3, 127.7, 128.2, 128.7, 129.3, 129.88, 129.91, 129.93, 130.7, 131.7, 132.5, 135.5, 136.1, 144.6, 145.3, 174.1. **HRMS** (ESI) calcd. for $C_{32}H_{30}N_3O_6S$+ [M+H]+ 584.1850, found 584.1849.



exo′-**3o**

Methyl (1*S*,3*R*,3a*S*,8b*S*)-3-isobutyl-8b-nitro-1-phenyl-4-tosyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-b]indole-3-carboxylate (*exo′*-3o): Prepared according to the general procedure from **1a** (63.2 mg, 0.200 mmol) and **2o** (60.0 mg, 0.240 mmol) to yield a 79:19:9 mixture of *exo′*:*exo*:*endo* diastereomers. The mixture was purified by flash column chromatography (95:5 to 85:15 hexanes:EtOAc) to yield *exo′*-**3o** (78.0 mg, 0.142 mmol, 71%) as a yellow foam with 75:20:0 *exo′*:*exo*:*endo* diastereomeric ratio. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 27.8 min (major); t_R 59.5 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 99:1, 1.0 mL/min] to be 30% ee. $[\alpha]_D^{25}$ = -45.9° (c 0.74, $CHCl_3$). ^{1}H NMR and ^{13}C NMR data are reported for the major diastereomer: **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 0.95 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 1.87 (dd, *J* = 14.4, 6.3 Hz, 1H), 2.29 (s, 3H), 2.39 (dd, *J* = 14.4, 6.3 Hz, 1H), 2.67 (bs, 1H), 3.99 (s, 3H), 4.83 (s, 1H), 5.74 (s, 1H), 5.80 (d, *J* = 7.7 Hz, 1H), 6.75 (appt, *J* = 8.2 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 2H), 7.05 (d, *J* = 7.6 Hz, 2H), 7.19-7.25 (m, 2H), 7.30-7.38 (m, 3H), 7.78 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 21.7, 24.2, 24.3, 24.9, 44.1, 53.4, 70.0, 71.9, 76.4, 101.1, 117.6,

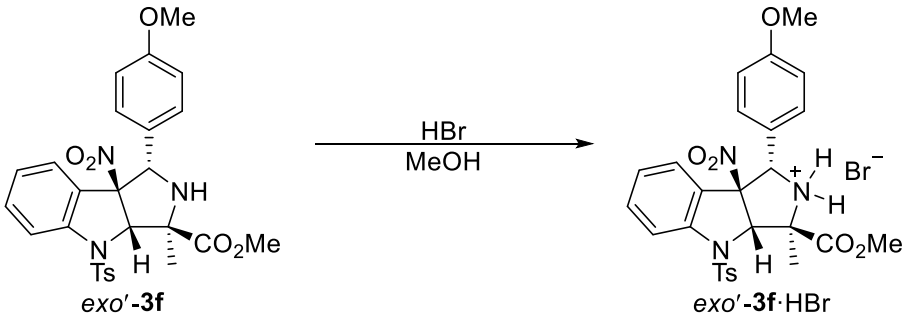
124.3, 124.5, 127.6, 128.2, 128.5, 129.3, 129.6, 129.8, 131.5, 132.5, 135.5, 144.7, 145.1, 175.6. **HRMS** (ESI) calcd. for $C_{29}H_{32}N_3O_6S$+ [M+H]+ 550.2006, found 550.2010.



exo′-**3p**

Methyl (1*S*,3*R*,3a*S*,8b*S*)-7-bromo-3-methyl-8b-nitro-1-phenyl-4-tosyl-1,2,3,3a,4,8b-hexahydropyrrolo[3,4-b]indole-3-carboxylate (*exo′*-3p): Prepared according to the general procedure from **1b** (79.0 mg, 0.200 mmol) and **2a** (45.9 mg, 0.240 mmol) to yield a >98:1:1 mixture of *exo′*:*exo*:*endo* diastereomers. The mixture was purified by flash column chromatography (100:0 to 80:20 hexanes:EtOAc) to yield *exo′*-**3p** (93.0 mg, 0.159 mmol, 79%) as a white foam with >95:5 diastereomeric ratio. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) t_R 6.1 min (major); t_R 8.4 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 80:20, 1.0 mL/min] to be 91% ee. $[\alpha]_D^{25}$ = -312.5° (c 0.51, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.71 (s, 3H), 2.33 (s, 3H), 2.69-2.77 (br s, 1H), 3.96 (s, 3H), 4.73 (d, *J* = 3.4 Hz, 1H), 5.80 (d, *J* = 2.0 Hz, 1H), 5.86 (d, *J* = 1.2 Hz, 1H), 7.00 (d, *J* = 7.6 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.28 (dd, *J* = 7.6, 7.4 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.42-7.47 (m, 3H), 7.64 (d, *J* = 8.7 Hz, 1H) **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 21.8, 22.1, 53.6, 69.1, 69.3, 74.7, 100.9, 116.9, 118.3, 126.1, 127.6, 128.3, 128.5, 129.7, 130.1, 132.2, 132.4, 134.5, 134.7, 143.7, 145.5, 175.6. **HRMS** (ESI) calcd. for $C_{26}H_{25}BrN_3O_6S$+ [M+H]+ 586.0642, found 586.0641.

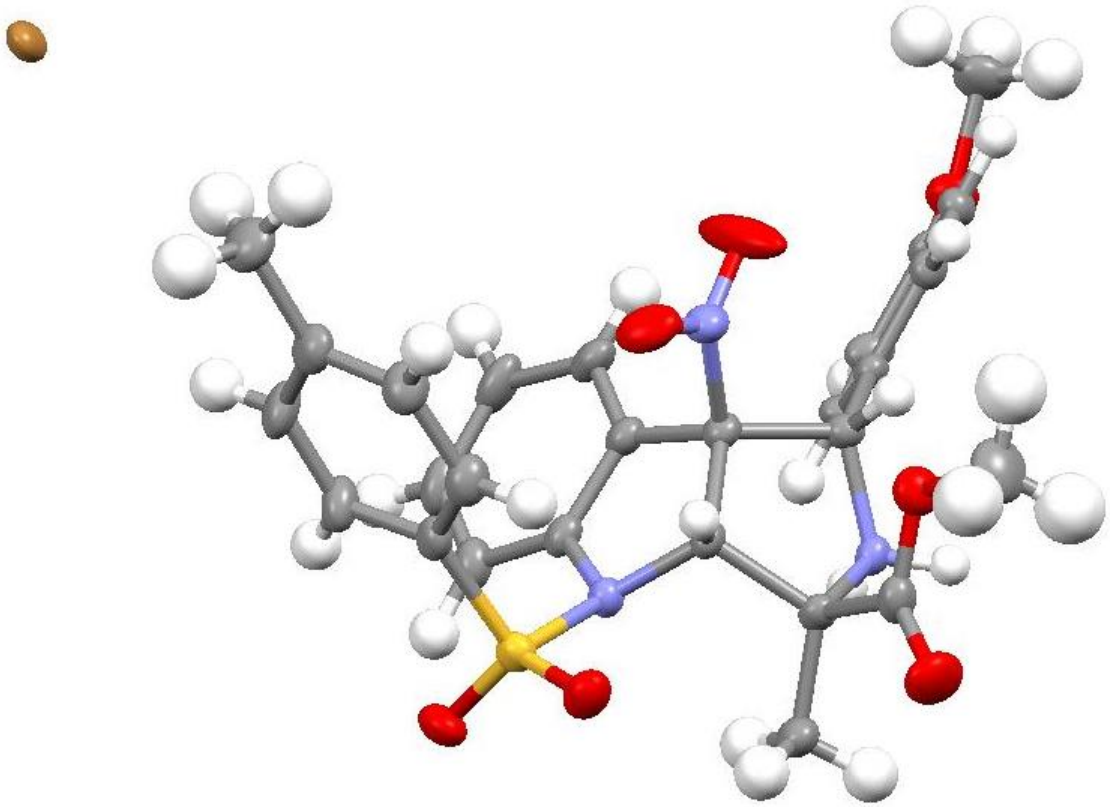
Synthesis of *exo´*-3f·HBr



Compound *exo´*-**3f** (153.0 mg, 0.284 mmol, 86% ee) was added to a 20 mL scintillation vial and dissolved in 6 mL of methanol. To this solution were added 6 drops of concentrated HBr. The vial was capped and the reaction was stirred overnight at room temperature. The volatiles were evaporated under reduced pressure to yield *exo´*-**3f**·HBr (175.0 mg, 0.283 mmol, >99%). $[\alpha]_D^{25}$ = -30.7° (c 0.52, $CHCl_3$). A single crystal of this compound was grown from hexane:dichloromethane. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H), 2.29 (s, 3H), 3.76 (s, 3H), 4.03 (s, 3H), 5.54-5.61 (m, 2H), 5.89 (d, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 2H), 6.88 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.29-7.40 (m, 4H), 7.47 (dd, *J* = 7.6, 7.4 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.87-8.17 (br s, 2H). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 19.2, 21.7, 54.9, 55.4, 68.9, 71.8, 74.2, 77.4, 99.7, 114.0, 118.9, 120.8, 125.3, 127.6, 129.5, 130.0, 131.2, 132.0, 133.5, 144.9, 145.7, 161.0, 169.8. **HRMS** (ESI) calcd. for $C_{27}H_{28}N_3O_7S^+$ [M+] 538.1642, found 538.1644.

Absolute stereochemistry and structure of 3f·HBr

The absolute configuration of *exo*′-**3f**·HBr was determined to be (1*S*,3*R*,3a*S*,8b*S*) by X-ray crystallographic analysis. Supplementary X-ray diffraction data and structure refinement for *exo*′-**3f**·HBr contained in CCDC 1434459. These data can be accessed free of charge from the Cambridge Crystallographic Data Center at https://summary.ccdc.cam.ac.uk/structure-summary-form



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CHAPTER 3

CATALYTIC, ENANTIOSELECTIVE, NITRILE IMINE CYCLOADDITIONS WITH METHYLENEINDOLINES

Modified from a paper published in *Organic and Biomolecular Chemistry*[a]

Anthony L. Gerten, Michael C. Slade, Kelsie M. Pugh, Levi M. Stanley[*]

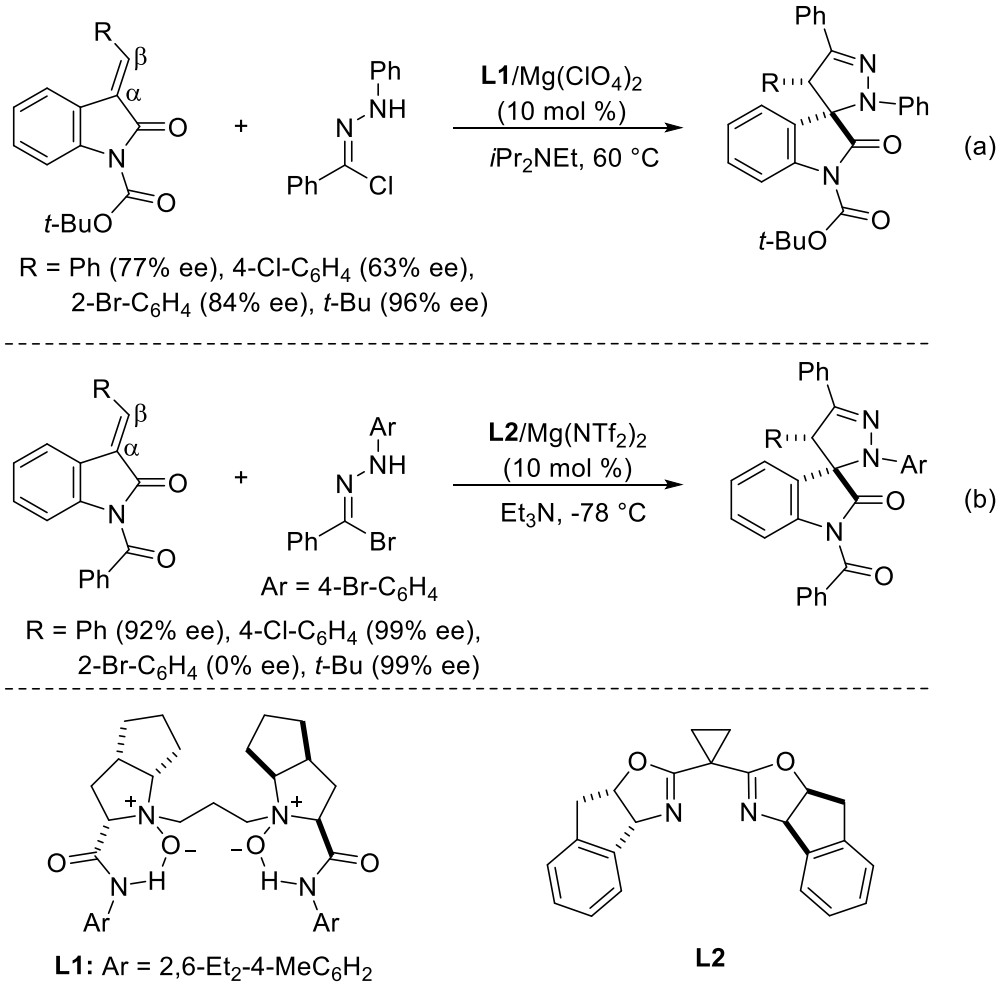
Abstract

Catalytic, enantioselective 1,3-dipolar cycloadditions of nitrile imines with methyleneindolinones are reported. The spiro[pyrazolin-3,3´-oxindole] products are formed in good yields (up to 98%) and high enantioselectivity (up to 99% ee).

Introduction

1,3-Dipolar cycloadditions of nitrile imines with alkenes represent an attractive strategy to generate pyrazolines. Reactions of nitrile imines with a wide variety of olefinic dipolarophiles have been developed to provide an array of compounds containing a pyrazoline motif.[1,2] Despite efforts to develop the utility of nitrile imine cycloadditions, controlling the enantioselectivity of nitrile imine cycloadditions remains difficult to achieve. The high reactivity of nitrile imines renders catalytic, enantioselective cycloadditions of this class of dipole challenging due to the high rates of uncatalyzed background cycloaddition. To date, only a select few examples of catalytic, enantioselective cycloadditions of nitrile imines have been reported. Sibi *et al.* showed that 1,3-dipolar cycloadditions of nitrile imines with α,β-unsaturated oxazolidinone and pyrazolidinone imides occur in high yields with high enantioselectivity in the presence of chiral, non-racemic magnesium catalysts.[3] However, the scope of dipolarophiles in enantioselective nitrile imine cycloadditions remains narrow.

The prevalence of pyrazoline motifs in bioactive compounds[4] and the growing importance of spirocyclic oxindole derivatives[5,6] led our group and others to investigate synthetic approaches to spiro[pyrazolin-3,3′-oxindoles]. During the course of our studies, Roth *et al.*[7] and Feng *et al.*[8] reported the first cycloadditions of nitrile imines with methyleneindolinones to



Scheme 1. *Catalytic, enantioselective cycloadditions of nitrile imines with methyleneindolinones*

generate spiro[pyrazolin-3,3′-oxindoles]. Roth and co-workers reported the first racemic synthesis of spiro[pyrazolin-3,3′-oxindoles] by uncatalyzed cycloadditions of nitrile imines with methyleneindolinones.[7] Shortly thereafter, Feng and co-workers reported the first catalytic, enantioselective cycloadditions of nitrile imines generated from hydrazonoyl chlorides with

methyleneindolinones (Scheme 1a).[8] These cycloadditions occur with high enantioselectivity (up to 99% ee) provided the β-substituent of the methyleneindolinone substrate is a bulky alkyl (*tert*-butyl) group or an *ortho*-substituted aryl group. Cycloadditions of nitrile imines with methyleneindolinones substituted with smaller β-alkyl (*e.g.* iso-propyl) groups or β-aryl (*e.g.* Ph, 4-Cl-C_6H_4) groups lacking *ortho*-substitution occur with lower enantioselectivity.

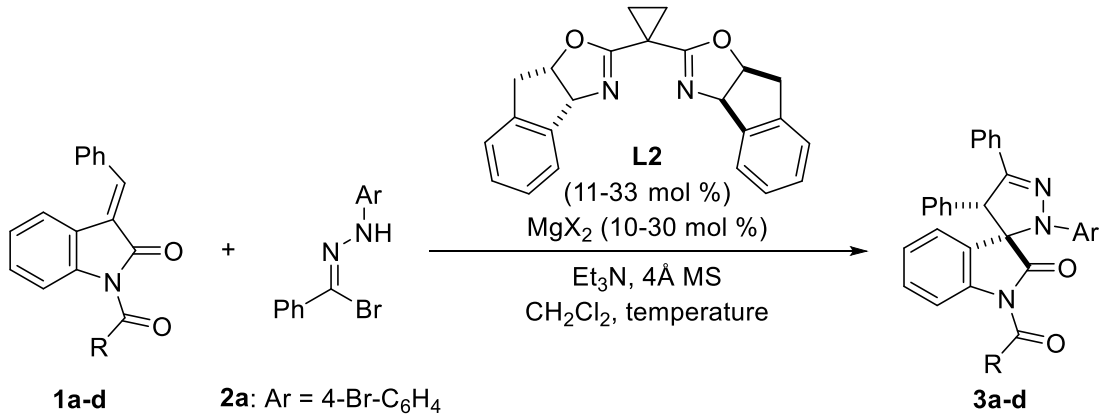
Herein, we report catalytic, enantioselective cycloadditions of nitrile imines generated from hydrazonoyl bromides with a variety of methyleneindolinones (Scheme 1b). The nitrile imine cycloadditions occur in the presence of a catalyst generated *in situ* from $Mg(NTf_2)_2$ and an aminoindanol-derived bisoxazoline ligand **L2**. The spiro[pyrazolin-3,3′-oxindole] products are formed in good to high yields with high enantioselectivities. Furthermore, the nitrile imine cycloadditions that occur with high enantioselectivity encompass methyleneindolinones containing β-aryl groups lacking substitution at the *ortho* position. This methodology expands the breadth of spiro[pyrazolin-3,3′-oxindoles] that can be accessed in highly enantioselective fashion and is complementary to the methodology reported by Feng.

Catalytic, enantioselective, 1,3-dipolar cycloadditions of nitrile imines with methyleneindolindolinones: identification of reaction conditions

Our initial studies focused on reactions of the nitrile imine generated from hydrazonoyl bromide **2a** with methyleneindolinones **1a–e**. Table 1 summarizes the effect of Lewis acid identity, Lewis acid loading, temperature, and substitution at the oxindole nitrogen on these reactions. We chose to begin our investigation by conducting cycloadditions catalyzed by 30 mol% loading of a complex prepared *in situ* from $Mg(NTf_2)_2$ and bisoxazoline ligand **L2**. The cycloaddition of the nitrile imine generated at room temperature from **2a** with **1a** (R = Ph) formed spirocycle **3a** in high yield but with poor enantioselectivity. While lowering the

temperature of the cycloaddition from room temperature to −78 °C did not significantly impact the yield of **3a**, this modification led to a dramatic increase in enantioselectivity (entries 1–3). The cycloaddition of the nitrile imine generated from **2a** with **1a** formed **3a** in 88% yield and 90% ee when the reaction was conducted at −78 °C (entry 3). Reducing the catalyst loading from 30 mol% to 10 mol% did not have a significant impact on the enantioselectivity of the cycloaddition (entries 3–5). In fact, the reaction performed with 10 mol% catalyst occurred in slightly higher yield (98%) and enantioselectivity (92% ee) than the reactions performed with 20 and 30 mol% catalyst. The reaction conducted in the presence of 5 mol% catalyst formed **3a** in high yield, but the enantioselectivity was marginally lower (89% ee, entry 6).

Table 1. *Identification of catalyst precursors and reaction conditions*



1a-d **2a**: Ar = 4-Br-C_6H_4 **3a-d**

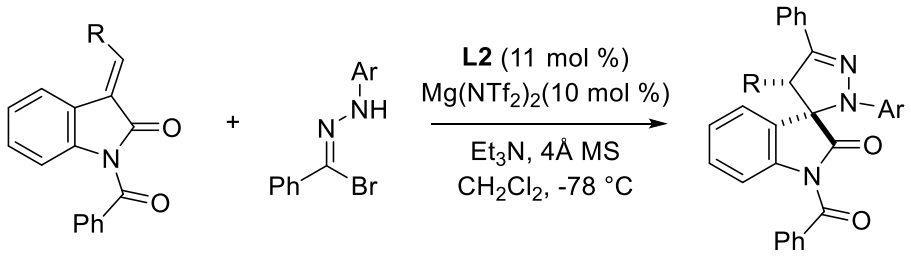
Entry	R (1)	MgX_2 (mol %)	Temp (°C)	3	Yield (%)	ee (%)
1	Ph (**1a**)	$Mg(NTf_2)_2$ (30)	rt	**3a**	82	29
2	Ph (**1a**)	$Mg(NTf_2)_2$ (30)	-20	**3a**	88	55
3	Ph (**1a**)	$Mg(NTf_2)_2$ (30)	-78	**3a**	88	90
4	Ph (**1a**)	$Mg(NTf_2)_2$ (20)	-78	**3a**	91	91
5	Ph (**1a**)	$Mg(NTf_2)_2$ (10)	-78	**3a**	98	92
6	Ph (**1a**)	$Mg(NTf_2)_2$ (5)	-78	**3a**	96	89
7	Ph (**1a**)	$Mg(ClO_4)_2$ (10)	-78	**3a**	98	44
8	Ph (**1a**)	MgI_2 (10)	-78	**3a**	95	64
9	Me (**1b**)	$Mg(NTf_2)_2$ (10)	-78	**3b**	76	94
10	*t*-Bu (**1c**)	$Mg(NTf_2)_2$ (10)	-78	**3c**	97	40
11	O*t*-Bu (**1d**)	$Mg(NTf_2)_2$ (10)	-78	**3d**	37	94

The identity of the Mg(II) salt and the oxindole nitrogen substituent proved important to the yields and/or selectivities of the cycloaddition reactions (entries 5, 7–11). Cycloadditions catalyzed by complexes of $Mg(ClO_4)_2$ or MgI_2 and **L2** occurred with low enantioselectivity relative to the cycloaddition catalyzed by a complex of $Mg(NTf_2)_2$ and **L2** (compare entries 7 and 8 with entry 5). Cycloadditions of *N*-acetyl and *N*-Boc arylidine methyleneindolinones **1b** and **1d** with the nitrile imine generated from **2a** formed spiro[pyrazolin-3,3′-oxindoles] **3b** and **3d** in 94% and 98% ee, but the yields were substantially lower than the corresponding reaction with **1a** (entries 9 and 11). In contrast, the reaction of *N*-pivaloyl methyleneindolinone **1c** generated spiro[pyrazolin-3,3′-oxindole] **3c** in high yield, but the enantioselectivity was poor (40% ee, entry 10).

Catalytic, enantioselective, 1,3-dipolar cycloadditions of nitrile imines with methyleneindolindolinones: scope of dipolarophiles

The scope of the Mg-catalyzed cycloaddition of the nitrile imine generated from **2a** with a variety of methyleneindolinones is summarized in Table 2. The reactions of an electron-rich methyleneindolinone and halogenated methyleneindolinones generated products **3e–g** in moderate to good yields with high enantioselectivities (entries 1–3). The absolute configuration of spiro[pyrazolin-3,3′-oxindole] **3h** was determined to be (3*S*,4′*S*) by X-ray crystallographic analysis (Fig. 1). In contrast, the reaction of an electron-deficient dipolarophile **1h** furnished the corresponding cycloadduct **3h** with modest enantioselectivity (entry 4). The reaction of a *meta*-substituted methyleneindolinone **1i** formed spiro[pyrazolin-3,3′-oxindole] **3i** in high yield with high enantioselectivity (entry 5).

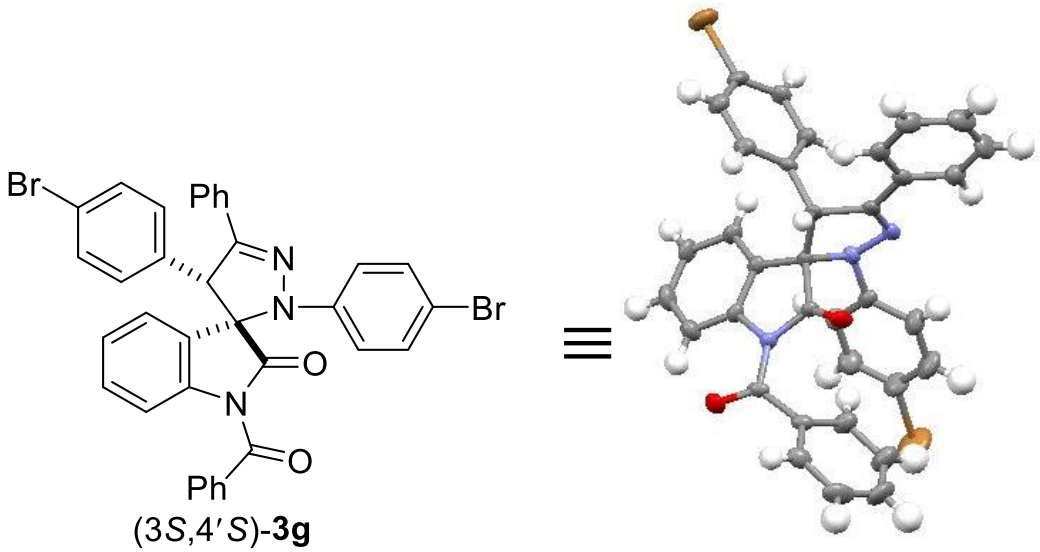
Table 3. *Scope of Nitrile Imine cycloadditions with various methyleneindolinones*



1e-m **2a:** Ar = 4-Br-C_6H_4 **3e-m**

Entry	1	R	3	Yield (%)	ee (%)
1	**1e**	4-MeO-C_6H_4	**3e**	81	99
2	**1f**	4-Cl-C_6H_4	**3f**	86	99
3	**1g**	4-Br-C_6H_4	**3g**	63[a]	94
4	**1h**	4-CF_3-C_6H_4	**3h**	81	80
5	**1i**	3-MeO-C_6H_4	**3i**	90[b]	94
6	**1j**	3,4,5-$(MeO)_3$-C_6H_2	**3j**	91	61
7	**1j**	3,4,5-$(MeO)_3$-C_6H_2	**3j**	88[c]	91
8	**1k**	2-F-C_6H_4	**3k**	84	92
9	**1l**	2-Br-C_6H_4	**3l**	43	0
10	**1m**	(*E*)-*tert*-butyl	**3m**	70	99

[a]Isolated as a 10:1 mixture of diastereomers and an 11:1 mixture of regioisomers. [b]Isolated as a 9:1 mixture of diastereomers. [c]The reaction was conducted in the presence of 100 mol % of the Mg catalyst.



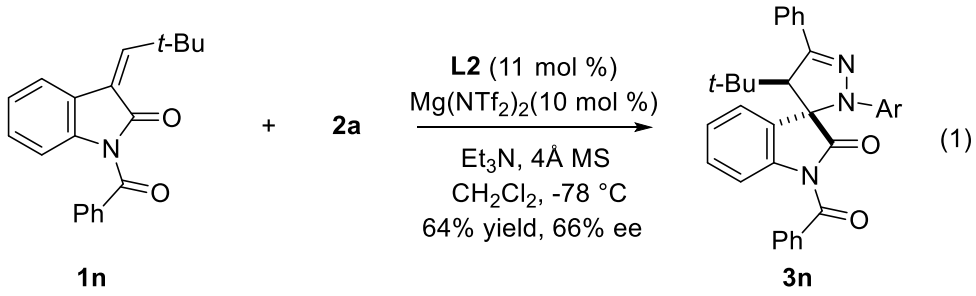
(3*S*,4′*S*)-**3g**

Figure 1. *Absolute stereochemistry and structure of* **3g** *based on X-ray diffraction data*

The reaction of a highly electron-rich dipolarophile proved more challenging. The reaction of methyleneindolinone **1j** occurred with 61% ee in the presence of 10 mol% catalyst (Table 2, entry 6). The observed decrease in enantioselectivity likely results from product inhibition instead of poor facial selection, as product **3j** was formed with 91% ee in the presence of 100 mol% catalyst (entry 7).

Reactions of methyleneindolinones containing an *ortho*-substituted aryl group were sensitive to the size of the *ortho* substituent. The reaction of *ortho*-fluorinated dipolarophile **1k** formed cycloadduct **3k** in high yield with high enantioselectivity (entry 8), but the reactivity of *ortho*-brominated dipolarophile **1l** was poor and the corresponding product **3l** was generated as a racemic mixture (entry 9).

Although aryl groups with large *ortho*-substituents are not well tolerated by the current catalyst, bulky β-alkyl substituents are well tolerated. The reaction of (*E*)-methyleneindolinone **1m** (R = *t*-Bu) furnished cycloadduct **3m** in 70% yield and 99% ee (Table 2, entry 10). However, the enantioselectivity of the cycloaddition is sensitive to the geometry of the alkene unit. The reaction of (*Z*)-methyleneindolinone **1n** (R = *t*-Bu) furnished the diastereomeric cycloadduct **3n** with only 66% ee (eqn (1)).



(1)

Catalytic, enantioselective, 1,3-dipolar cycloadditions of nitrile imines with methyleneindolindolinones: scope of dipoles

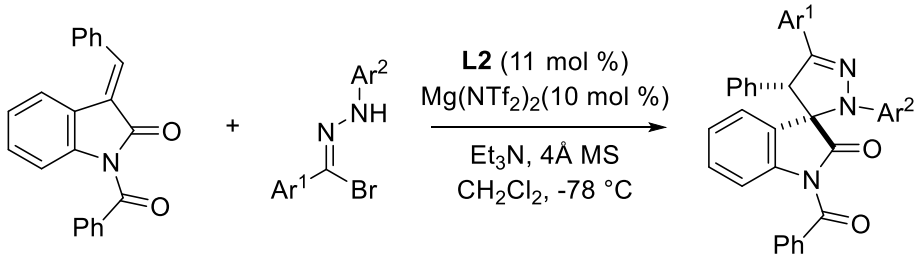
The scope of the Mg-catalyzed cycloaddition of **1a** with a selection of nitrile imines is summarized in Table 3. As illustrated in Table 1, entry 5, the nitrile imine generated from benzaldehyde-derived hydrazonoyl bromide **2a** furnished cycloadduct **3a** in high yield with excellent enantioselectivity. The reaction of a nitrile imine bearing an electron-deficient aryl group (Ar^1 = 4-CF_3-C_6H_4) at the C-terminus of the dipole also generated the corresponding spiro[pyrazolin-3,3´-oxindole] **3o** in high yield with high enantioselectivity (Table 3, entry 1). The reaction of a nitrile imine containing a 3-bromophenyl group at the C-terminus furnished cycloadduct **3p** in 72% yield with 84% ee (entry 2). The reaction also appears sensitive to the size of the substituent at the 2-position of the C-terminal aryl ring: whereas the reaction of a nitrile imine containing with a smaller 2-fluoro substituent afforded product **3q** in 90% yield with 90% ee (entry 3), the reaction to afford product **3r** with a larger 2-bromo substituent occurred in 81% yield with 62% ee (entry 4).

Nitrile imines with electron-deficient aryl groups at the N-terminus of the dipole were also well tolerated. Reactions of nitrile imines substituted with N-terminal 4-fluorophenyl and 4-trifluoromethyl groups formed the corresponding cycloadducts **3s** and **3t** in 83% and 87% yields with 91% and 90% ee, respectively (entries 5 and 6).

The scope of cycloadditions with methyleneindolinone **1a** encompasses a wide range of sterically and electronically distinct nitrile imines. However, the hydrazonoyl bromide precursors to nitrile imines with electron-rich aryl groups at either the C- or N-terminus were too unstable in our hands to generate reproducible results. In addition, attempts to utilize

hydrazonoyl chlorides as nitrile imine precursors resulted in either low reactivity or poor enantioselectivity.

Table 4. *Scope of 1,3-dipolar cycloadditions of methyleneindolinone* 1a *with nitrile imines*



1a **2b-g** **3o-t**

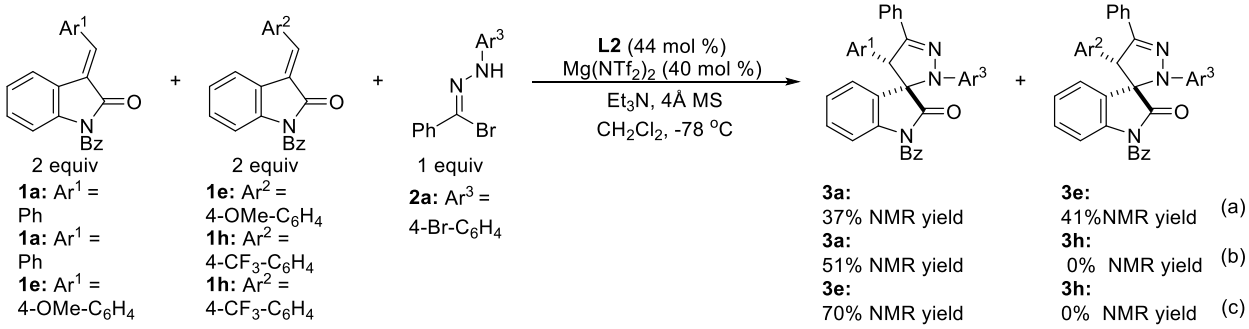
Entry	2	Ar^1	Ar^2	3	Yield (%)	ee (%)
1	**2b**	4-CF_3-C_6H_4	4-Br-C_6H_4	**3o**	86	94
2	**2c**	3-Br-C_6H_4	4-Br-C_6H_4	**3p**	72	84
3	**2d**	2-F-C_6H_4	4-Br-C_6H_4	**3q**	90	90
4	**2e**	2-Br-C_6H_4	4-Br-C_6H_4	**3r**	81	62
5	**2f**	Ph	4-F-C_6H_4	**3s**	83	91
6	**2g**	Ph	4-CF_3-C_6H_4	**3t**	87	90

Catalytic, enantioselective, 1,3-dipolar cycloadditions of nitrile imines with methyleneindolindolinones: competition reactions of dipolarophiles

While most of the methyleneindolinone substrates examined in our dipolarophile scope reacted to furnish cycloadducts with high enantioenrichment, we observed that extremely electron-withdrawing groups and extremely electron-donating groups on the β-aryl ring of the dipolarophile were detrimental to the enantioselectivity of the reaction. Electron-poor dipolarophile **1h** reacted with **2a** to furnish **3h** in 81% yield and 80% ee (Table 2, entry 4), while the reaction of very electron-rich **1j** with **2a** afforded cycloadduct **3j** in 91% yield and 62% ee at 10 mol % catalyst loading (entry 6) and 91% ee at 100 mol % catalyst loading (entry 7). These data led us to the two-fold hypothesis that 1) an electron-deficient methyleneindolinone binds weakly to the catalyst, leading to poor facial selectivity and thus lower ee (the racemic background reaction is likely not competitive with the catalyzed process, *vide infra*), and 2) a

very electron-rich methyleneindolinone binds strongly to the catalyst, slowing catalyst turnover and allowing the racemic background reaction to become competitive with the catalyzed reaction.

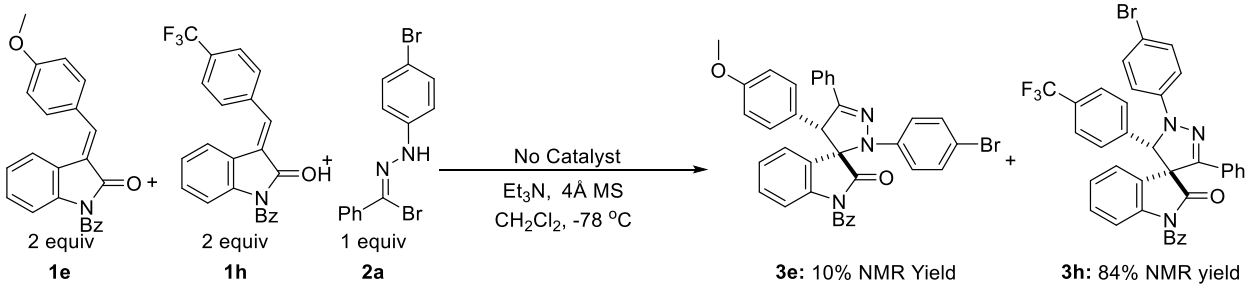
In order to confirm a correlation between the electron-density of the dipolarophile and the strength of catalyst binding, we set up competition reactions of dipolarophiles of varying electron densities. The competition reaction of electron-neutral **1a** and electron-rich **1b** with **2a** delivered cycloadducts **3a** and **3e** in 37% and 41% yield, respectively (Scheme 2a). The competition between electron-neutral **1a** and electron-poor **1h** with **2a** generated **3a** exclusively in 51% yield (Scheme 2b). Electron-rich **1e** was even more reactive compared to **1a** in competition against **1h**: the competition reaction between **1e** and **1h** generated **3e** as the sole product in 70% yield (Scheme 2c). In the latter two cases, the dipolarophile expected to have stronger catalyst affinity reacts exclusively with the dipole, lending support for our hypothesis that more electron-rich dipolarophiles bind more strongly to the catalyst.



Scheme 2. *Competition reactions of excess dipolarophile with limiting dipole under mg-catalyzed conditions*

In order to further demonstrate that the outcomes of these competition reactions were a result of catalyst affinity, we subjected substrates **1e** and **1h** to a competition reaction in the absence of catalyst, as shown in Scheme 3. This reaction delivered **3h** in 84% yield, while it furnished **3e** in only 10% yield. This was nearly a complete reversal of outcome from the corresponding catalyzed competition reaction where electron-rich **1e** was more reactive than

electron poor **1h**. Notably, the uncatalyzed reaction of **1h** with **2a** generated **3h** with regiochemistry opposite of that observed in the corresponding catalyzed reaction, with fusion of the dipole N-terminus with the β-position of the dipolarophile and fusion of the dipole C-terminus with the α-position of the dipolarophile. Such a reversal of regiochemistry is consistent with previous observations in 1,3-dipolar cycloaddition reactions of nitrile imines with electron-deficient dipolarophiles in the absence of Lewis-acids.[9] The delivery of the product with typical regioselectivity in the presence of Lewis-acid but with diminished enantioselectivity (Table 2, entry 4) suggests that substrate **1h** interacts strongly enough with the catalyst in the reaction to deliver only the typical regioisomer, but weakly enough to reduce facial selectivity, leading to lower enantioselectivity.

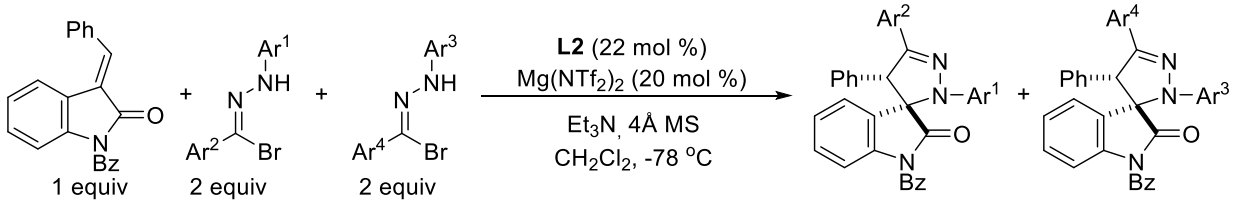


Scheme 3. *Uncatalyzed Competition Reaction of* **1e** *and* **1h** *with dipole* **2a**

Catalytic, enantioselective, 1,3-dipolar cycloadditions of nitrile imines with methyleneindolindolinones: competition reactions of dipoles

We conducted competition reactions of excess dipoles in the presence of limiting dipolarophile to determine whether or not the electronics of the dipole had an influence on reaction rates. The competition reaction outcomes are shown in Scheme 4. The competition reaction of **2a** and **2a** in the presence of the catalyst delivered a 95:5 ratio of **3a**:**3o** (Scheme 4a), while the competition of **2a** and **2j** resulted in a 44:56 **3a**:**3t** ratio (Scheme 4b). These competition reactions revealed that 1) dipoles with more electron-rich C-termini greatly are far

more reactive under our conditions than dipoles with less electron-rich C-termini (Scheme 4a), and 2) dipoles with electron-poor N-termini, and thus more acidic anilinic protons, are slightly more reactive than dipoles with more electron-rich N-termini under our conditions (Scheme 4b). Despite these differences in reaction rates, there appears to be no correlation between dipole electronics and enantioselectivity (Table 3), thus demonstrating that resulting yields and enantioselectivities in the presence of the catalyst are influenced far more by dipolarophile electronics.



1a | **2a:** Ar^1 = 4-Br-C_6H_4, Ar^2 = Ph | **2b:** Ar^3 = 4-Br-C_6H_4, Ar^4 = 4-CF_3-C_6H_4 | **3a:** 95 : **3o:** 5 (a)

2a: Ar^1 = 4-Br-C_6H_4, Ar^2 = Ph | **2g:** Ar^3 = 4-CF_3-C_6H_4, Ar^4 = Ph | **3a:** 44 : **3t:** 56 (b)

Scheme 4. *Competition reactions of excess dipole with limiting dipolarophile under mg-catalyzed conditions*

Catalytic, enantioselective, 1,3-dipolar cycloadditions of nitrile imines with methyleneindolindolinones: conclusion

In summary, we have developed a method for 1,3-dipolar cycloadditions of nitrile imines to form spiro[pyrazolin-3,3´-oxindole] in high yields with high enantioselectivity. This process is complementary to extant methods, allowing for the formation of spiro[pyrazolin-3,3´-oxindoles] that could not previously be accessed in highly enantioenriched form. Specifically, spiro[pyrazolin-3,3´-oxindole] cycloadducts are formed with high enantioselectivity from methyleneindolinones lacking *ortho*-substituted aryl group at the β-position of the dipolarophile. Studies to develop asymmetric cycloadditions of nitrile imines with additional classes of dipolarophiles are ongoing in our laboratory.

Experimental Details

General experimental details

All air-sensitive procedures were conducted under inert atmosphere in a nitrogen-filled dry box or by standard Schlenk techniques. All reactions were performed under an atmosphere of nitrogen unless otherwise stated. All glassware for moisture sensitive reactions was dried at 140 °C in an oven. THF and CH_2Cl_2 were degassed by purging with argon for 45 minutes and dried with a solvent purification system by passing through a one-meter column of activated alumina. Flash column chromatography was performed on Fisher brand silica gel 60 (230-400 mesh). Products of reactions were visualized on TLC plates under UV light or by staining with $KMnO_4$, phosphomolybdic acid, or ceric ammonium molybdate.

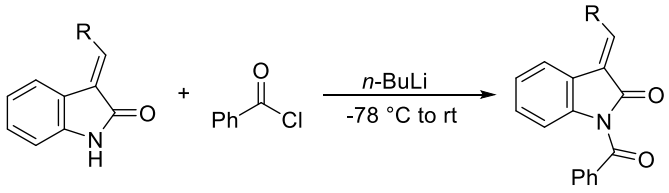
HRMS (ESI) analysis was performed at the Iowa State University Chemical Instrumentation Facility on an Agilent 6540 QTOF spectrometer. Optical rotations were measured on an Atago AP-300 automatic polarimeter. HPLC analyses were carried out on a Water Alliance HPLC system with an e2695 Separations Module and a 2489 (UV/Vis) dual wavelength detector. NMR spectra were acquired on Varian MR-400 and Bruker Avance III 600 spectrometers at the Iowa State University Chemical Instrumentation Facility. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to residual $CHCl_3$ in $CDCl_3$ (7.26 ppm for ^{1}H and 77.23 ppm for ^{13}C). ^{19}F NMR shifts are reported in ppm relative to trifluoroacetic acid as an external standard (F_3CCO_2H = -76.55 ppm).

Materials

Unless otherwise stated, reagents were purchased from Sigma-Aldrich and used without further purification. Methyleneindolinones **S1a-k** were synthesized according to literature procedures from oxindole and the appropriate aldehyde.[8,10] Methyleneindolinone 1d was

prepared according to a previously reported procedure.[8] 4-Fluorophenylhydrazine and 4-trifluoromethylphenylhydrazine were purchased from AK Scientific. Hydrazones **S2a-g** were synthesized by stirring an equimolar mixture of the appropriate hydrazines and aldehydes in CH_2Cl_2 (0.33 M) in the presence of $MgSO_4$ until TLC analysis indicated consumption of the aldehyde. Filtration and concentration under reduced pressure afforded the hydrazone which was used without further purification or recrystallized from EtOH if necessary. Hydrazonoyl bromide **2a** was prepared according to a literature procedure from benzaldehyde phenylhydrazone.[3b] Bisoxazoline ligand **L2** was prepared according to a previously reported procedure from (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol.[11] (1R,2S)-(+)-cis-1-Amino-2-indanol was purchased from Carbosynth. Magnesium bis(trifluoromethylsulfonyl)imide was purchased from Strem Chemicals and used without further purification. Magnesium perchloroate was purchased from Fisher Scientific and used without further purification. Powdered 4Å molecular sieves were purchased from Sigma-Aldrich and flame-dried under vacuum prior to use. N-bromosuccinimide (NBS) and N-chlorosuccinimide (NCS) were purchased from Sigma Aldrich and recrystallized from water before use.

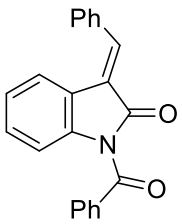
General procedure for synthesis of N-acyl methyleneindolinones 1a, 1e-n



S1a R = Ph
S1b R = 4-MeO-C_6H_4
S1c R = 4-Cl-C_6H_4
S1d R = 4-Br-C_6H_4
S1e R = 4-CF_3-C_6H_4
S1f R = 3-MeO-C_6H_4
S1g R = 3,4,5-MeO-C_6H_2
S1h R = 2-F-C_6H_4
S1i R = 2-Br-C_6H_4
S1j R = (*E*)-*t*-Bu
S1k R = (*Z*)-*t*-Bu

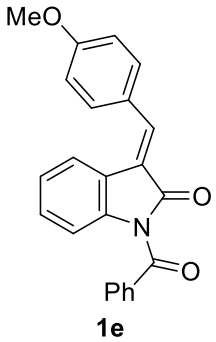
1a R = Ph
1e R = 4-MeO-C_6H_4
1f R = 4-Cl-C_6H_4
1g R = 4-Br-C_6H_4
1h R = 4-CF_3-C_6H_4
1i R = 3-MeO-C_6H_4
1j R = 3,4,5-MeO-C_6H_2
1k R = 2-F-C_6H_4
1l R = 2-Br-C_6H_4
1m R = (*E*)-*t*-Bu
1n R = (*Z*)-*t*-Bu

To a solution of the appropriate methyleneindolinone **S1** (1.0 equiv) in THF (0.1 M) at -78 °C was added *n*-BuLi (1.05 equiv as a 2.5 M solution in hexanes). The reaction mixture was allowed to stir for 30 minutes before dropwise addition of benzoyl chloride (1.05 equiv). After addition of benzoyl chloride, the reaction was allowed to warm to room temperature until TLC analysis showed consumption of **S1**. After the reaction was judged to be complete by TLC analysis, the mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was separated and washed with water and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting crude product was recrystallized from ethanol to give a mixture of *E*- and *Z*-methyleneindolinone isomers. Pure *E*-methyleneindolinones **1** were isolated by fractional recrystallization from ethanol.



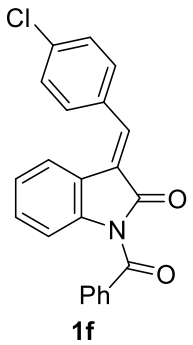
1a

(*E*)-1-Benzoyl-3-benzylideneindolin-2-one (1a): Prepared according to the general procedure from **S1a** (5.50 g, 24.9 mmol) to give **1a** (5.27 g, 16.2 mmol, 65%) as a yellow solid. m.p. = 153-154 °C **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.07 (dt, *J* = 7.8, 1.2 Hz 1H), 7.37 (dt, *J* = 1.2, 8.4 Hz 1H), 7.44-7.54 (m, 5H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.64-7.69 (m, 2H), 7.76 (dd, *J* = 7.8, 0.6 Hz, 1H), 7.79-7.82 (m, 2H), 7.83 (s, 1H), 7.93 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 115.4, 122.3, 122.7, 124.5, 126.1, 128.3, 129.0, 129.4, 129.6, 130.3, 130.4, 133.0, 134.6, 134.7, 139.2, 140.7, 167.8, 169.6. **HRMS** (ESI) calcd. for $C_{22}H_{16}NO_2^+$ $[M+H]^+$ 326.1181, found 326.1178.



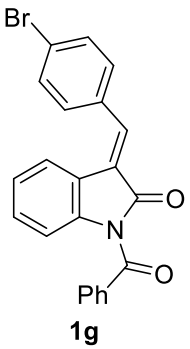
1e

(*E*)-1-Benzoyl-3-(4-methoxybenzylidene)indolin-2-one (1e): Prepared according to the general procedure from **S1b** (2.50 g, 9.95 mmol) to give **1e** (2.32g, 6.27 mmol, 63%) as a yellow solid. m.p. = 160-162 °C **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.90 (s, 3H), 7.01 (d, *J* = 8.4 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.75-7.83 (m, 3H), 7.86-7.96 (m, 2H). **^{13}C NMR** (CDCl3, 151 MHz) δ 55.5, 114.3, 115.2, 122.2, 122.6, 123.9, 124.2, 126.8, 128.2, 129.5, 129.8, 131.6, 132.7, 134.7, 139.3, 140.2, 161.3, 168.0, 169.6. **HRMS** (ESI) calcd. for $C_{23}H_{18}NO_3^+$ $[M+H]^+$ 356.1287, found 356.1272.



1f

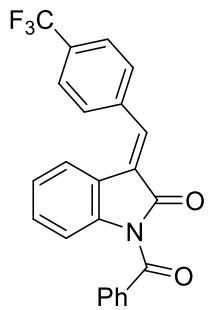
(*E*)-1-Benzoyl-3-(4-chlorobenzylidene)indolin-2-one (1f): Prepared according to the general procedure from **S1c** (1.00 g, 7.82 mmol) to give **1f** (0.52 g, 2.9 mmol, 37%) as a yellow solid. m.p. = 203-205 °C **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.08 (t, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.43-7.54 (m, 4H), 7.55-7.65 (m, 3H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.74 (s, 1H), 7.79 (d, *J* = 7.2 Hz, 2H), 7.91 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 115.5, 122.1, 122.7, 124.6, 126.6, 128.4, 129.3, 129.7, 130.7, 130.8, 133.0, 133.1, 134.6, 136.2, 137.5, 140.8, 167.6, 169.6. **HRMS** (ESI) calcd. for $C_{22}H_{15}NO_2Cl^+$ $[M+H]^+$ 360.0791, found 360.0790.



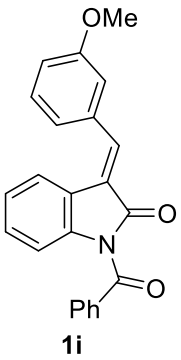
1g

(*E*)-1-Benzoyl-3-(4-bromobenzylidene)indolin-2-one (1g): Prepared according to the general procedure from **S1d** (2.00 g, 6.66 mmol) to give **1g** (1.28 g, 3.19 mmol, 48%) as yellow solid. m.p. = 182-186 °C **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.08 (t, *J* = 8.0 Hz, 1H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.44-7.56 (m, 4H), 7.58-7.66 (m, 3H), 7.67-7.73 (m, 2H), 7.79 (d, *J* = 7.6 Hz, 2H), 7.91 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 115.6, 122.1, 122.7, 124.5, 124.6, 126.7, 128.4, 129.7, 130.7, 130.9, 132.3, 133.1, 133.5, 134.6, 137.5, 140.9, 167.6, 169.6. **HRMS** (ESI) calcd. for $C_{22}H_{15}NO_2Br^+$ $[M+H]^+$ 404.0286, found 404.0285.

(*E*)-1-Benzoyl-3-(4-(trifluoromethyl)benzylidene)indolin-2-one (1h): Prepared according to the general procedure from **S1e** (1.00 g, 3.46 mmol) to give **1h** (0.40 g, 1.0 mmol, 29%) as a yellow solid. m.p. = 175-177 °C **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.09 (t, *J* = 7.8 Hz, 1H) 7.41 (t, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.58-7.66 (m, 2H), 7.74-7.83 (m, 7H), 7.93 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 115.7, 121.8, 122.9, 124.0 (q, *J* = 272.3 Hz), 124.7, 126.0 (q, *J* = 3.5 Hz) 128.0, 128.4, 129.5, 129.7, 131.1, 131.8 (q, *J* = 31.4 Hz), 133.2, 134.5, 136.5, 138.3, 141.1, 167.4, 169.5. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -63.5. **HRMS** (ESI) calcd. for $C_{23}H_{15}F_3NO_2^+$ $[M+H]^+$ 394.1055, found 394.1062.

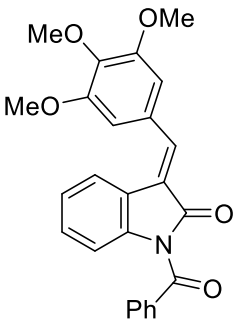


1h



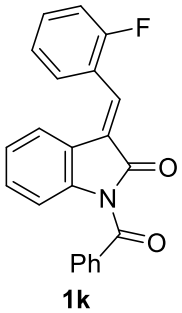
1i

(*E*)-1-Benzoyl-3-(3-methoxybenzylidene)indolin-2-one (1i): Prepared according to the general procedure from **S1f** (5.00 g, 21.6 mmol) to give **1i** (4.09 g, 12.5 mmol, 58%) as a yellow solid. m.p. = 135-137 °C **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 3.85 (s, 3H), 7.01 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.08 (dt, *J* = 1.2, 12.0 Hz, 1H), 7.16 (s, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.34-7.44 (m, 2H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.77-7.82 (m, 4H), 7.92 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 55.6, 114.4, 115.4, 116.2, 121.8, 122.3, 123.0, 124.5, 126.4, 128.4, 129.6, 130.1, 130.4, 133.0, 134.7, 135.9, 139.0, 140.7, 160.0, 167.8, 169.6. **HRMS** (ESI) calcd. for $C_{23}H_{18}NO_3^+$ $[M+H]^+$ 356.1287, found 356.1283.



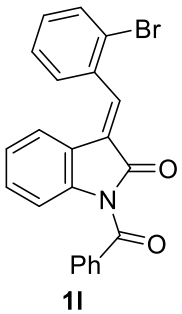
1j

(*E*)-1-Benzoyl-3-(3,4,5-trimethoxybenzylidene)indolin-2-one (1j): Prepared according to the general procedure from **S1g** (7.50 g, 24.09 mmol) to give **1j** (2.67 g, 6.50 mmol, 27%) as a yellow solid. m.p. =191-192 °C **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 3.86 (s, 6H), 3.91 (s, 3H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.55 (s, 1H), 7.56-7.60 (m, 3H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.77-7.83 (m, 3H). **^{13}C NMR** ($CDCl_3$, 151 MHz,) δ 56.3, 61.0, 110.1, 114.7, 118.7, 123.5, 124.4, 125.5, 128.1, 128.9, 129.1, 129.6, 132.7, 134.6, 138.6, 139.2, 141.0, 152.7, 165.6, 169.8. **HRMS** (ESI) calcd. for $C_{25}H_{22}NO_5^+$ $[M+H]^+$ 416.1498 found 416.1493.



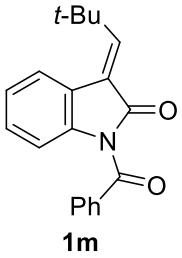
1k

(*E*)-1-Benzoyl-3-(2-fluorobenzylidene)indolin-2-one (1k): Prepared according to the general procedure from **S1h** (1.00 g, 4.18 mmol) to give **1k** (0.83 g, 2.4 mmol, 58%) as a yellow solid. m.p. = 209-211 °C **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.08 (dt, *J* = 1.2, 7.8 Hz, 1H), 7.21 (t, *J* = 9.6 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.45-7.53 (m, 3H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.71 (dt, *J* = 1.2, 7.2 Hz, 1H), 7.78-7.82 (m, 3H), 7.92 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 115.5, 116.5 (d, *J* = 21.1 Hz), 122.2, 122.8 (d, *J* = 14.7 Hz), 123.0, 124.4 (d, *J* = 3.6 Hz), 124.6, 128.0, 128.4, 129.7, 130.4, 130.8, 131.4, 132.2 (d, *J* = 8.4 Hz), 133.1, 134.7, 140.9, 160.7 (d, *J* = 252.5 Hz), 167.3, 169.6 **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -110.1 **HRMS** (ESI) calcd. for $C_{22}H_{15}NO_2F^+$ $[M+H]^+$ 344.1087, found 344.1087.



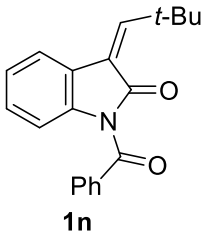
1l

(*E*)-1-Benzoyl-3-(2-bromobenzylidene)indolin-2-one (1l): Prepared according to the general procedure from **S1i** (1.20 g, 4.00 mmol) to give **1l** (0.70 g, 1.7 mmol, 43%) as a yellow solid. m.p. = 197-199 °C **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 7.03 (dt, *J* = 1.2, 8.4 Hz, 1H), 7.30-7.45 (m, 4H), 7.51 (t, *J* = 7.8 Hz, 2H), 7.62 (tt, *J* = 7.8, 1.2 Hz, 1H), 7.69 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.72 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.78-7.82 (m, 3H), 7.92 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 115.5, 121.8, 122.8, 124.2, 124.4, 127.2, 127.4, 128.2, 129.4, 130.0, 130.6, 131.2, 132.8, 133.4, 134.5, 135.1, 137.2, 140.7, 167.1, 169.4. **HRMS** (ESI) calcd. for $C_{22}H_{15}NO_2Br^+$ $[M+H]^+$ 404.0286 found 404.0280.



1m

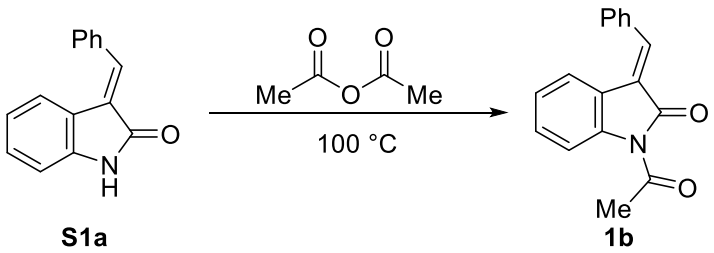
(*E*)-1-Benzoyl-3-(2,2-dimethylpropylidene)indolin-2-one (1m): Prepared according to a modified version of the general procedure from **S1j** (5.30 g, 26.3 mmol) to give **1m** (0.77 g, 2.63 mmol, 10%) as a light green oil. Compound **1m** was purified by flash column chromatography (98:2 hexanes:EtOAc) instead of purification by recrystallization. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.18 (s, 9H), 6.95-7.05 (m, 2H), 7.11 (t, *J* = 3.6 Hz, 1H), 7.22 (t, *J* = 4.0 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.51-7.57 (m, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 28.9, 32.7, 114.9, 121.4, 124.1, 125.4, 126.1, 127.9, 129.0, 129.3, 132.5, 134.5, 140.4, 154.7, 167.8, 169.2. **HRMS** (ESI) calcd. for $C_{20}H_{20}NO_2^+$ $[M+H]^+$ 306.1494, found 306.1496.



1n

(*Z*)-1-Benzoyl-3-(2,2-dimethylpropylidene)indolin-2-one (1n): Prepared according to a modified version of the general procedure from **S1k** (5.30 g, 26.3 mmol) to give **1n** (0.21 g, 0.68 mmol, 3%) as a light green oil. Compound **1n** was purified by flash column chromatography (98:2 hexanes:EtOAc) instead of purification by recrystallization. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.36 (s, 9H), 7.07 (s, 1H) 7.16 (dt, *J* = 0.8, 7.6 Hz 1H), 7.31 (dt, *J* = 1.2, 8.0 Hz 1H), 7.41-7.50 (m, 3H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.72-7.78 (m, 2H), 7.81 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 29.3, 34.0, 114.9, 118.8, 124.4, 125.0, 125.9, 128.3, 129.0, 129.5, 132.8, 134.8, 138.8, 155.2, 165.0, 169.8. **HRMS** (ESI) calcd. for $C_{20}H_{20}NO_2^+$ $[M+H]^+$ 306.1494, found 306.1493.

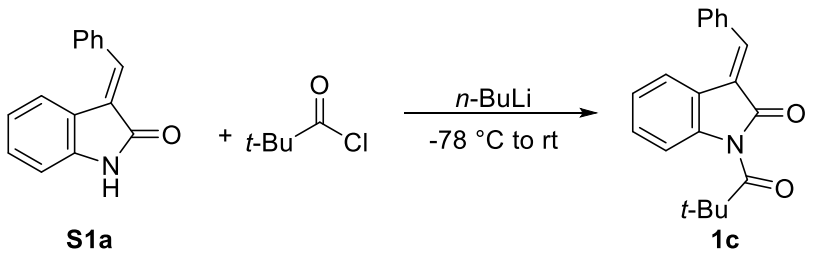
Synthesis of (*E*)-1-acetyl-3-benzylideneindolin-2-one 1b



S1a **1b**

A suspension of (*E*)-3-benzylideneindolin-2-one **S1a** (13.5 g, 61 mmol) in acetic anhydride (300 mL) was heated to 100 ºC (bath temperature) with stirring overnight, during which time the suspension cleared to a deep red-brown solution. The mixture was cooled and poured into 1.4 L of H_2O. A yellow-orange product precipitated and was dissolved by shaking with 300 mL of 1:1 ^{t}BuOMe:Et_2O. The organic layer was separated, and the aqueous layer was extracted twice more with 300 mL of 1:1 ^{t}BuOMe:Et2O. The combined organic extracts were washed with aqueous 2M NaOH (2 x 350 mL), H_2O (2 x 500 mL), and brine (1 x 300 mL), then dried over Na_2SO_4. Filtration and concentration under reduced pressure afforded a crude orange-red solid, which was recrystallized from EtOH (~125 mL), to afford the **1b** (11.2 g, 42.5 mmol, 70%) as yellow needles. m. p. = 123-124 °C. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.77 (s, 3H), 7.04 (t, *J* = 7.6 Hz, 1H), 7.33 (dt, *J* = 0.8, 8.0 Hz, 1H), 7.42-7.53 (m, 3H), 7.61-7.67 (m, 2H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.89 (s, 1H), 8.32 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 27.1, 116.9, 122.1, 122.4, 124.7, 126.3, 129.0, 129.4, 130.3, 130.5, 134.6, 138.9, 140.5, 168.8, 171.1. **HRMS** (ESI) calcd. For $C_{17}H_{14}NO_2^+$ $[M+H]^+$ 264.1025, found 264.1023.

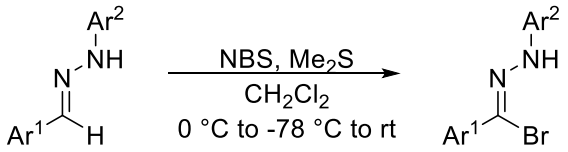
Synthesis of (*E*)-3-benzylidene-1-pivaloylindolin-2-one 1c



S1a **1c**

To a solution of **S1a** (0.50 g, 2.24 mmol) in THF (50 ml) at -78 °C was added *n*-BuLi (1.10 equiv as a 2.5 M solution in hexanes). The reaction mixture was allowed to stir for 30 minutes before dropwise addition of pivaloyl chloride (1.05 equiv). After addition of pivaloyl chloride, the reaction was allowed to warm to room temperature until TLC analysis showed consumption of **S1a**. After the reaction was judged to be complete by TLC analysis, the mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was separated and washed with water and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Crude mixture was purified by flash column chromatography to afford **1c** in 75% yield (0.512 g, 1.68 mmol). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.25 (s, 9H), 6.88 (t, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.42-7.50 (m, 3H), 7.63-7.69 (m, 3H), 7.85 (s, 1H) **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 27.3, 38.8, 110.5, 121.9, 122.2, 123.3, 127.7, 128.9, 129.6, 123.0, 130.1, 135.0, 138.1, 141.7, 170.8, 184.1. **HRMS** (ESI) calcd. For $C_{20}H_{20}NO_2^+$ $[M+H]^+$ 306.1489, found 306.1492.

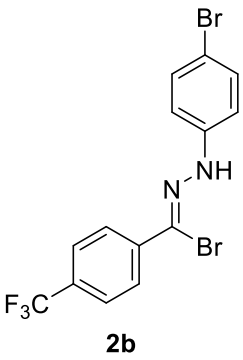
General procedure for synthesis of hydrazonoyl bromides 2b-g



S2a Ar^1 = Ph, Ar^2 = Ph
S2b Ar^1 = 4-CF_3-C_6H_4, Ar^2 = Ph
S2c Ar^1 = 3-Br-C_6H_4, Ar^2 = Ph
S2d Ar^1 = 2-F-C_6H_4, Ar^2 = Ph
S2e Ar^1 = 2-Br-C_6H_4, Ar^2 = Ph
S2f Ar^1 = Ph, Ar^2 = 4-F-C_6H_4
S2g Ar^1 = Ph, Ar^2 = 4-CF_3-C_6H_4

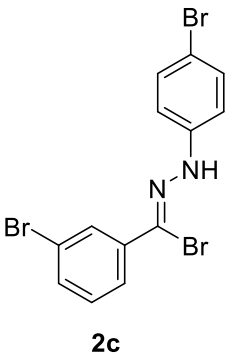
2a Ar^1 = Ph, Ar^2 = 4-Br-C_6H_4
2b Ar^1 = 4-CF_3-C_6H_4,Ar^2 = 4-Br-C_6H_4
2c Ar^1 = 3-Br-C_6H_4, Ar^2 = 3-Br-C_6H_4
2d Ar^1 = 2-F-C_6H_4, Ar^2 = 3-Br-C_6H_4
2e Ar^1 = 2-Br-C_6H_4, Ar^2 = 3-Br-C_6H_4
2f Ar^1 = Ph, Ar^2 = 4-F-C_6H_4
2g Ar^1 = Ph, Ar^2= 4-CF_3-C_6H_4

The following general procedure was adapted from the literature.[3b] To a suspension of NBS (3 equiv) in dry CH_2Cl_2 [0.2M] at 0 ºC under N_2 was added Me_2S (6 equiv). After stirring for 15 min at 0 ºC, the mixture was cooled to -78 ºC for 10 min and a solution of the appropriate hydrazone **S2a-g** (1 equiv) in CH_2Cl_2 [0.5M] was added. The reaction was stirred at -78 ºC for 1 hr and then warmed to RT for 4 hr at which point the heterogeneous reaction mixture was filtered through a plug of silica gel, rinsing with 10 % EtOAc/hexanes, to remove the solid precipitates. The resulting solution was concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel using 30% CH_2Cl_2/hexanes as eluent. This eluent system typically afforded better separation between the desired hydrazonoyl bromide and the hydrazone resulting from dehalogenation at the formyl position. Chromatography was performed as rapidly as possible due to the instability of the hydrazonoyl bromides on silica gel.



2b

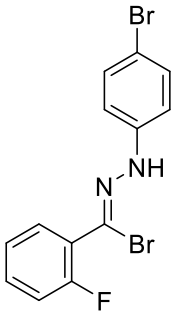
(*Z*)-*N′*-(4-bromophenyl)-4-(trifluoromethyl)benzohydrazonoyl bromide (2b): Prepared according to the general procedure from (*E*)-1-(4 bromophenyl)-2-(4-(trifluoromethyl)benzylidene)hydrazine **S2b** (1.50 g, 5.68 mmol) and the Corey-Kim complex of NBS (3.03 g, 17.0 mmol) and dimethyl sulfide (2.11 g, 2.50 mL, 34.08 mmol) as the brominating agent. After chromatography, the title compound **2b** was isolated as a pink solid in 29% yield (0.700 g, 1.66 mmol). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.07 (dd, *J* = 1.2, 7.8 Hz, 2H), 7.43 (dd, *J* = 1.2, 7.8 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 8.4 Hz, 2H), 8.13 (s, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 114.2, 115.6, 118.6, 124.1 (q, *J* = 272.3 Hz), 125.6 (q, *J* = 3.8 Hz), 127.9, 131.3 (q, *J* = 32.5 Hz), 132.6, 138.9 (q, *J* = 1.4 Hz), 141.9. **^{19}F NMR** ($CDCl_3$, 565 MHz): δ -63.2. **HRMS** (ESI) calcd. for $C_{28}H_{17}Br_2F_6N_4^+$ [nitrile imine dimer + H]$^+$ 680.9719, found 680.9716.



2c

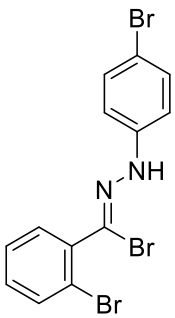
(*Z*)-3-bromo-*N*-(4-bromophenyl)benzohydrazonoyl bromide (2c): Prepared according to the general procedure from (*E*)-1-(3-bromobenzylidene)-2-(4-bromophenyl)hydrazine S**2c** (0.825 g, 3.00 mmol) and the Corey-Kim complex of NBS (1.60 g, 9.00 mmol) and dimethyl sulfide (1.12 g, 1.32 mL, 18.0 mmol) as the brominating agent. After chromatography, the title compound **2c** was isolated as a red/purple solid in 67% yield (0.900 g, 2.00 mmol). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.06 (d, *J* = 8.8 Hz, 2H), 7.26 (dd, *J* = 9.8, 7.8 Hz, 1H), 7.42 (d, *J* = 8.8 Hz), 7.49 (ddd, *J* = 9.0, 1.8, 1.2 Hz, 1H), 7.81 (ddd J = 7.8, 1.8, 1.2 Hz), 8.02 (t, *J* = 1.8 Hz, 1H), 8.05 (s, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 113.9, 115.5, 118.4, 122.8, 126.4, 130.1, 130.5, 132.5 (two coincident signals, as determined by

HSQC), 137.6, 142.0. **HRMS** (ESI) calcd. for $C_{26}H_{17}Br_4N_4^+$ [nitrile imine dimer + H]$^+$ 700.8181, found 700.8170.



2d

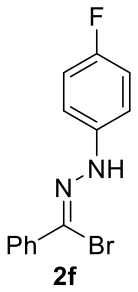
(*Z*)-*N′*-(4-bromophenyl)-2-fluorobenzohydrazonoyl bromide (2e): Prepared according to the general procedure from (*E*)-1-(4-bromophenyl)-2-(2-fluorobenzylidene)hydrazine **S2e** (2.48 g, 11.58 mmol) and the Corey-Kim complex of NBS (6.18 g, 34.73 mmol) and dimethyl sulfide (4.31 g, 5.10 mL, 69.5 mmol) as the brominating agent. After chromatography, the title compound **2e** was isolated as a red solid in 28% yield (1.22 g, 3.30 mmol). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 7.03-7.08 (m, 2H), 7.13 (ddd, *J* = 10.2, 8.9, 1.2 Hz, 1H), 7.21 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.31-7.37 (m, 1H), 7.37-7.42 (m, 2H), 7.66 (dt, *J* = 1.8, 7.6 Hz, 1H), 8.07 (s, 1H). **^{13}C NMR** ($CDCl_3$, 101 MHz): δ 112.7 (d, *J* = 4.9 Hz), 113.7, 115.5, 116.7 (d, *J* = 22.3 Hz), 124.2 (d, *J* = 3.9 Hz), 124.6 (d, *J* = 10.4 Hz), 131.1 (d, *J* = 8.6 Hz), 131.5, 132.5, 142.1, 159.7 (d, *J* = 257.4 Hz). **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -112.88. **HRMS** (ESI) calcd. for $C_{26}H_{17}Br_2F_2N_4^+$ [nitrile imine dimer + H]$^+$ 580.9783, found 580.9773.



2e

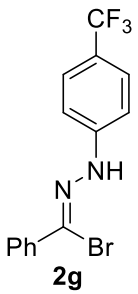
(*Z*)-2-bromo-*N′*-(4-bromophenyl)benzohydrazonoyl bromide (2e): Prepared according to the general procedure from (*E*)-1-(2-bromobenzylidene)-2-(4-bromophenyl)hydrazine **S2e** (2.00 g, 7.27 mmol) and the Corey-Kim complex of NBS (3.88 g, 21.81 mmol) and dimethyl sulfide (2.70 g, 3.20 mL, 43.6 mmol) as the brominating agent. After chromatography, the title compound **2e** was isolated as a brown solid in 32% yield (1.00 g, 2.30 mmol). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.06 (d, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 1H), 7.37-7.39 (m, 3H), 7.5 (dd, *J* = 7.2, 1.8 Hz,

1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.99 (s, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 113.7, 115.5, 115.6, 122.6, 127.6, 130.9, 131.9, 132.4, 133.8, 137.8, 142.2. **HRMS** (ESI) for $C_{26}H_{17}Br_4N_4^+$ [nitrile imine dimer + H]$^+$ 700.8181, found 700.8169.



2f

(*Z*)-*N′*-(4-fluorophenyl)benzohydrazonoyl bromide (2f): Prepared according to the general procedure using (*E*)-1-benzylidene-2-(4-fluorophenyl)hydrazine (2.5 g, 11.67 mmol) and the Corey-Kim complex of NBS (6.23 g, 35.01 mmol) and dimethyl sulfide (4.35 g, 5.14 mL, 70.01 mmol) as the brominating agent. Upon chromatography, the title compound **2f** was isolated as a red solid in 54% yield (1.84 g, 6.29 mmol). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 6.99-7.06 (m, 2H), 7.11-7.16 (m, 2H), 7.34-7.43 (m, 3H), 7.87-7.92 (m, 2H), 7.98 (s, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 114.9 (d, *J* = 7.7 Hz), 116.2 (d, *J* = 22.8 Hz), 119.7, 127.9, 128.6, 129.6, 135.9, 139.7 (d, *J* = 2.3 Hz), 158.1 (d, *J* = 239.2 Hz). **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -123.5. **HRMS** (ESI) calcd. for $C_{26}H_{19}F_2N_4^+$ [nitrile imine dimer + H]$^+$ 425.1572, found 425.1569.

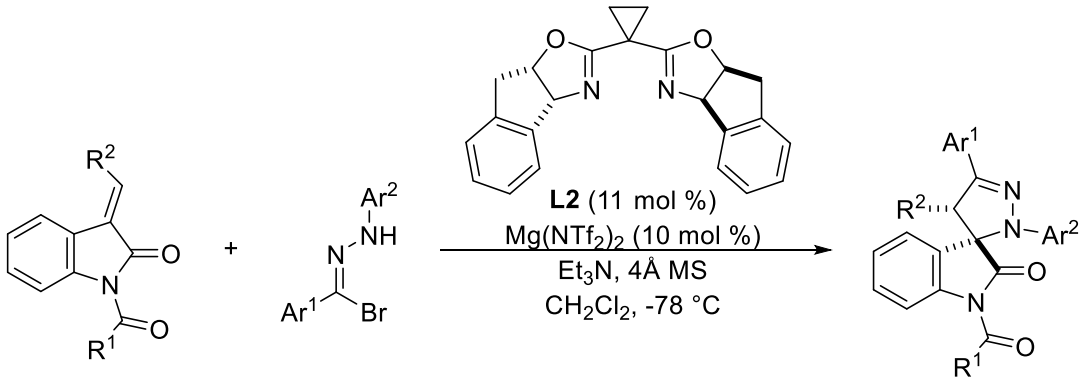


2g

(*Z*)-*N′*-(4-(trifluoromethyl)phenyl)benzohydrazonoyl bromide (2g): Prepared according to the general procedure from (*E*)-1-benzylidene-2-(4-(trifluoromethyl)phenyl)hydrazine **S2g** (0.700 g, 2.65 mmol) and the Corey-Kim complex of NBS (1.41 g, 7.95 mmol) and dimethyl sulfide (0.99 g, 1.17 mL, 15.9 mmol) as the brominating agent. After chromatography, the title compound **2g** was isolated as a red solid in 44% yield (0.400 g, 1.17 mmol). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.24 (d, *J* = 8.4 Hz, 2H), 7.38-7.46 (m, 3H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.86-7.96 (m, 2H), 8.20 (s, 1H).

^{13}C NMR ($CDCl_3$, 151 MHz): δ 113.5, 121.7, 123.2 (q, *J* = 32.8 Hz), 124.7 (q, *J* = 270.9 Hz), 127.0 (q, *J* = 3.8 Hz), 128.1, 128.7, 130.1, 135.6, 145.8 (q, *J* = 1.2 Hz). **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -62.0. **HRMS** (ESI) calcd. for $C_{28}H_{19}F_6N_4^+$ [nitrile imine dimer + H]$^+$ 525.1508, found 525.1508.

General procedure for synthesis of spiro[pyrazolin-3,3′-oxindoles] 3a-t

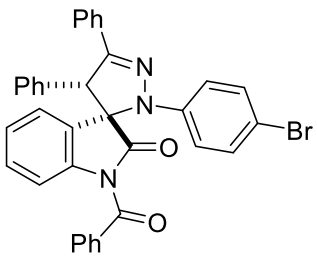


1a R^1 = Ph, R^2 = Ph
1b R^1 = Me, R^2 = Ph
1c R^1 = *t*-Bu, R^2 = Ph
1d R^1 = O*t*-Bu, R^2 = Ph
1e R^1 = Ph, R^2 = 4-MeO-C_6H_4
1f R^1 = Ph, R^2 = 4-Cl-C_6H_4
1g R^1 = Ph, R^2 = 4-Br-C_6H_4
1h R^1 = Ph, R^2 = 4-CF_3-C_6H_4
1i R^1 = Ph, R^2= 3-MeO-C_6H_4
1j R^1 = Ph, R^2 = 3,4,5-MeO-C_6H_2
1k R^1= Ph, R^2 = 2-F-C_6H_4
1l R^1 = Ph, R^2 = 2-Br-C_6H_4
1m R^1 = Ph, R^2 = (*E*)-*t*-Bu
1n R^1 = Ph, R^2 = (*Z*)-*t*-Bu

2a Ar^1 = Ph, Ar^2 = 4-Br-C_6H_4
2b Ar^1 = 4-CF_3-C_6H_4, Ar^2 = 4-Br-C_6H_4
2c Ar^1 = 3-Br-C_6H_4, Ar^2 = 3-Br-C_6H_4
2d Ar^1 = 2-F-C_6H_4, Ar^2 = 3-Br-C_6H_4
2e Ar^1 = 2-Br-C_6H_4, Ar^2 = 3-Br-C_6H_4
2f Ar^1 = Ph, Ar^2 = 4-F-C_6H_4
2g Ar^1 = Ph, Ar^2 = 4-CF_3-C_6H_4

In a nitrogen-filled dry-box, $Mg(NTf_2)_2$ (11.7 mg, 0.0200 mmol, 0.100 equiv), **L2** (7.8 mg, 0.022 mmol, 0.11 equiv), the appropriate methyleneindolinone **1** (0.200 mmol, 1.00 equiv), and powdered 4Å molecular sieves (100 mg) were added to a 1-dram vial. The appropriate hydrazonoyl bromide **2** (0.240 mmol, 1.20 equiv) was added to a second 1-dram vial. Both vials were sealed with a PFTE/silicone-lined septum cap and removed from the dry-box. The mixture

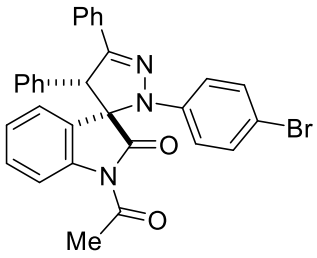
of $Mg(NTf_2)_2$, **L2**, methyleneindolinone **1**, and 4Å molecular sieves was suspended in CH_2Cl_2 (1 mL), allowed to stir for 15 minutes at room temperature, and cooled to -78 °C in a dry ice/acetone bath. Hydrazonoyl bromide **2** was dissolved in CH_2Cl_2 (1 mL) and added to the mixture of catalyst, dipolarophile and 4Å molecular sieves. The resulting mixture was allowed to stir for five minutes at -78 °C, then triethylamine (33 μL, 0.24 mmol) was added to initiate the cycloaddition reaction. The reaction mixture was allowed to stir for 4 h at -78 °C and monitored by TLC. Upon consumption of the methyleneindolinone **1**, the reaction mixture was filtered through a pad of silica (eluting with EtOAc). The crude reaction mixture was concentrated under reduced pressure. $CDCl_3$ (0.5-0.7 mL) was added to dissolve the crude reaction mixture, and the diastereomeric ratio was determined by ^{1}H NMR spectroscopy. The crude reaction mixture was purified by flash column silica gel chromatography (hexanes:EtOAc) to yield spiro[pyrazolin-3,3′-oxindoles] **3a-t**.



3a

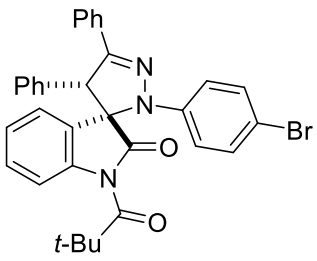
(3*S*,4′*S*)-1-Benzoyl-2′-(4-bromophenyl)-4′,5′-diphenyl-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (3a) (Table 1, entry 5): Prepared according to the general procedure at half of the typical scale from **1a** (32.5 mg, 0.100 mmol) and **2a** (42.5 mg, 0.120 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 hexanes:EtOAc) to yield **3a** (58.5 mg, 0.98 mmol, 98%) as a yellow foam with >95:5 diastereomeric and regioisomeric ratios. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 7.1 min (major); tR 14.7 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 90:10, 1.0 mL/min] to be 92% ee. $[\alpha]D^{25}$ = -495.6° (c 0.46, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.10 (s, 1H), 6.44 (d, *J* = 7.2

Hz, 1H), 6.78-6.90 (m, 3H), 7.06 (bs, 2H), 7.18-7.42 (m, 13H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.60-7.72 (m, 2H), 7.77 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 63.1, 77.8, 114.9, 115.6, 119.6, 124.7, 125.0, 126.8, 127.2, 128.5, 128.6, 128.7, 129.2, 129.5, 129.6, 130.5, 131.1, 132.2, 133.5, 133.6, 134.0, 140.1, 144.3, 151.3, 169.3, 174.9. **HRMS** (ESI) calcd. for $C_{35}H_{25}N_3O_2Br^+$ $[M+H]^+$ 598.1130, found 598.1129.



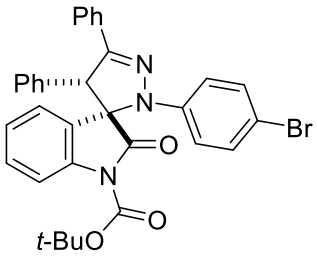
3b

(3*S*,4′*S*)-1-Acetyl-2′-(4-bromophenyl)-4′,5′-diphenyl-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (3b) (Table 1, entry 9): Prepared according to the general procedure from **1b** (52.7 mg, 0.200 mmol) and **2a** (85.0 mg, 0.240 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 hexanes:EtOAc) to yield **3b** (81.3 mg, 0.152 mmol, 76%) as a yellow foam with >95:5 diastereomeric and regioisomeric ratios. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 6.7 min (major); tR 13.9 min (minor) [Chiracel AD-H (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 90:10, 1.0 mL/min] to be 94% ee. $[\alpha]D^{25}$ = -436.8° (c 0.55, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 2.76 (s, 3H), 5.19 (s, 1H), 6.51 (d, *J* = 7.2 Hz, 1H), 6.82-6.90 (m, 3H), 7.03 (bs, 2H), 7.22-7.42 (m, 9H), 7.73-7.81 (m, 2H), 8.32 (d, *J* = 7.8 Hz, 1H) **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 26.8, 63.8, 77.2, 114.2, 116.8, 117.5, 124.2, 125.2, 126.0, 127.1, 128.6, 128.7, 129.0, 129.3, 129.4, 130.3, 131.3, 132.1, 133.8, 139.5, 143.3, 149.5, 170.7, 176.5. **HRMS** (ESI) calcd. for $C_{30}H_{23}BrN_3O_2^+$ $[M+H]^+$ 536.0974, found 536.0969.



3c

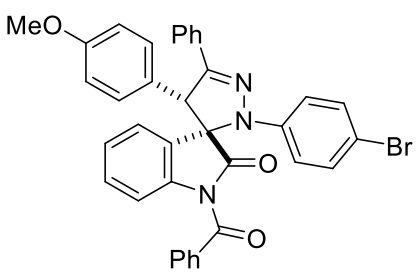
(3*S*,4′*S*)-2′-(4-bromophenyl)-4′,5′-diphenyl-1-pivaloyl-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (3c) (Table 1, entry 10): Prepared according to the general procedure at half of the typical scale from **1c** (30.5 mg, 0.100 mmol) and **2a** (42.5 mg, 0.120 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 hexanes:EtOAc) to yield **3c** (56.0 mg, 0.97 mmol, 97%) as a yellow foam with >95:5 diastereomeric and regioisomeric ratios. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 7.8 min (major); tR 28.9 min (minor) [Chiracel AD-H (0.46 cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 80:20, 1.0 mL/min] to be 40% ee. $[\alpha]D^{23}$ = -84.0° (c 0.88, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.24 (s, 9H), 5.16 (s, 1H), 6.35 (d, *J* = 7.2 Hz, 1H), 6.60 (t, *J* = 7.8 Hz, 1H), 6.77-6.82 (m, 2H), 6.96 (bs, 2H), 7.09 (t, *J* =7.8 Hz, 1H), 7.12-7.21 (m, 5H), 7.27-7.30 (m, 3H), 7.64-7.69 (m, 2H), 8.57 (s, 1H) **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 27.2, 38.7, 62.9, 77.2, 110.7, 113.7, 117.2, 122.9, 125.4, 126.7, 127.1, 128.3, 128.6, 128.9, 129.2, 129.3, 129.9, 131.6, 132.0, 134.6, 134.0, 143.5, 149.8, 178.4, 184.1.**HRMS** (ESI) calcd. for $C_{28}H_{20}BrN_3O^+$ $[M-C_5HO]^+$ 494.0863, found 494.0861.



3d

(3*S*,4′*S*)-*tert*-Butyl 2′-(4-bromophenyl)-2-oxo-4′,5′-diphenyl-2′,4′-dihydrospiro[indoline-3,3′-pyrazole]-1-carboxylate (3d) (Table 1, entry 11): Prepared according to the general procedure from **1d** (64.3 mg, 0.200 mmol) and **2a** (85.0 mg, 0.240 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 hexanes:EtOAc) to yield **3d** (44.0 mg, 0.074 mmol, 37%) as a yellow foam with >95:5

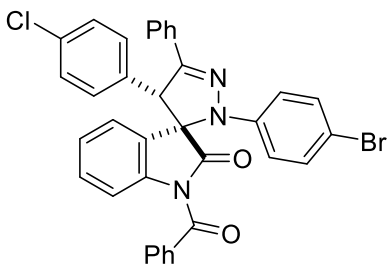
diastereomeric and regioisomeric ratios. The enantiomeric excess of **3d** was determined to be 98% after cleavage of the Boc group to form **S3a**. $[\alpha]D^{24}$ = -345.9 (c 0.37, CHCl3). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.64 (s, 9H), 5.13 (s, 1H), 6.38 (d, *J* = 3.6 Hz, 1H), 6.71 (t, *J* = 7.8 Hz, 1H), 6.76 (d, *J* = 9.0 Hz, 2H), 6.92 (bs, 2H), 7.11-7.24 (m, 6H), 7.26-7.30 (m, 3H), 7.62-7.68 (m, 2H), 7.87 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 28.3, 63.6, 77.1, 85.4, 113.9, 115.4, 117.4, 123.9, 124.4, 126.1, 127.1, 128.4, 128.6, 128.9, 129.2, 129.4, 130.1, 131.4, 132.0, 134.2, 139.2, 143.2, 149.2, 149.3, 173.8. **HRMS** (ESI) calcd. for $C_{33}H_{29}N_3O_3Br^+$ $[M+H]^+$ 594.1392, found 594.1384.



3e

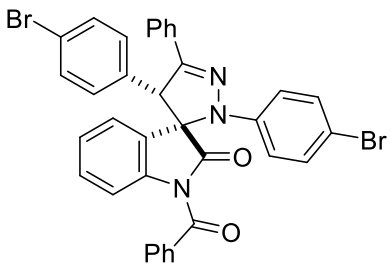
(3*S*,4′*S*)-1-benzoyl-2′-(4-bromophenyl)-4′-(4-methoxyphenyl)-5′-phenyl-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (3e) (Table 2, entry 1): Prepared according to the general procedure from **1e** (71.1 mg, 0.200 mmol) and **2a** (85.0 mg, 0.240 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 hexanes:EtOAc) to yield **3e** (102 mg, 0.162 mmol, 81%) as a yellow foam with >95:5 diastereomeric and regioisomeric ratios. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 11.0 min (major); tR 21.9 min (minor) [Chiracel AD-H (0.46 cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 90:10, 1.0 mL/min] to be 99% ee. $[\alpha]D^{25}$ = -627.1° (c 0.47, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.67 (s, 3H), 4.95 (s, 1H), 6.41 (d, *J* = 7.2 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 2H), 6.72-6.83 (m, 3H), 6.87 (bs, 2H), 7.14-7.29 (m, 10H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.49-7.60 (m, 2H), 7.68 (d, *J* = 8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 55.5, 62.4, 77.8, 114.5, 114.9, 115.6, 119.6, 124.8, 125.1, 126.0, 126.9, 127.2, 128.5, 128.6, 129.4, 129.5, 130.4, 130.8,

131.2, 132.2, 133.5, 133.6, 140.1, 144.3, 151.6, 159.8, 169.3, 174.9. **HRMS** (ESI) calcd. for $C_{36}H_{27}N_3O_3Br^+$ $[M+H]^+$ 628.1236, found 628.1225.



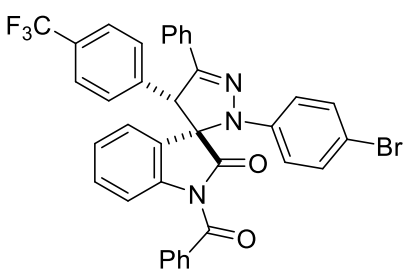
3f

(3*S*,4′*S*)-1-benzoyl-2′-(4-bromophenyl)-4′-(4-chlorophenyl)-5′-phenyl-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (3f) (Table 2, entry 2): Prepared according to the general procedure from **1f** (72.0 mg, 0.200 mmol) and **2a** (85.0 mg, 0.240 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 hexanes:EtOAc) to yield **3f** (109 mg, 0.172 mmol, 86%) as a yellow foam with >95:5 diastereomeric and regioisomeric ratios. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 8.4 min (major); tR 16.5 min (minor) [Chiracel AD-H (0.46 cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 90:10, 1.0 mL/min] to be 99% ee. $[\alpha]D^{24}$ = -396.1° (c 0.62, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.09 (s, 1H), 6.51 (d, *J* = 6.6 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 2H), 6.96 (dt, *J* = 0.6, 7.8 Hz, 1H), 7.01 (bs, 2H), 7.21-7.39 (m, 13H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.58-7.66 (m, 2H), 7.80 (d, *J* = 8.4 Hz, 1H) **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 62.2, 77.7, 115.1, 115.9, 119.7, 124.4, 125.2, 126.7, 127.1, 128.5, 128.7, 129.4, 129.6, 129.7, 130.7, 130.8, 130.9, 132.2, 132.4, 133.4, 133.6, 134.7, 140.2, 144.1, 151.0, 169.2, 174.6. **HRMS** (ESI) calcd. for $C_{35}H_{24}N_3O_2BrCl^+$ $[M+H]^+$ 632.0740, found 632.0720.



3g

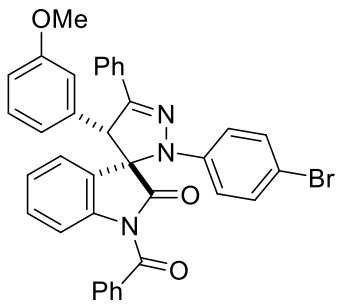
(3*S*,4′*S*)-1-benzoyl-2′,4′-bis(4-bromophenyl)-5′-phenyl-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (3g) (Table 2, entry 3): Prepared according to the general procedure from **1g** (80.8 mg, 0.200 mmol) and **2a** (85.0 mg, 0.240 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 hexanes:EtOAc) to yield **3g** (85.3 mg, 0.126 mmol, 63%) as a yellow foam with a 90:10 diastereomeric ratio and a >95:5 regioisomeric ratio. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 9.0 min (major); tR 17.2 min (minor) [Chiracel AD-H (0.46 cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 90:10, 1.0 mL/min] to be 94% ee. $[\alpha]D^{26}$ = -506.8° (c 0.59, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.12 (s, 1H), 6.40 (dd, *J* = 7.8, 0.6 Hz, 1H), 6.68 (dt, *J* = 0.6, 7.2 Hz, 1H), 6.77-6.86 (m, 7H), 7.13 (dt, *J* = 1.2, 7.8 Hz, 2H), 7.16-7.19 (m, 2H), 7.27-7.31 (m, 6H) 7.59-7.64 (m, 3H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 62.2, 77.6, 115.1, 115.9, 119.7, 122.8, 124.3, 125.2, 126.7, 127.1, 128.5, 128.7, 129.6, 129.7, 130.7, 130.8, 131.2, 132.2, 132.4, 133.2, 133.4, 133.56, 140.7, 144.1, 151.0, 169.2, 174.5. **HRMS** (ESI) calcd. for $C_{35}H_{24}N_3O_2Br_2^+$ $[M+H]^+$ 676.0235, found 676.0204.



3h

(3*S*,4′*S*)-1-benzoyl-2′-(4-bromophenyl)-5′-phenyl-4′-(4-(trifluoromethyl)phenyl)-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (3h) (Table 2, entry 4): Prepared according to the general procedure from **1h** (78.7 mg, 0.200 mmol) and **2a** (85.0 mg, 0.240 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 hexanes:EtOAc) to yield **3h** (108 mg, 0.162 mmol, 81%) as a yellow foam with >95:5 diastereomeric and regioisomeric ratios. The

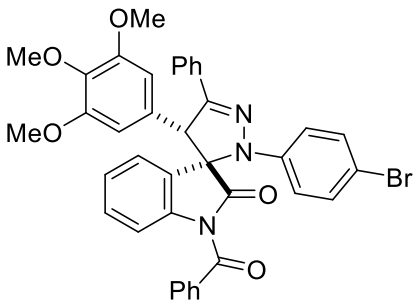
enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 7.4 min (major); tR 15.3 min (minor) [Chiracel AD-H (0.46 cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 90:10, 1.0 mL/min] to be 80% ee. $[\alpha]D^{24}$ = -433.4° (c 0.65, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.12 (s, 1H), 6.36 (d, *J* = 7.6 Hz, 1H), 6.80-6.90 (m, 3H), 7.17 (bs, 2H), 7.22-7.37 (m, 10H), 7.46-7.55 (m, 3H), 7.55-7.63 (m, 2H), 7.75 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 62.4, 77.8, 115.1, 116.1, 119.8, 124.0 (q, *J* = 272.25 Hz), 124.2, 125.1, 126.1 (q, *J* = 3.62 Hz), 126.5, 127.0, 128.5, 128.8, 129.6, 129.8, 130.1, 130.70, 130.74 (*q*, *J* = 32.8 Hz), 130.9, 132.3, 133.4, 133.6, 138.3, 140.2, 144.0, 150.7, 169.2, 174.4. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -63.1. **HRMS** (ESI) calcd. for $C_{36}H_{24}F_3N_3O_2Br^+$ $[M+H]^+$ 666.1004, found 666.0973.



3i

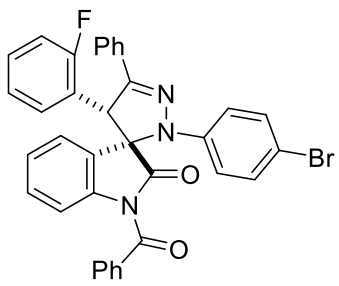
(3*S*,4′*S*)-1-benzoyl-2′-(4-bromophenyl)-4′-(3-methoxyphenyl)-5′-phenyl-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (3i) (Table 2, entry 5): Prepared according to the general procedure from **1i** (71.1 mg, 0.200 mmol) and **2a** (85.0 mg, 0.24 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 hexanes:EtOAc) to yield **3i** (113 mg, 0.180 mmol, 90%) as a yellow foam with a 90:10 diastereomeric ratio and a >95:5 regioisomeric ratio. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 8.2 min (major); tR 19.9 min (minor) [Chiracel AD-H (0.46 cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 90:10, 1.0 mL/min] to be 94% ee. $[\alpha]D^{26}$ = -497.4° (c 0.39, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 3.68 (s, 3H), 5.06 (s, 1H), 6.54 (d, *J* = 7.8 Hz, 1H), 6.62-6.73 (m, 1H), 6.78-6.83 (m, 1H), 6.84-6.93 (m, 3H), 7.17 (t, *J* = 7.8 Hz, 1H), 7.24-7.39 (m, 11H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.62-7.70 (m, 2H), 7.78 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 55.5,

63.0, 77.8, 114.1, 114.9, 115.3, 115.6, 119.6, 121.9, 124.6, 125.0, 126.7, 127.1, 128.5, 128.6, 129.48, 129.53, 130.2, 130.5, 131.2, 132.2, 133.47, 133.53, 135.4, 140.1, 144.2, 151.3, 160.2, 169.3, 174.8. **HRMS** (ESI) calcd. for $C_{36}H_{27}N_3O_3Br^+$ $[M+H]^+$ 628.1236, found 628.1219.



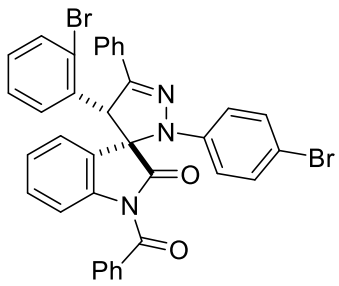
3j

(3*S*,4′*S*)-1-benzoyl-2′-(4-bromophenyl)-5′-phenyl-4′ (3,4,5-trimethoxyphenyl)-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (3j) (Table 2, entry 6): Prepared according to the general procedure from **1j** (83.0 mg, 0.200 mmol) and **2a** (85.0 mg, 0.240 mmol). The crude reaction mixture was purified by flash column chromatography (80:20 hexanes:EtOAc) to yield **3j** (125 mg, 0.182 mmol, 91%) as a yellow foam with >95:5 diastereomeric and regioisomeric ratios. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 6.7 min (major); tR 37.6 min (minor) [Chiracel AD-H (0.46cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 80:20, 1.0 mL/min] to be 61% ee. $[\alpha]D^{26}$ = -22.2 (c 0.63, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 3.56 (s, 6H), 3.89 (s, 3H), 5.28 (s, 1H), 6.14 (s, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 7.8 Hz, 2H), 7.21-7.34 (m, 8H), 7.40-7.49 (m, 2H), 7.52-7.62 (m, 3H), 7.70 (d, *J* = 7.2 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 56.2, 61.1, 68.3, 78.7, 107.3, 113.8, 116.3, 116.8, 123.8, 126.5, 127.0, 128.1, 128.6, 129.2, 129.6, 130.2, 130.6, 131.1, 132.2, 133.1, 133.3, 138.4, 139.9, 143.2, 147.6, 153.5, 168.7, 171.6. **HRMS** (ESI) calcd. for C38H31N3O5Br+ [M+H]+ 688.1447, found 688.1440.



3k

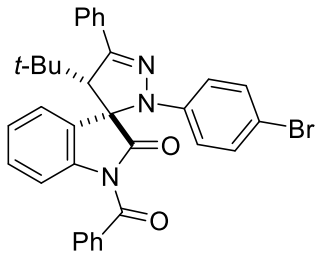
(3*S*,4′*S*)-1-benzoyl-2′-(4-bromophenyl)-4′-(2-fluorophenyl)-5′-phenyl-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (3k) (Table 2, entry 8): Prepared according to the general procedure from **1k** (68.7 mg, 0.200 mmol) and **2a** (85.0 mg, 0.24 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 hexanes:EtOAc) to yield **3k** (104 mg, 0.168 mmol, 84%) as a yellow foam with >95:5 diastereomeric and regioisomeric ratios. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 8.1 min (major); tR 12.4 min (minor) [Chiracel AD-H (0.46 cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 90:10, 1.0 mL/min] to be 92% ee. $[\alpha]D^{24}$ = -323.0° (c 0.52, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.55 (s, 1H), 6.45 (d, *J* = 7.8 Hz, 1H), 6.78-6.91 (m, 4H), 7.08 (t, *J* = 7.8 Hz, 1H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.20-7.26 (m, 1H), 7.28-7.37 (m, 6H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.62-7.69 (m, 2H), 7.84 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 55.4, 115.2, 115.8 (d, *J* = 21.9 Hz), 118.7, 121.8 (d, *J* = 15.1 Hz), 124.5, 124.61, 124.62, 124.8, 126.1, 126.9, 128.5, 128.7, 129.46, 129.56, 130.5, 130.6, 130.9, 132.2, 133.4, 133.7, 140.4, 143.7, 149.1, 160.7 (d, *J* = 248.1Hz), 169.0, 174.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ 116.5. **HRMS** (ESI) calcd. for $C_{35}H_{24}N_3O_2BrF^+$ $[M+H]^+$ 616.1036, found 616.1030.



3l

(3*S*,4′*S*)-1-benzoyl-4′-(2-bromophenyl)-2′-(4-bromophenyl)-5′-phenyl-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (3l) (Table 2, entry 9): Prepared according to the general procedure from **1l** (80.8 mg, 0.200 mmol) and **2a** (85.0 mg, 0.240 mmol). The crude reaction mixture was purified by flash column

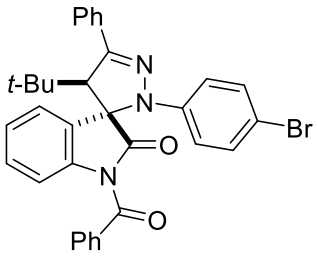
chromatography (95:5 hexanes:EtOAc) to yield **3l** (58.3 mg, 0.086 mmol, 43%) as a yellow foam with >95:5 diastereomeric and regioisomeric ratios. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 7.3 min (major); tR 13.0 min (minor) [Chiracel AD-H (0.46 cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 90:10, 1.0 mL/min] to be 0% ee. **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 5.56 (s, 1H), 6.24 (d, *J* = 11.4 Hz, 1H), 6.66-6.79 (m, 3H), 6.96-7.06 (m, 1H), 7.09-7.21 (m, 8H), 7.22-7.35 (m, 6H), 7.42 (t, *J* = 10.8 Hz, 1H), 7.45-7.51 (m, 2H), 7.71 (d, *J* = 12 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 61.4, 77.4, 115.2, 115.6, 119.4, 124.5, 124.8, 126.1, 126.4, 127.0, 128.1, 128.5, 128.8, 129.57, 129.61, 130.2, 130.6, 130.8, 131.0, 132.2, 133.3, 133.4, 133.6, 133.8, 141.1, 144.0, 150.5, 169.0, 174.6. **HRMS** (ESI) calcd. for $C_{35}H_{24}N_3O_2Br_2^+$ $[M+H]^+$ 676.0235, found 676.0228.



3m

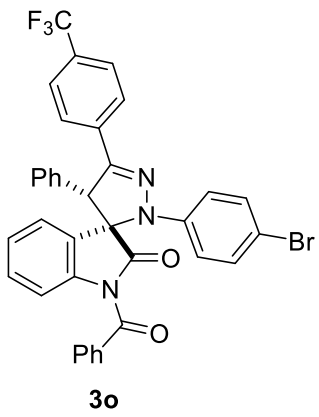
(3*S*,4′*S*)-1-benzoyl-2′-(4-bromophenyl)-4′-(tert-butyl)-5′-phenyl-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (3m) (Table 2, entry 10): Prepared according to the general procedure from **1m** (61.1 mg, 0.200 mmol) and **2a** (85.0 mg, 0.240 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 hexanes:EtOAc) to yield **3m** (81.0 mg, 0.140 mmol, 70%) as a tan foam with >95:5 diastereomeric and regioisomeric ratios. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 4.8 min (major); tR 39.5 min (minor) [Chiracel AD-H (0.46 cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 90:10, 1.0 mL/min] to be 99% ee. $[\alpha]D^{25}$ = -258.6 (c 0.52, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 0.87 (s, 9H), 4.17 (s, 1H), 6.76 (d, *J* = 9 Hz, 2H), 7.19-7.26 (m, 3H), 7.36-7.43 (m, 3H), 7.43-7.50 (m, 3H), 7.51-7.57 (m, 2H), 7.57-7.64 (m, 3H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151

MHz) δ 29.9, 34.8, 70.8, 78.2, 114.9, 115.7, 119.1, 125.0, 125.2, 128.2, 128.4, 128.5, 128.6, 129.1, 129.7, 130.9, 131.9, 133.6, 133.7, 135.2, 140.5, 143.6, 153.9, 169.2, 176.5. **HRMS** (ESI) calcd. for $C_{33}H_{29}N_3O_2Br^+$ $[M+H]^+$ 578.1443, found 578.1440.



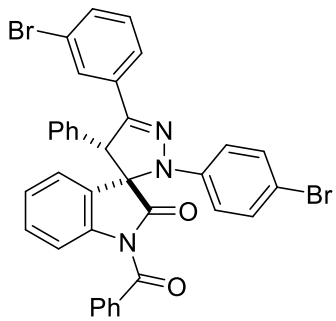
3n

(3*S*,4′*R*)-1-benzoyl-2′-(4-bromophenyl)-4′-(tert-butyl)-5′-phenyl-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (3n) (Equation 1): Prepared according to the general procedure from **1n** (61.1 mg, 0.200 mmol) and **2a** (85.0 mg, 0.240 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 hexanes:EtOAc) to yield **3n** (74.0 mg, 0.128 mmol, 64%) as a tan foam with >95:5 diastereomeric and regioisomeric ratios. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 6.5 min (minor); tR 13.8 min (major) [Chiracel AD-H (0.46 cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 90:10, 1.0 mL/min] to be 66% ee. $[\alpha]D^{26}$ = -194.4 (c 0.36, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 0.97 (s, 9H), 4.01 (s, 1H), 6.86 (d, *J* = 9.0 Hz, 2H), 7.24 (t, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 9.0 Hz, 2H), 7.35-7.52 (m, 9H), 7.55-7.64 (m, 3H), 7.70 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 29.7, 35.0, 73.2, 78.3, 115.4, 115.6, 120.0, 123.4, 126.2, 128.1, 128.5, 128.6, 129.1, 129.7, 130.4, 131.0, 132.0, 133.5, 133.9, 135.2, 138.8, 143.5, 153.6, 169.4, 172.7. **HRMS** (ESI) calcd. for $C_{33}H_{29}N_3O_2Br^+$ $[M+H]^+$ 578.1443, found 578.1444.



3o

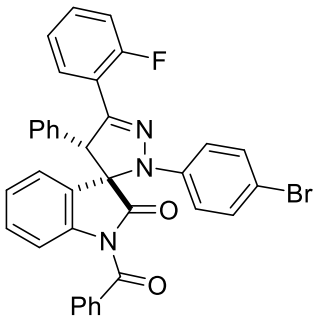
(3*S*,4′*S*)-1-benzoyl-2′-(4-bromophenyl)-4′-phenyl-5′-(4-(trifluoromethyl)phenyl)-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (3o) (Table 3, entry 1): Prepared according to the general procedure from **1a** (65 mg, 0.20 mmol) and **2b** (101 mg, 0.24 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 hexanes:EtOAc) to give **3o** (114 mg, 0.172 mmol, 86%) as a yellow foam with >95:5 diastereomeric and regioisomeric ratios. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 8.22 min (major); tR 20.84 min (minor) [Chiracel AD-H (0.46 cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 90:10, 1.0 mL/min] to be 94% ee. $[\alpha]D^{25}$= -370.5 (c 0.50, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 5.11 (s, 1H), 6.45 (dd, *J* = 1.2, 7.8, Hz, 1H), 6.82-6.90 (m, 3H), 6.95-7.10 (br s, 2H), 7.23-7.30 (br s, 2H), 7.31-7.35 (m, 5H), 7.37 (t, *J* = 8.4 Hz, 2H), 7.49-7.53 (m, 3H), 7.55 (t, 7.2 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 2H), 7.77 (d, *J* = 7.2 Hz, 1H). **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -63.2. **HRMS** (ESI) Exact mass calcd. for $C_{36}H_{24}BrF_3N_3O_2^+$ $[M+H]^+$ 666.0999, found: 666.0996. This material was contaminated by traces of the starting alkylidene oxindole; to separate them, the *N*-benzoyl group was cleaved as described below.



3p

(3*S*,4′*S*)-1-benzoyl-5′-(3-bromophenyl)-2′-(4-bromophenyl)-4′-phenyl-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (3p) (Table 3, entry 2): Prepared according to the general procedure from **1a** (65 mg, 0.20 mmol) and **2c** (104 mg, 0.24 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 hexanes:EtOAc) to give **3p** (98.0 mg, 0.145 mmol, 72%) as a yellow

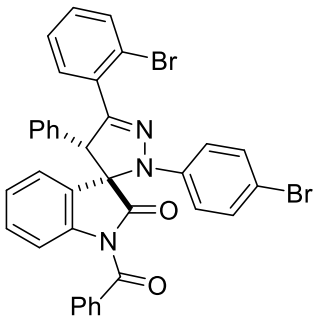
foam with >95:5 diastereomeric and regioisomeric ratios. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 6.81 min (major); tR 10.90 min (minor) [Chiracel AD-H (0.46 cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 90:10, 1.0 mL/min] to be 84% ee. $[\alpha]D^{25}$= -420.0 (c 0.50, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 5.04 (s,1H), 6.42 (dd, *J* = 1.2, 7.8 Hz, 1H), 6.81-6.88 (m, 3H)), 6.95-7.08 (br s, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.24-7.28 (br s, 3H), 7.29-7.34 (m, 5H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.40 (dt, *J* = 1.2, 7.8 Hz, 2H), 7.54 (tt, *J* = 1.2, 7.2 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.93 (t, *J* = 1.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 62.7, 77.9, 115.0, 115.9, 119.6, 122.9, 124.3, 125.0, 125.6, 126.7, 128.5, 128.9, 129.3, 129.5, 129.8, 130.1 (two coincident resonances, as determined by HSQC), 130.6, 132.2, 132.3, 133.2, 133.47, 133.52, 133.54, 140.2, 143.8, 149.8, 169.2, 174.7. **HRMS** (ESI) Exact mass calcd. for $C_{35}H_{24}Br_2N_3O_2^+$ $[M+H]^+$ 676.0230, found 676.0254.



3q

(3*S*,4′*S*)-1-benzoyl-2′-(4-bromophenyl)-5′-(2-fluorophenyl)-4′-phenyl-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (3q) (Table 3, entry 3): Prepared according to the general procedure from **1a** (65 mg, 0.20 mmol) and **2e** (89 mg, 0.24 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 hexanes:EtOAc) to give **3q** (111 mg, 0.180 mmol, 90%) as a yellow foam with >95:5 diastereomeric and regioisomeric ratios. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 6.51 min (major); tR 11.07 min (minor) [Chiracel AD-H (0.46 cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 90:10, 1.0 mL/min] to be 90% ee. $[\alpha]D^{25}$= -539.3 (c 0.51, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.27 (d, *J* = 2 Hz, 1H), 6.40 (d, *J* = 8 Hz, 1H), 6.78-6.85 (m, 3H), 6.90 (dd, *J* = 8.4, 11.6 Hz, 1H), 6.98-

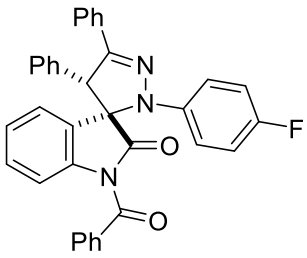
7.03 (m, 2H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.16-7.25 (m, 4H), 7.25-7.38 (m, 7H), 7.51 (dt, *J* = 0.8,7.2 Hz, 1H), 7.75 (d, *J* = 8 Hz, 1H), 8.00 (t, *J* = 7.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 64.4 (d, *J* = 6.5 Hz), 77.5 (d, *J* = 4.8 Hz), 114.9, 115.7, 116.6 (d, *J* = 22.5 Hz), 119.4 (d, *J* = 11.0 Hz), 119.5, 124.4, 124.4 (d, *J* = 8.5 Hz), 125.0, 126.6, 128.48, 128.51, 128.9, 129.45, 129.49, 129.54, 130.5, 131.2 (d, *J* = 8.6 Hz), 132.2, 133.47, 133.53, 133.9, 140.1, 144.0, 148.2 (d, *J* = 3.8 Hz), 160.4 (d, *J* = 254.7 Hz), 169.2, 174.7. **^{19}F NMR** ($CDCl_3$, 376 MHz) δ -112.88. **HRMS** (ESI) Exact mass calcd. for $C_{35}H_{24}BrFN_3O_2^+$ $[M+H]^+$ 616.1030; found: 616.1028.



3r

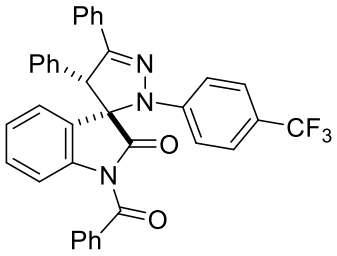
(3*S*,4′*S*)-1-benzoyl-5-(2-bromophenyl)-2′-(4-bromophenyl)-4′-phenyl-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (3r) (Table 3, entry 4): Prepared according to the general procedure from **1a** (65 mg, 0.20 mmol) and **2e** (104 mg, 0.24 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 hexanes:EtOAc) to give **3r** (110 mg, 0.162 mmol, 81%) as a yellow foam with >95:5 diastereomeric and regioisomeric ratios. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 9.38 min (major); tR 20.16 min (minor) [Chiracel AD-H (0.46 cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 90:10, 1.0 mL/min] to be 62% ee. $[\alpha]D^{25}$= -247.0 (c 0.51, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 5.70 (s, 1H), 6.61 (dd, *J* = 1.2, 7.8 Hz, 1H), 6.83-6.88 (m, 3H), 7.02-7.05 (m, 2H), 7.13 (dt, *J* = 1.2, 7.8 Hz, 1H), 7.18-7.22 (m, 3H), 7.23-7.27 (m, 2H), 7.28-7.31 (m, 2H), 7.40 (t, *J* = 8.4 Hz, 2H), 7.44 (dd, *J* = 1.8, 7.8 Hz, 2H), 7.55-7.59 (m, 2H), 7.60 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz): δ 64.8, 77.9, 114.9, 115.5, 119.1, 122.0, 124.3, 124.9, 126.5, 127.5, 128.5, 128.6, 128.9, 129.7, 129.8, 130.39, 130.44, 131.6, 132.0, 132.2, 133.2, 133.5,

133.6, 134.6, 139.9, 143.7, 150.5, 169.1, 174.8. **HRMS** (ESI) Exact mass calcd. for $C_{35}H_{24}Br_2N_3O_2^+$ $[M+H]^+$ 676.0230, found 676.0225.



3s

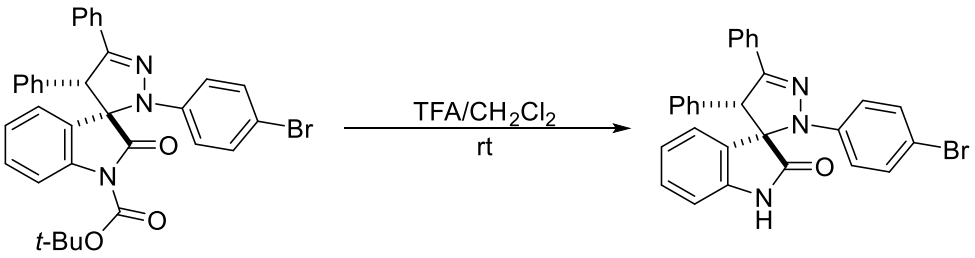
(3*S*,4′*S*)-1-benzoyl-2′-(4-fluorophenyl)-4′,5′-diphenyl-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (3s) (Table 3, entry 5): Prepared according to the general procedure from **1a** (65 mg, 0.20 mmol) and **2f** (70 mg, 0.24 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 hexanes:EtOAc) to give **3s** (89.0 mg, 0.166 mmol, 83%) as a yellow foam with >95:5 diastereomeric and regioisomeric ratios. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 6.05 min (major); tR 10.70 min (minor) [Chiracel AD-H (0.46 cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 90:10, 1.0 mL/min] to be 91% ee. $[\alpha]D^{24}$= -617.0 (c 0.56, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.09 (s, 1H), 6.45 (dd, J = 8, 0.8 Hz, 1H), 6.87 (dt, J = 0.8, 7.6 Hz 1H), 6.92-6.97 (m, 4H), 7.10 (bs, 2H), 7.21 (dd, J = 8, 1.2 Hz, 2H), 7.24-7.30 (m, 6H), 7.31-7.37 (m, 3H), 7.52 (t, J = 7.6 Hz, 1H), 7.62-7.69 (m, 2H), 7.76 (d, J = 8.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 101 MHZ) δ 62.6, 78.4, 114.8, 115.7, 115.9, 120.8 (d, J = 7.9 Hz) 124.8, 124.9, 126.9, 127.1, 128.4, 128.6, 129.2, 129.4, 129.5, 129.7, 130.4, 131.2, 133.4, 133.6, 134.1, 140.4, 141.5 (d, J = 2.4 Hz) 151.7, 159.5 (d, J = 243.9 Hz) 169.3, 174.8. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -120.1. **HRMS** (ESI) Exact mass calcd. for $C_{35}H_{25}FN_3O_2^+$ $[M+H]^+$ 538.1925, found 538.1925.



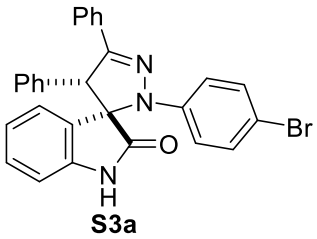
3t

(3*S*,4′*S*)-1-benzoyl-4′,5′-diphenyl-2′-(4-(trifluoromethyl)phenyl)-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (3t) (Table 3, entry 6): Prepared according to the general procedure from **1a** (65 mg, 0.20 mmol) and **2g** (82 mg, 0.24 mmol). The crude reaction mixture was purified by flash column chromatography (95:5 hexanes:EtOAc) to give **3t** (103 mg, 0.174 mmol, 87%) as a yellow foam with >95:5 diastereomeric and regioisomeric ratios. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 5.18 min (major); tR 8.61 min (minor) [Chiracel AD-H (0.46 cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 90:10, 1.0 mL/min] to be 90% ee. $[\alpha]D^{24}$= -450.9 (c 0.51, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 5.16 (s, 1H), 6.47 (d, *J* = 7.8 Hz, 1H), 6.83 (t, *J* = 7.8 Hz, 1H), 6.95-7.05 (br m, 2H), 7.05 (d, *J* = 7.8 Hz, 2H), 7.24-7.35 (m, 9H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.44-7.47 (m, 4H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.58-7.73 (m, 2H), 7.83 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 63.6, 77.2, 115.2, 115.9, 123.7 (q, *J* = 32.6 Hz), 124.5, 124.6 (q, *J* = 270.9), 125.1, 126.6, 126.6 (q, *J* = 3.5 Hz), 127.3, 128.5, 128.7, 128.7, 129.2, 129.5, 129.6, 129.7, 130.5, 131.0, 133.5, 133.6, 134.0, 139.8, 147.5, 151.1, 169.1, 174.9. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -62.19. **HRMS** (ESI) Exact mass calcd. for $C_{36}H_{25}F_3N_3O_2^+$ $[M+H]^+$ 588.1893, found 588.1898.

Synthesis of S3a from 3d



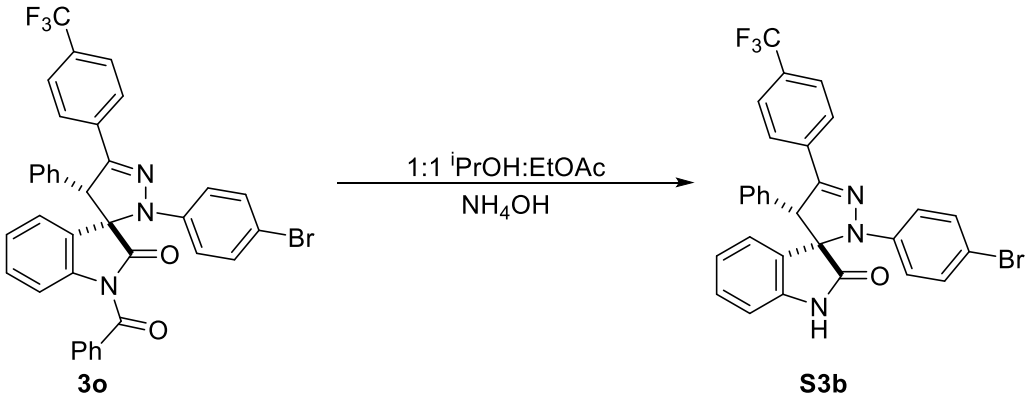
3d **S3a**



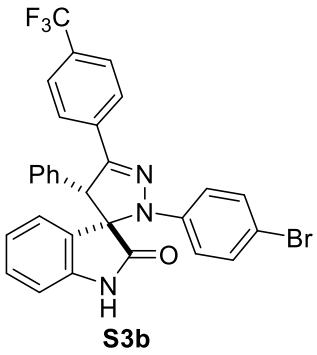
S3a

(3*S*,4′*S*)-2′-(4-bromophenyl)-4′,5′-diphenyl-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (S3a): A 1:1 mixture of CH_2Cl_2:trifluoroacetic acid (1 ml) was added to compound **3d** (44 mg, 0.074 mmol) under an atmosphere of nitrogen, and the mixture was stirred at room temperature until TLC showed complete consumption of **3d**. The volatiles were evaporated under reduced pressure to yield **S3a** (34 mg, 0.069 mmol, 92%) as a tan powder. The enantiomeric excess was determined by HPLC analysis (254 nm, 25 °C) tR 7.6 min (major); tR 28.3 min (minor) [Chiracel AD-H (0.46 cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 80:20, 1.0 mL/min] to be 98% ee. $[\alpha]D^{24}$= -141.1 (c 0.68, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 5.17 (s, 1H), 6.34 (d, J = 7.2 Hz, 1H), 6.60 (t, J = 7.6 Hz, 1H), 6.72-6.83 (m, 3H), 6.91-7.02 (m, 2H), 7.08 (dt, J = 0.8 Hz, 7.8 Hz 1H), 7.12-7.20 (m, 5H), 7.27-7.31 (m, 3H), 7.63-7.70 (m, 2H), 8.61 (s, 1H). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 62.9, 77.4, 110.8, 113.6, 117.0, 122.9, 125.3, 126.7, 127.1, 128.3, 128.6, 128.9, 129.2, 129.3, 129.9, 131.5, 132.0, 134.6, 139.9, 143.4, 149.7, 178.5. **HRMS** (ESI) Exact mass calcd. for $C_{28}H_{21}BrN_3O^+$ $[M+H]^+$ 494.0868, found 494.0868.

Synthesis of S3b from 3o



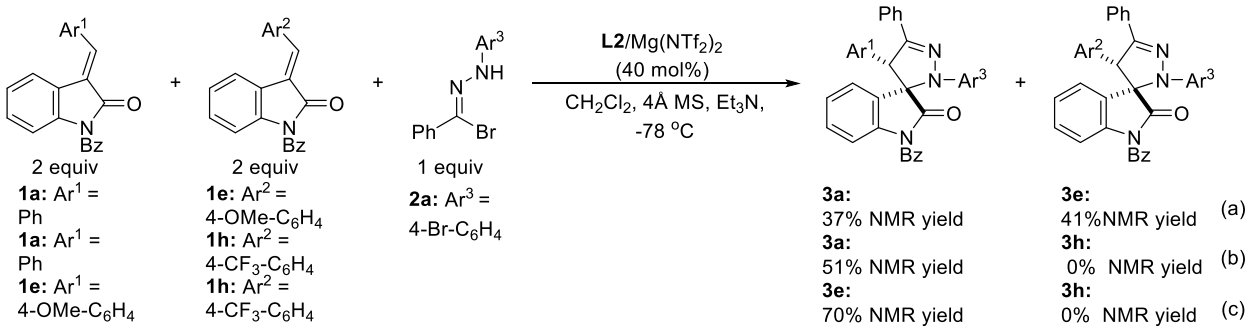
3o S3b



S3b

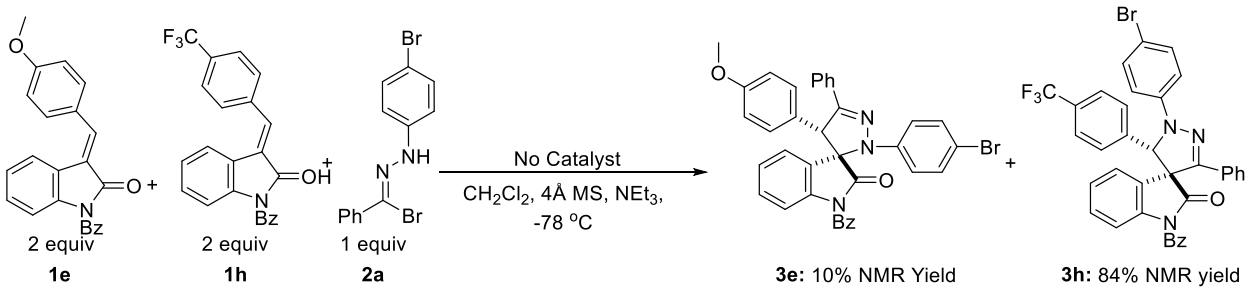
(3*S*,4′*S*)-2′-(4-bromophenyl)-4′-phenyl-5′-(4-(trifluoromethyl)phenyl)-2′,4′-dihydrospiro[indoline-3,3′-pyrazol]-2-one (S3b): To a solution of **3o** (121 mg, 0.181 mmol) in 1:1 *i*PrOH:EtOAc (4 mL) was added ammonium hydroxide (0.03 mL). The reaction mixture was stirred at room temperature until TLC analysis indicated complete consumption of **3o**, at which point brine (3 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 2mL), and the combined organic extracts were passed through a glass Pasteur pipette packed with ~2 cm of silica gel. The resulting solution was concentrated under reduced pressure to yield the crude **3o**. The crude product was purified by flash column chromatography (80:20 hexanes:EtOAc) to afford **3o** (48 mg, 0.085 mmol, 73%) as a yellow. HPLC analysis confirmed that no racemization had occurred during the cleavage reaction, although ~5% of a minor diastereomer had formed. HPLC analysis (254 nm, 25 °C) tR 5.64 min (major); tR 12.5 min (minor) [Chiracel AD-H (0.46 cm x 25cm)(from Daicel Chemical Ind., Ltd.) hexane/i-PrOH, 80:20, 1.0 mL/min] to be 92% ee. $[\alpha]D^{25}$= -273.5 (c 0.49, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.17 (s, 1H), 6.34 (d, *J* = 8.4 Hz, 1H), 6.60 (t, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.94 (br s, 2H), 7.08 (t, *J* = 7.6 Hz, 1H), 7.13-7.23 (m, 5H), 7.53 (d, *J* = 8.4Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H), 8.74 (br s, 1H). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 62.6, 77.3, 110.9, 114.2, 117.1, 123.0, 123.7 (q, *J* = 273.5 Hz), 124.9, 125.6 (q, *J* = 3.5 Hz), 126.7, 127.1, 128.6, 129.1, 129.2, 130.1, 130.5 (q, *J* = 32.4 Hz), 132.1, 134.1, 135.0 (q, *J* = 1.1 Hz), 139.9, 142.9, 148.1, 178.2. **^{19}F NMR** ($CDCl_3$, 376 MHz): δ -63.2 **HRMS** (ESI) Exact mass calcd. for $C_{29}H_{19}BrF_3N_3O_2^+$ $[M+H]^+$ 562.0736, found 562.0737.

Competition reactions of dipolarophiles under catalyzed conditions



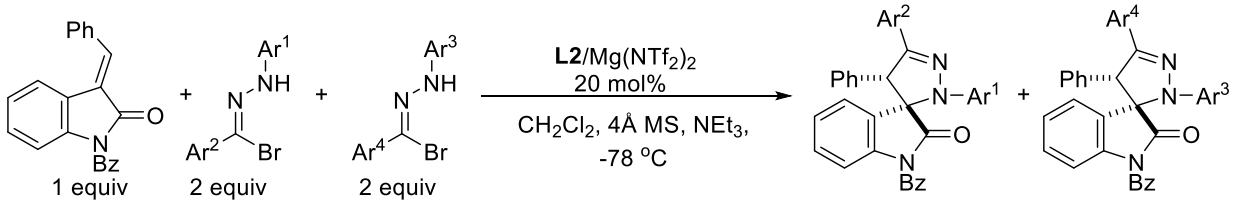
In a nitrogen-filled dry-box, $Mg(NTf_2)_2$ (23.4 mg, 0.040 mmol, 0.400 equiv), **L2** (15.6 mg, 0.044 mmol, 0.440 equiv), the appropriate methyleneindolinones **1** (each 0.200 mmol, 2 equiv), and powdered 4Å MS (100 mg) were added to a 1-dram vial. Hydrazonoyl bromide **2a** (35.4 mg, 0.100 mmol, 1 equiv) was added to a second 1-dram vial. Both vials were sealed with a PTFE/silicone-lined septum cap and removed from the dry-box. The mixture of $Mg(NTf_2)_2$, **L2**, the methyleneindolinones, and the 4Å MS was suspended in CH_2Cl_2 (1 mL), allowed to stir for 15 minutes at room temperature, and cooled to -78 °C in a dry ice/acetone bath. Hydrazonal bromide **2a** was dissolved in CH_2Cl_2 (1 mL) and added to the mix of catalyst, dipolarophiles, and 4Å molecular sieves. The resulting mixture was allowed to stir for five minutes at -78 °C, then triethylamine (14 μL, 0.100 mmol) was added to initiate the cycloaddition reaction. The reaction mixture was allowed to stir for 4 h at -78 °C and was then filtered through a pad of silica (eluting with EtOAc). The crude mixture was the concentrated under reduced pressure, and the nmr yields of the products were determined with integration against 1,3,5-trimethoxybenzene.

Competition reactions of dipolarophiles under uncatalyzed conditions



In a nitrogen-filled dry-box, **1e** (73.5 mg, 0.200 mmol, 2 equiv), **1h** (78.6 mg, 0.200 mmol, 2 equiv), **2a** (35.4 mg, 0.100 mmol, 1 equiv), and 4Å MS (100 mg) were added to a 1-dram vial. The vial was sealed with a PTFE/silicone-lined septum cap and removed from the drybox. The mixture was suspended in CH_2Cl_2 (2 mL) and cooled to -78 °C in a dry ice/acetone bath. Triethylamine (14 μL, 0.100 mmol) was added to initiate the cycloaddition reaction. The reaction mixture was allowed to stir for 4 h at -78 °C and was then filtered through a pad of silica (eluting with EtOAc). The crude mixture was the concentrated under reduced pressure, and the nmr yields of the products were determined with integration against 1,3,5-trimethoxybenzene.

Competition reactions of dipoles under catalyzed conditions



1a

2a: Ar^1 = 4-Br-C_6H_4, Ar^2 = Ph
2b: Ar^3 = 4-Br-C_6H_4, Ar^4 = 4-CF_3-C_6H_4
3a: 95 : **3o:** 5 (a)

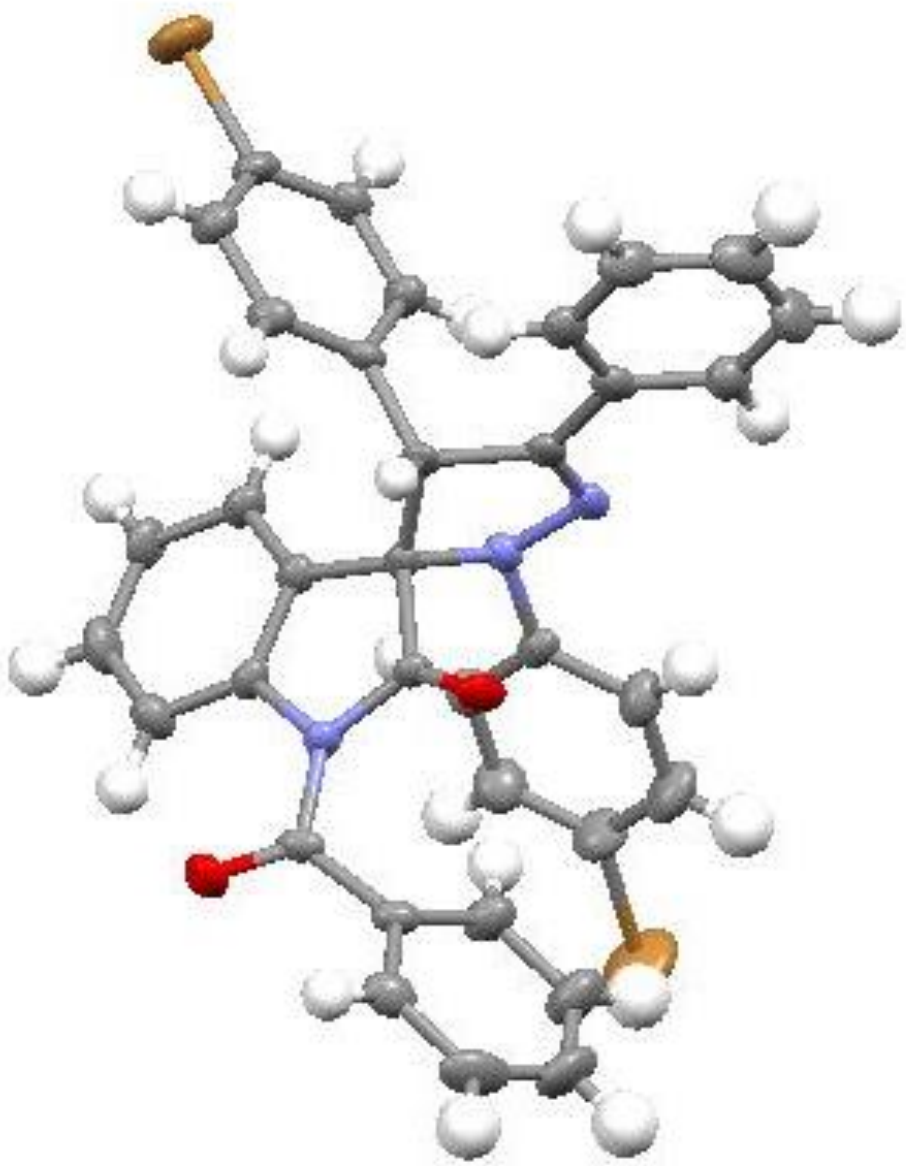
2a: Ar^1 = 4-Br-C_6H_4, Ar^2 = Ph
2g: Ar^3 = 4-CF_3-C_6H_4, Ar^4 = Ph
3a: 44 : **3t:** 56 (b)

In a nitrogen-filled dry-box, $Mg(NTf_2)_2$ (11.7 mg, 0.020 mmol, 0.2 equiv), **L2** (7.8 mg, 0.022 mol, 0.22 equiv), 4Å MS, and **1a** (32.5 mg, 0.100 mmol, 1 equiv) were added to a 1-dram vial. To each of two additional vials were added the appropriate hydrazonoyl halides **2** (each

0.200 mmol, 2 equiv). The three vials were sealed with PTFE/silicone-lined caps and removed from the dry-box. The mixture of $Mg(NTf_2)_2$, **L2**, 4Å MS, and **1a** was suspended in CH_2Cl_2 (1 mL), allowed to stir for 15 minutes at room temperature, and cooled to -78 °C in a dry ice/acetone bath. To each of the vials containing hydrazonoyl bromides **2** was added CH_2Cl_2 (0.5 mL each), and the solutions were added to the mixture of catalyst, dipolarophile, and the 4Å molecular sieves. The resulting mixture was allowed to stir at -78 °C for 4 hours and was then filtered through a pad of silica (eluting with EtOAc). The crude mixture was the concentrated under reduced pressure, and the ratio of products was determined by NMR spectroscopy of the crude reaction mixture. Note: In the case of the competition reaction between **2a** and **2b**, the resulting product mixture was subjected to debenzoylation of the oxindole nitrogen to allow for better resolution of diagnostic peaks in the NMR spectrum. See procedure for **Synthesis of S3b from 3o**.

Absolute stereochemistry and structure of 3g

Supplementary X-ray diffraction data and structure refinement for **3g** is contained in CCDC 958182. These data can be accessed free of charge from the Cambridge Crystallographic Data Center at www.ccdc.cam.ac.uk/data_request/cif.



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CHAPTER 4

PALLADIUM-CATALYZED CONJUGATE ADDITION OF ARYLBORONIC ACIDS TO 2-SUBSTITUTED CHROMONES IN AQUEOUS MEDIA

Modified from a paper submitted to *Tetrahedron Letters*[a]

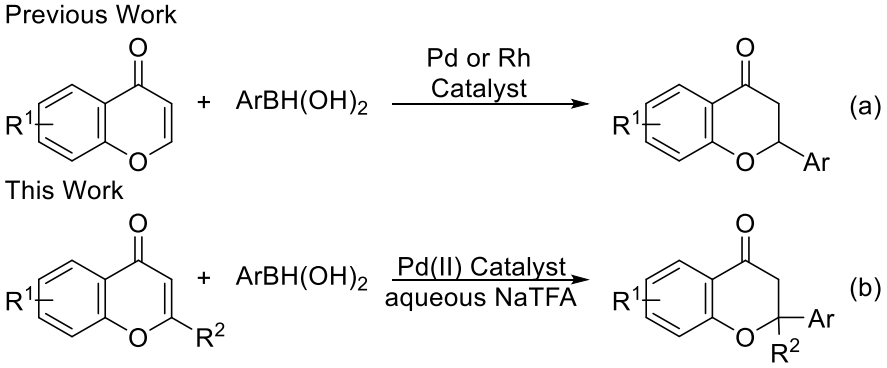
Anthony L. Gerten and Levi M. Stanley*

Abstract

Palladium-catalyzed conjugate additions of arylboronic acids to 2-alkylchromones are reported. The conjugate additions occur in aqueous media in the presence of a catalyst generated from $Pd(TFA)_2$ and 1,10-phenanthroline, and the flavanone derivatives containing a fully-substituted carbon center are formed in up to 90% yield.

Introduction

Flavanone-containing scaffolds are present in an array of natural products, and the biological activity associated with many of these compounds renders them attractive synthetic



Scheme 1. *Synthesis of flavanone derivatives by conjugate additions of arylboronic acids to chromones*

targets.[1] Conjugate additions of organometallic reagents to chromones have emerged as a powerful means to access these structures.[1a] In 2010, Huang and coworkers reported conjugate additions of arylboronic acids to chromones catalyzed by palladium complexes.[2] Since then,

numerous reports of conjugate additions of arylboronic acids to chromones catalyzed by palladium[3] and rhodium[4] complexes have been disclosed (Scheme 1a).

However, there are currently no reports of conjugate additions of arylboronic acids to 2-substituted chromones. In fact, a report by the Stoltz group demonstrated that 2-methylchromone was unreactive under their conditions as a conjugate addition acceptor in palladium-catalyzed conjugate additions of arylboronic acids.[3a]

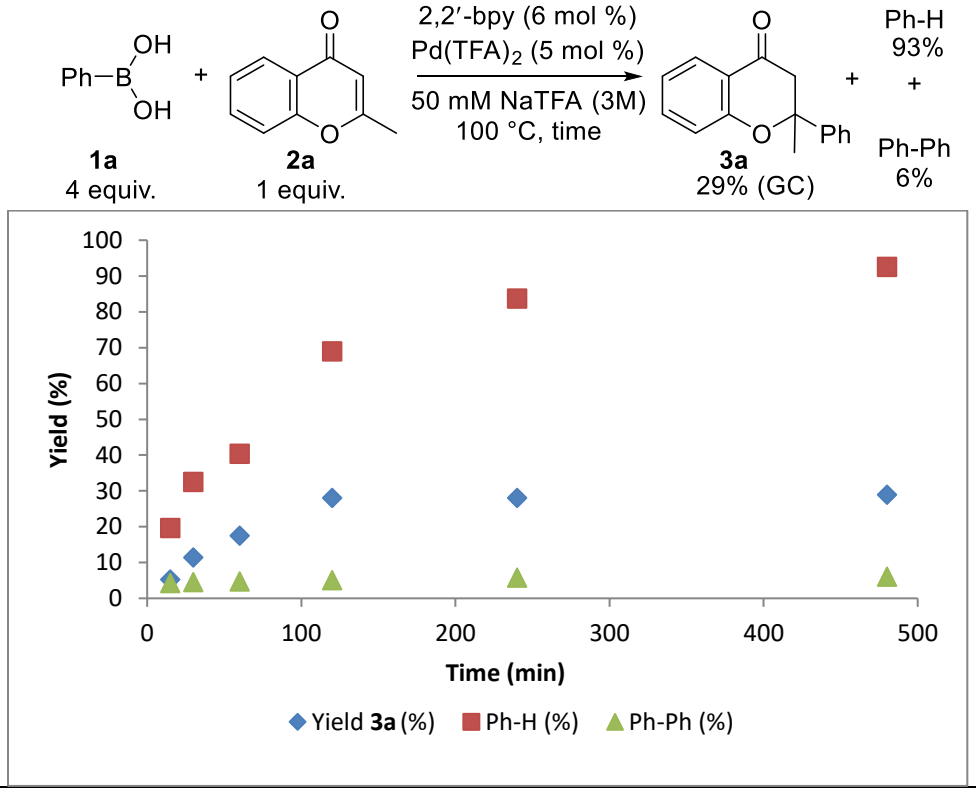
Recent work from our laboratory showed that conjugate additions of arylboronic acids to sterically demanding β-aryl cycloalkenones catalyzed by a palladium(II) complex of 2,2′-bipyridine (2,2′-bpy) occur in high yields when carried out in aqueous sodium trifluoroacetate (NaTFA).[5] This work built upon studies by Stoltz that demonstrate the presence of water in palladium-catalyzed conjugate additions of arylboronic acids to β-substituted cyclic enones is important to protonate the palladium enolate intermediate and facilitate catalyst turnover.[6] We sought to leverage the increased reactivity toward challenging enone substrates when palladium-catalyzed conjugate additions of arylboronic acids are carried out in aqueous media. To this end, palladium-catalyzed conjugate additions of arylboronic acids to 2-substituted chromones are disclosed herein (Scheme 1b).

Palladium-catalyzed conjugate addition of arylboronic acids to 2-substituted chromones in aqueous media: identification of reaction conditions

We began our studies by evaluating the model conjugate addition of phenylboronic acid **1a** to 2-methylchromone **2a** to form 2-methyl-2-phenylchroman-4-one **3a** as the desired product (Table 1). The reaction conditions and catalyst identified for conjugate additions of arylboronic acids to β-aryl cycloalkenones were initially evaluated in the current model reaction.[5] The addition of **1a** (4 equiv) to **2a** catalyzed by a complex prepared from 2,2′-bipyridine and

palladium trifluoroacetate ($Pd(TFA)_2$) occurs to form **3a** in low yield (29%) when the reaction is run at 100 °C in aqueous NaTFA. In addition to the desired product, we observed >90% protodeboronation of phenylboronic acid **1a** to form benzene and a small amount biphenyl from homocoupling of **1a**.

Table 1. *Reaction profile for conjugate addition of phenylboronic acid* **1a** *to 2-methylchromone* **2a**



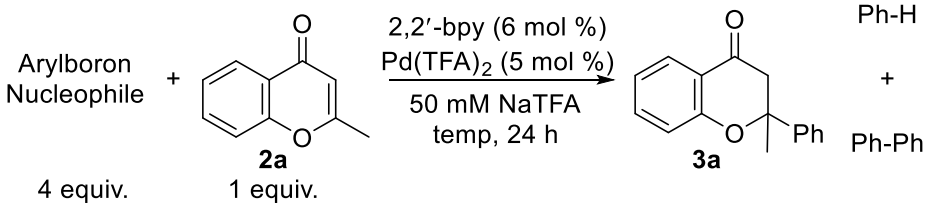
Entry	Time (min)	Yield 3a (%)	Ph-H (%)	Ph-Ph (%)
1	15	5	19	4
2	30	11	33	5
3	60	18	40	5
4	120	28	69	5
5	240	28	84	6
6	480	29	93	6

The low yield of conjugate addition product **3a** and the undesired protodeboronation and homocoupling pathways prompted us to follow the reaction over time. After two hours, we observed 28% yield of 3a with 69% protodeboronation (Table 1, entry 4). The yield of **3a** did

not increase after approximately two hours, while protodeboronation continued to occur. After 8 hours, the phenylboronic acid was completely consumed, and 93% protodeboronation was observed (Table 1, entry 6).

In our initial efforts to mitigate the undesired protodeboronation reaction and increase the yield of **3a**, we evaluated a variety of arylboron nucleophiles, reaction temperatures, and reaction concentrations, with results shown in Table 2.[7] Reduction of the temperature to 60 °C in the reaction of phenylboronic acid with **2a** in the presence of the palladium catalyst increased the yield slightly in comparison with the reaction conducted at 100 °C to 38%, with a decrease in protodeboronation to 70% (entry 2). The reaction of phenylboronic acid with **2a** at 100 °C and 1.5 M concentration based on **2a** resulted in 32% yield of **3a** and only 9% protodeboronation

Table 2. *Initial evaluation of reaction conditions for addition of arylboron nucleophiles to* **2a**



Entry	Conc. (M)	Arylboron Nucleophile	Temp (°C)	Yield 3a (%)[a]	Ph-H (%)[a]	Ph-Ph (%)[a]
1	3	$PhB(OH)_2$	100	29	93	6
2	3	$PhB(OH)_2$	60	38	70	7
3	1.5	$PhB(OH)_2$	100	32	9	2
4	0.5M	$PhB(OH)_2$	100	38	75	6
5	3	PhBPin	100	15[b]	ND	ND
6	3	PhB-MIDA	100	31	49	2
7[c]	3	$PhB(OH)_2$	100	<5	<5	1

[a] Yields determined by GC using tridecane as internal standard. [b] Yield determined by ^1H NMR spectroscopy with CH_2Br_2 as internal standard. [c] Under N_2 with deoxygenated 50 mM NaTFA.

(entry 3). Attempts to optimize further at 1.5 M concentration did not lead to higher yields, and the reason for the greatly decreased protodeboronation at 1.5 M concentration is not clear at this time. At 0.5 M concentration, protodeboronation increased to 75% (entry 4). The employment

of phenylBPin and PhB-MIDA in place of free phenylboronic acid did not lead to respectable yields of **3a** (entries 5 and 6). Notably, the reaction conducted under inert atmosphere in deoxygenated solvent led to complete inhibition of the reaction (entry 7) (*vide infra*).

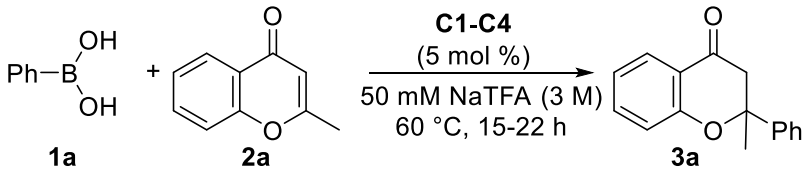
After our early efforts to mitigate protodeboronation did not lead to an acceptable solution, we next examined the issue of biphenyl formation in our reactions. The generally accepted mechanism for palladium-catalyzed conjugate additions of arylboronic acids to enones is a non-redox process involving Pd(II) intermediates.[6a] The observed homocoupling of phenylboronic acid led us to believe that this undesired side reaction was removing the requisite Pd(II) from the catalytic cycle by reductive elimination from a $PdAr_2$ species to form a Pd(0) species.[8] Greatly diminished yields of **3a** under rigorously oxygen-free conditions lent even greater evidence to the formation of an off-cycle Pd(0) species. The inclusion of oxygen is necessary to reoxidize Pd(0) species to Pd(II) species to ensure that the desired conjugate addition pathway remains operative.

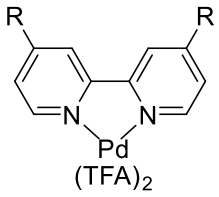
The observation that the yield of product **3a** does not increase after two hours led us to hypothesize that once the concentration of 2-methylchromone **2a** was low relative to the concentration of phenylboronic acid **1a**, the desired conjugate addition reaction ceases and protodeboronation becomes the dominant reaction pathway for phenylboronic acid **1a**. With this hypothesis in mind and further inspired by a report from Minaard,[9] we examined the impact of increasing the concentration of chromone **2a** relative to phenylboronic acid **1a** in an attempt to mitigate protodeboronation.

The results presented in Table 3, entries 1-3 demonstrate that the relative rate of protodeboration versus conjugate addition is highly dependent on the concentration of **2a**. The model reaction catalyzed by complex **C1**, prepared in situ from $Pd(TFA)_2$ and 2,2′-bpy, occurred

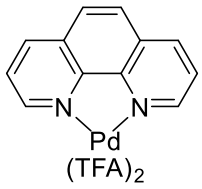
to form product **3a** in 38% yield when the reaction was run at 60 °C with a 1:4 ratio of **2a**:**1a** (entry 1). However, we still observed 70% protodeboronation under these reaction conditions. When the reaction was run with a 1:1 ratio of **2a**:**1a**, we observed 27% yield of product **3a**, 35% protodeboronation, and 21% biphenyl formation (entry 2). Encouraged by the lower relative rate of protodeboronation versus desired conjugate addition observed under these conditions, we ran the reaction with a 2:1 ratio of **2a**:**1a**. This reaction delivered product **3a** in 56% yield and decreased protodeboronation and biphenyl formation to 19% and 12%, respectively (entry 3).

Table 3. *Identification of reaction conditions to minimize protodeboronation*





C1: R = H
C2: R = OMe
C3: R = CF_3



C4

Entry	Catalyst	Ratio 2a:1a	Yield 3a (%)[a,b]	Ph-H (%)[a]	Ph-Ph (%)[a]
1[c]	**C1**	1:4	38	70	7
2	**C1**	1:1	27	35	21
3	**C1**	2:1	56	19	12
4	**C2**	2:1	49	30	12
5	**C3**	2:1	53	13	15
6	**C4**	2:1	68	16	13
7[d]	**C4**	2:1	65	22	12
8[e]	**C4**	2:1	49	25	11
9[f]	**C4**	2:1	72 (76)	14	10
10[f]	**C4**	3:1	84 (87)	6	6

[a] Yields determined by GC using tridecane as internal standard. [b] Isolated yields in parentheses. [c] Catalyst **C1** generated in situ from $Pd(TFA)_2$ and 2,2′-bpy. [d] Reaction run at 80 °C. [e] Reaction run at 100 °C. [f] 4.5 M in 50 mM aq. NaTFA.

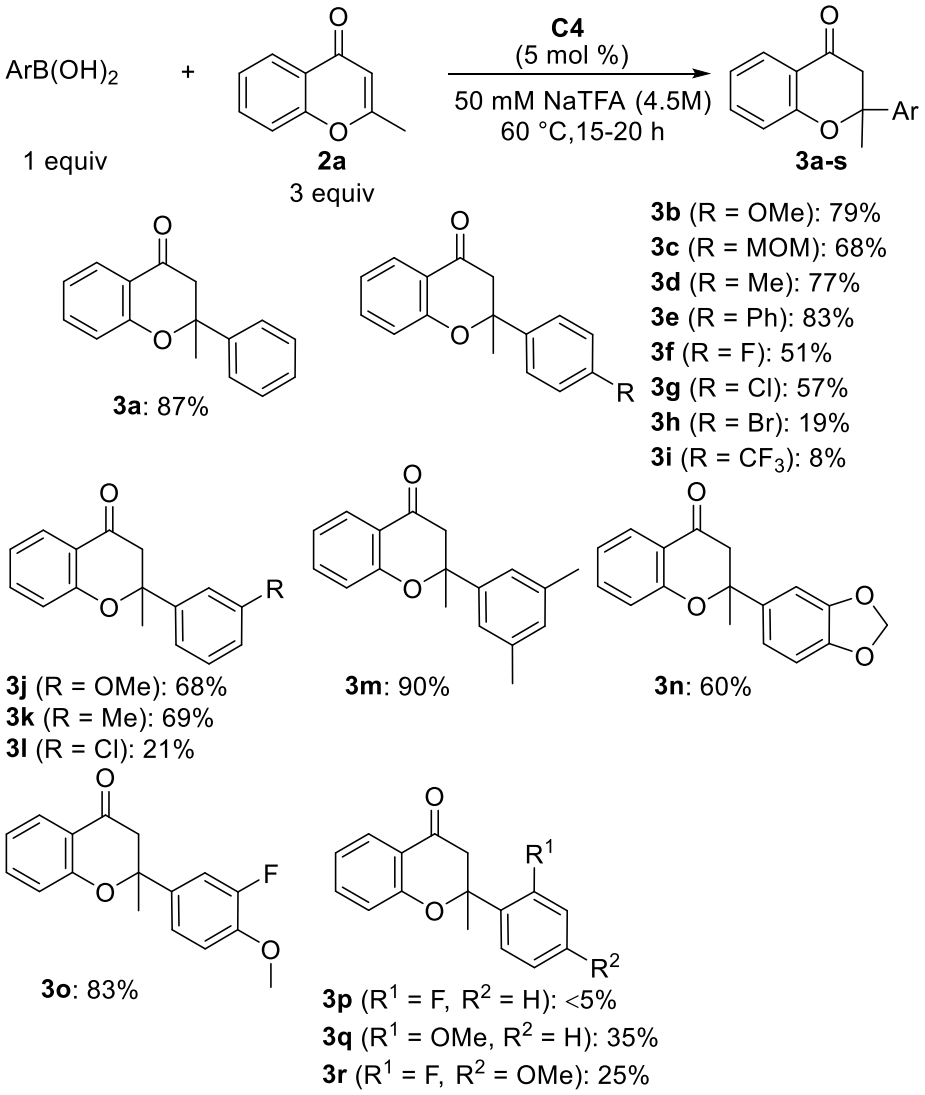
To further improve upon our reaction conditions, we examined the impact of electronically distinct bipyridine ligands on the activity of the palladium catalyst (entries 3-5). A more electron-rich palladium center proved detrimental. The reaction catalyzed by complex **C2** (R = OMe) formed **3a** in slightly lower yield with 30% protodeboronation (entry 4). The outcome of the reaction conducted in the presence of the electron-poor catalyst complex **C3** (R = CF_3) was essentially unchanged from that observed with complex **C1** (compare entry 5 with entry 3).

Notably, the complex derived from 1,10-phenanthroline (**C4**) led to higher yield of product **3a** relative to the palladium complexes of bipyridine ligands. Complex **C4** catalyzed the addition of **1a** to **2a** to form **3a** in 68% yield with 16% protodeboronation and 13% biphenyl formation (entry 6). We hypothesize that the palladium complex of 1,10-phenanthroline eliminates the potential for rollover C-H activation of 2,2′-bipyridine ligands that may remove palladium from the catalytic cycle.[10]

Encouraged by the results of reactions catalyzed by complex **C4**, we sought to identify reaction conditions to further increase the yield of **3a** and limit protodeboronation. Increasing the temperature of the reaction to 80 or 100 °C led to a decrease in the yield of **3a** and an increase in protodeboronation (entries 7 and 8). Increasing the concentration of the reaction to 4.5 M based on phenylboronic acid led to the formation of **3a** in 76% isolated yield (entry 9). Protodeboronation and biphenyl formation could be further suppressed by conducting the reaction with a 3:1 ratio of **2a**:**1a** (entry 10), and 2-methyl-2-phenylchroman-4-one **3a** was isolated in 87% yield.

Palladium-catalyzed conjugate addition of arylboronic acids to 2-substituted chromones in aqueous media: scope of arylboronic acids

With a practical catalyst system identified, we proceeded to evaluate conjugate additions of a variety of arylboronic acids to 2-methylchromone **2a**. These results are summarized in



Scheme 2. *Palladium-catalyzed conjugate additions of arylboronic acids to* **2a**

Additions of arylboronic acids containing electron-donating and electron-neutral groups at the *para*-position to **2a** formed the corresponding 2-methyl-2-arylchroman-4-ones **3b**-**3e** in

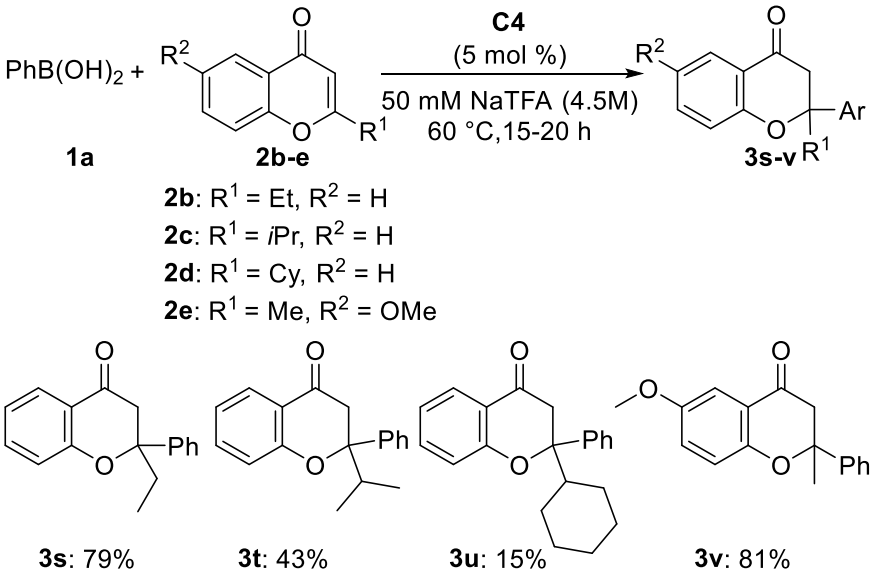
68-83% yield. Moderately electron-deficient *p*-fluorophenyl and *p*-chlorophenylboronic acids reacted with **2a** to generate 2-methyl-2-arylchroman-4-ones **3f** and **3g** in 51% and 57% yield, respectively. However, the additions of *p*-bromophenylboronic acid and electron-poor *p*-trifluoromethylphenylboronic acid to **2a** formed **3h** and **3i** in low yields. Additions of *m*-methoxy- and *m*-methylphenylboronic acid generated **3j** and **3k** in good yields (68-69%), while a *m*-halogenated arylboronic acid led to low yields of the corresponding 2-methyl-2-arylchroman-4-one **3l**. Additions of electron-rich 3,4- and 3,5-disbustituted arylboronic acids to **2a** formed 2-methyl-2-arylchroman-4-ones **3m**-**3o** in good-to-excellent yields (60-90%).

Notably, *o*-substituted arylboronic acids displayed decreased reactivity in conjugate additions to **2a**. The addition of *o*-fluorophenylboronic acid to **2a** formed **3p** in <5% yield. *o*-Methoxyphenylboronic acid displayed increased reactivity toward the desired conjugate addition reaction relative to *o*-fluorophenylboronic acid and led to the formation of **3q** in 35% yield. The addition of 2-fluoro-4-methoxyphenylboronic acid provides further evidence to the impact of *o*-substitution on the arylboronic acid. This reaction generated the corresponding 2-methyl-2-arylchromanone **3r** in 25% yield. In contrast, the addition of an electronically similar arylboronic acid, 3-fluoro-4-methoxyphenylboronic acid, led to the formation of **3o** in high yield.

Palladium-catalyzed conjugate addition of arylboronic acids to 2-substituted chromones in aqueous media: scope of enones

To further expand the scope of this reaction, we evaluated conjugate additions of phenylboronic acid to a variety of 2-alkylchromones (Scheme 3). The reaction of 2-ethylchromone **2b** with phenylboronic acid formed chromanone **3s** in 79% yield. Increasing the steric volume of the substituent at the 2-position of the chromone resulted in decreased acceptor reactivity toward conjugate addition: the reaction of 2-isopropylchromone **2c** occurred to give

chromanone **3t** in 43% yield, and the reaction of 2-cyclohexylchromone **2d** formed chromanone **3u** in 15% yield. 2-Phenylchromone (flavone) did not react under our reaction conditions. This trend of decreased acceptor reactivity with increasing steric volume at the 2-position of the chromone is consistent with a slower rate of turnover-limiting insertion of the enone into the palladium-arene bond.[6a] Substitution on the 2-alkylchromone backbone is also tolerated. The reaction of 6-methoxy-2-methylchromone with phenylboronic acid formed chromanone **3v** in 81% yield.



Scheme 3. *Palladium-catalyzed conjugate additions of $PhB(OH)_2$ to chromones* **2b-e**

Palladium-catalyzed conjugate addition of arylboronic acids to 2-substituted chromones in aqueous media: conclusion

In conclusion, we developed the first conjugate additions of arylboronic acids to 2-substituted chromones. Additions of arylboronic acids to these challenging substrates are enabled by the use of a readily accessible palladium(II) catalyst in aqueous media. This catalyst system overcomes the low reactivity of 2-alkylchromones and reduces undesired protodeboronation and

homocoupling pathways. The scope of these reactions encompasses a variety of arylboronic acids and 2-alkylchromones and enables the formation of an array of 2-alkyl-2-arylchromanone products. Studies are ongoing in our laboratory to develop an enantioselective variant of this reaction and to expand these conjugate addition reactions to additional classes of acceptors.

Experimental Details

General experimental details

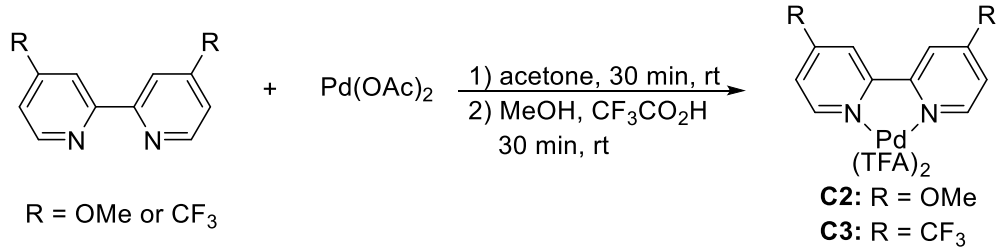
All reactions were carried out on the benchtop under an atmosphere of air unless otherwise stated. All glassware for moisture sensitive reactions was dried at 140 °C in an oven. THF, diethyl ether, toluene and dimethylformamide were degassed by purging with argon for 45 minutes and dried with a solvent purification system by passing through a one-meter column of activated alumina. Flash column chromatography was performed on Fisher brand silica gel 60 (230-400 mesh) or Silacycle Siala-P silica gel or on a Teledyne Isco CombiFlash Rf automated chromatography system with RediSep Rf Gold normal-phase silica columns. Products of reactions were visualized on TLC plates under UV light.

HRMS (ESI) analysis was performed at the Iowa State University Chemical Instrumentation Facility on an Agilent 6540 QTOF spectrometer. Fourier transform infrared (FTIR) spectra were recorded within the 4000−400 cm^{-1} range using a Bruker VERTEX 80 IR spectrometer. Samples were diluted with KBr and pellets prepared for analysis in transmission mode. NMR spectra were acquired on Varian MR-400 and Bruker Avance III 600 spectrometers at the Iowa State University Chemical Instrumentation Facility. ^{1}H and ^{13}C NMR chemical shifts are reported in ppm relative to residual $CHCl_3$ in $CDCl_3$ (7.26 ppm for ^{1}H and 77.23 ppm for ^{13}C) or to residual DMSO in DMSO-d_6 (2.50 for ^{1}H). ^{19}F NMR shifts are reported based on indirect reference to $CDCl_3$ or DMSO-d_6.[11]

Materials

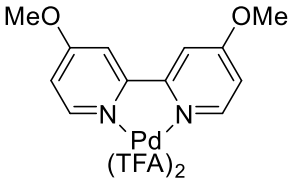
CH_2Br_2 was purchased from Acros and used without further purification. Phenylboronic acid, 4-methoxyphenylboronic acid, 4-fluorophenylboronic acid, 3-methoxyphenylboronic acid, 3-chlorophenylboronic acid, 2,2´-bipyridine and 1,10-phenanthroline were purchased from AK Scientific and used without further purification. 3-methylphenylboronic acid was purchased from Arkpharm and used without further purification. 4-methylphenylboronic acid and 3,5-dimethylphenylboronic acid were purchased from Combi-Blocks Inc. and used without further purification. Acetic acid and trifluoroacetic acid were purchased from Fisher Scientific and used without further purification. 4-phenylboronic acid, 4-methoxymethylphenylboronic acid, 4-bromophenylboronic acid, 4-trifluoromethylphenylboronic acid, 3-fluoro-4-methoxyphenylboronic acid, 2-fluoro-4-methoxyphenylboronic acid, and 3,4-methylenedioxyphenylboronic acid were purchased from Frontier Scientific and used without further purification. Palladium acetate was purchased from Johnson Matthey and used without further purification. 4-Chlorophenylboronic acid, 2-methoxyphenylboronic acid, tridecane phenyl-BPin, and palladium trifluoroacetate were purchased from Sigma-Aldrich and used without purification. 2-methylchromone **2a**, 2-ethylchromone **2b**, 2-isopropylchromone **2c**, 2-cyclohexylchromone **2d**, and 6-methoxy-2-methylchromone **2e** were synthesized according to previously reported procedures.[12] 4,4´-Dimethoxy-2,2´-bipyridine and 4,4´-di(trifluoromethyl)-2,2´-bipyridine were synthesized according to a known procedure.[13] The spectra obtained matched previously reported spectra.[14] Palladium trifluoroacetate complexes **C1**-**C4** were synthesized by previously reported methods,[15] and the characterization data for **C2** and **C3** are reported below. Phenyl-MIDA-boronate was synthesized by a known procedure[16] and matched previously reported spectral data.[17]

Synthesis and characterization data for complexes C2 and C3



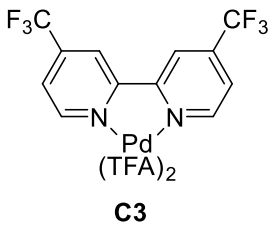
R = OMe or CF_3

C2: R = OMe
C3: R = CF_3



C2

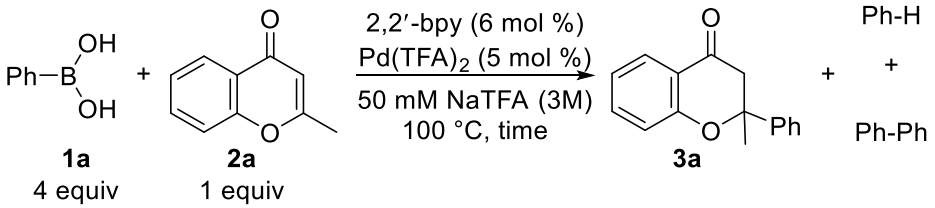
(4,4´-methoxy-2,2´-bipyridyl)palladium(II)bis(trifluoroacetate) (C2): Complex **C2** was synthesized by a modification to a reported procedure:[15a] A roundbottom flask was charged with $Pd(OAc)_2$ (187 mg, 0.833 mmol, 1.00 equiv). Acetone (18 ml) was added to the flask, and the mixture was stirred for 30 minutes at room temperature. The solution was then filtered through fine filter paper. To the filtrate was added acetic acid (9.35 µL), followed by 4,4´-methoxy-2,2´-bipyridine (216 mg, 1.00 mmol, 1.2 equiv). The reaction was then stirred for 30 minutes at room temperature. The precipitate was collected by filtration and dried under high vacuum. The precipitate was then redissolved in methanol (26 mL) and trifluoroacetic acid (3.19 mL, 18.7 mmol, 25.0 equiv) was added. The reaction mixture was stirred for 30 minutes at room temperature and the resulting precipitate was filtered and dried under high vacuum to yield **C2** (117 mg, 0.260 mmol, 26%) as a white powder. **^{1}H NMR** (DMSO-d_6, 600 MHz) δ 4.06 (s, 6H), 7.26-7.50 (m, 2H), 7.54-8.05 (m, 2H), 8.18-8.30 (m, 2H). **^{19}F NMR** (DMSO-d_6, 565 MHz) δ -73.53. IR: λ_{max} 1233, 1701. Anal. Calc. for: C, 35.07; H, 2.21; N, 5.11. Found: C, 34.75; H, 2.01; N, 5.09.

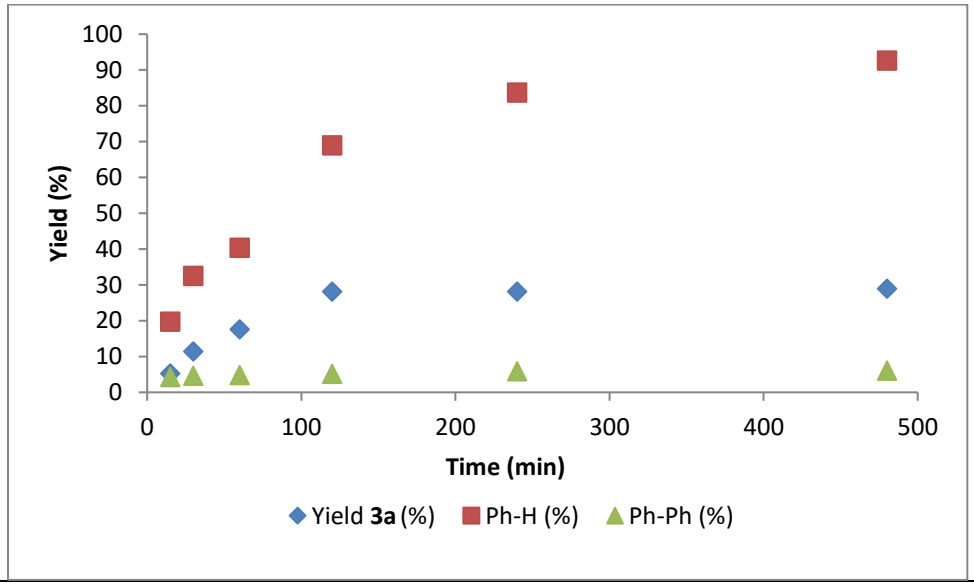


C3

(4,4´-trifluoromethyl-2,2´-bipyridyl)palladium(II)bis(trifluoroacetate (C3): Complex **C3** was synthesized by a modification to a reported procedure:[15a] A roundbottom flask was charged with $Pd(OAc)_2$ (187 mg, 0.833 mmol, 1.00 equiv). Acetone (18 ml) was added to the flask, and the mixture was stirred for 30 minutes at room temperature. The solution was then filtered through fine filter paper. To the filtrate was added acetic acid (9.35 µL), followed by 4,4´-trifluoromethyl-2,2´-bipyridine (292 mg, 1.00 mmol, 1.20 equiv). The reaction was then stirred for 30 minutes at room temperature. The precipitate was collected by filtration and dried under high vacuum. The precipitate was then redissolved in methanol (26 mL) and trifluoroacetic acid (3.19 mL, 18.7 mmol, 25.0 equiv) was added. The reaction mixture was stirred for 30 minutes at room temperature and the resulting precipitate was filtered and dried under high vacuum to yield **C3** (372 mg, 0.720 mmol, 72%) as a yellow powder. **^{1}H NMR** (DMSO-d_6, 600 MHz) δ 8.20-8.54 (m, 4H), 9.28-9.39 (m, 2H). **^{19}F NMR** (DMSO-d_6, 565 MHz) δ -73.42, -63.51. IR: λ_{max} 1187, 1727. Anal. Calc. for: C, 30.77; H, 0.97; N, 4.49. Found: C, 30.46; H, 0.78; N, 4.65.

Table S1. Reaction profile for conjugate addition of phenylboronic acid 1a to 2-methylchromone 2a



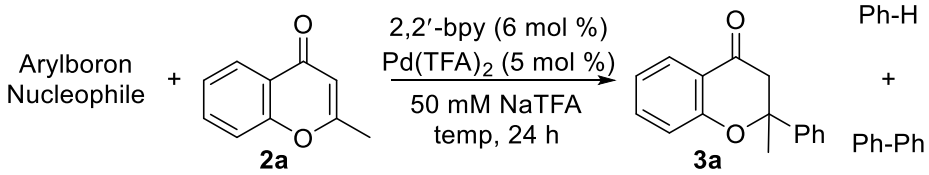


Entry	Time (min)	Yield 3a (%)	Ph-H (%)	Ph-Ph (%)
1	15	5	19	4
2	30	11	33	5
3	60	18	40	5
4	120	28	69	5
5	240	28	84	6
6	480	29	93	6

To a 1-dram vial were added $Pd(TFA)_2$ (8.3 mg, 0.025 mmol, 0.050 equiv), 2,2´-bipyridine (4.7 mg, 0.030 mmol, 0.060 equiv), 2-methylchromone **2a** (80.1 mg, 0.500 mmol, 1.00 equiv), and phenylboronic acid **1a** (243.9 mg, 2.00 mmol, 4.00 equiv). Sodium trifluoroacetate solution (167 μL of a 50 mM solution in water) was added to the 1-dram vial. The vial was sealed with a PTFE-silicone-lined septum cap. The reaction mixture was stirred for the indicated time at 100 °C and then allowed to cool to room temperature. A solution of tridecane (1 ml, 0.1M in EtOAC) was then added to the vial, followed by enough ethyl acetate to

fill the rest of the vial. Once all solid material was dissolved, then solution was then transferred to a 2 mL vial and the mixture was then analyzed by GC-FID to determine the yields of **3a**, benzene, and biphenyl.

Table S2. Initial evaluation of reaction conditions for addition of arylboron nucleophiles to 2a

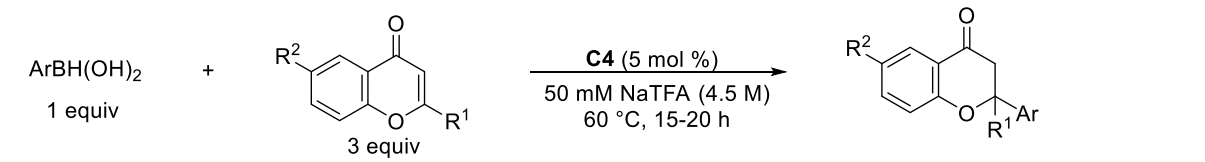


Entry	Conc. (M)	Arylboron Nucleophile	Temp (°C)	Yield 3a (%)[a]	Ph-H (%)[a]	Ph-Ph (%)[a]
1	3	$PhB(OH)_2$	100	29	93	6
2	3	$PhB(OH)_2$	60	38	70	7
3	1.5	$PhB(OH)_2$	100	32	9	2
4	0.5M	$PhB(OH)_2$	100	38	75	6
5	3	PhBPin	100	15[b]	ND	ND
6	3	PhB-MIDA	100	31	49	2
7[c]	3	$PhB(OH)_2$	100	<5	<5	1

[a] Yields determined by GC using tridecane as internal standard. [b] Yield determined by ^1H NMR spectroscopy with CH_2Br_2 as internal standard. [c] Under N_2 with deoxygenated 50 mM NaTFA.

To a 1-dram vial were added $Pd(TFA)_2$ (8.3 mg, 0.025 mmol, 0.050 equiv), 2,2´-bipyridine (4.7 mg, 0.030 mmol, 0.060 equiv), 2-methylchromone **2a** (80.1 mg, 0.500 mmol, 1.00 equiv), and the appropriate arylboron nucleophile (2.00 mmol, 4.00 equiv). Sodium trifluoroacetate as a 50 mM solution in water was added to the vial to the indicated concentration. The vial was sealed with a PTFE-silicone-lined septum cap. The reaction mixture was stirred for the indicated time at 100°C and then allowed to cool to room temperature. A solution of tridecane (1 ml, 0.1M in EtOAC) was then added to the vial, followed by enough ethyl acetate to fill the rest of the vial. Once all solid material was dissolved, the solution was transferred to a 2 mL vial, and the mixture was analyzed by GC-FID to determine the yields of **3a**, benzene, and biphenyl.

General procedure for synthesis of 2-alkyl-2-arylchromones 3a-3v



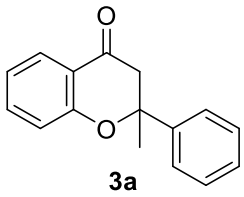
1a: Ar = C_6H_5
1b: Ar = 4-OMe-C_6H_4
1c: Ar = 4-OCH_2OCH_3-C_6H_4
1d: Ar = 4-Me-C_6H_4
1e: Ar = 4-Ph-C_6H_4
1f: Ar = 4-F-C_6H_4
1g: Ar = 4-Cl-C_6H_4
1h: Ar = 4-Br-C_6H_4
1i: Ar = 4-CF_3-C_6H_4
1j: Ar = 3-OMe-C_6H_4
1k: Ar = 3-Me-C_6H_4
1l: Ar = 3-Cl-C_6H_4
1m: Ar = 3,5-Me_2-C_6H_4
1n: Ar = 3,4-OCH_2O-C_6H_3
1o: Ar = 3-F,4-OMe-C_6H_3
1p: Ar = 2-F-C_6H_4
1q: Ar = 2-OMe-C_6H_4
1r: Ar = 2-F, 4-OMe-C_6H_4

2a: R^1 = Me, R^2 = H
2b: R^1 = Et, R^2 = H
2c: R^1 = *i*Pr, R^2 = H
2d: R^1 = Cy, R^2 = H
2e: R^1 = Me, R^2 = OMe

3a: Ar = C_6H_5, R^1 = Me, R^2 = H
3b: Ar = 4-OMe-C_6H_4, R^1 = Me, R^2 = H
3c: Ar = 4-OCH_2OCH_3-C_6H_4, R^1 = Me, R^2 = H
3d: Ar = 4-Me-C_6H_4, R^1 = Me, R^2 = H
3e: Ar = 4-Ph-C_6H_4, R^1 = Me, R^2 = H
3f: Ar = 4-F-C_6H_4, R^1 = Me, R^2 = H
3g: Ar = 4-Cl-C_6H_4, R^1 = Me, R^2 = H
3h: Ar = 4-Br-C_6H_4, R^1 = Me, R^2 = H
3i: Ar = 4-CF_3-C_6H_4, R^1 = Me, R^2 = H
3j: Ar = 3-OMe-C_6H_4, R^1 = Me, R^2 = H
3k: Ar = 3-Me-C_6H_4, R^1 = Me, R^2 = H
3l: Ar = 3-Cl-C_6H_4, R^1 = Me, R^2 = H
3m: Ar = 3,5-Me_2-C_6H_4, R^1 = Me, R^2 = H
3n: Ar = 3,4-OCH_2O-C_6H_3, R^1 = Me, R^2 = H
3o: Ar = 3-F,4-OMe-C_6H_3, R^1 = Me, R^2 = H
3p: Ar = 2-F-C_6H_4, R^1 = Me, R^2 = H
3q: Ar = 2-OMe-C_6H_4, R^1 = Me, R^2 = H
3r: Ar = 2-F, 4-OMe-C_6H_4, R^1 = Me, R^2 = H
3s: Ar = C_6H_5, R^1 = Et, R^2 = H
3t: Ar = C_6H_5, R^1 = *i*Pr, R^2 = H
3u: Ar = C_6H_5, R^1 = Cy, R^2 = H
3v: Ar = C_6H_5, R^1 = Me, R^2 = OMe

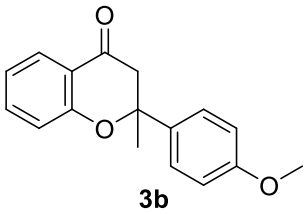
Catalyst complex **C4** (6.4 mg, 0.013 mmol, 0.050 equiv), the appropriate arylboronic acid (**1a-1r**) (0.250 mmol, 1.00 equiv), and the appropriate 2-alkylsubstituted chromone (**2a-2e**) (0.750 mmol, 3.00 equiv) were added to a 1-dram vial. Sodium trifluoroacetate solution (56 μL, 50 mM solution in water) was added to the vial. The vial was sealed with a PTFE-silicone-lined septum cap. The reaction mixture was stirred overnight and monitored by TLC. Once the reaction was judged to be complete, the reaction mixture was diluted with ethyl acetate and filtered through a pad of silica (eluting with EtOAc). The reaction mixture was then concentrated and purified by flash column silica gel chromatography (hexanes:EtOAc) to yield 2-alkyl-2-arylchromones **3a-3v**.

Characterization data for 2-alkyl-2-arylchromanones 3a-3v



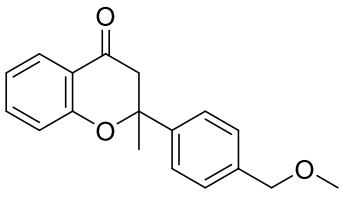
3a

2-methyl-2-phenylchroman-4-one (3a): Prepared according to the general procedure from phenylboronic acid **1a** (30.5 mg, 0.250 mmol) and 2-methylchromone **2a** (120 mg, 0.750 mmol). The crude product was purified by flash column chromatography (100:0 to 80:20 hexanes:EtOAc) to yield **3a** (51.8 mg, 0.218 mmol, 87%) as a yellow powder. The characterization data matched those previously reported in the literature.[18]



3b

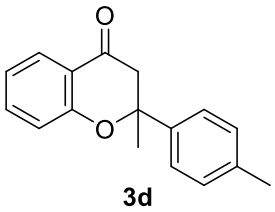
2-(4-methoxyphenyl)-2-methylchroman-4-one (3b): Prepared according to the general procedure from 4-methoxyphenylboronic acid **1b** (38.0 mg, 0.250 mmol) and 2-methylchromone **2a** (120 mg, 0.750 mmol). The crude product was purified by flash column chromatography (100:0 to 70:30 hexanes:EtOAc) to yield **3b** (47.0 mg, 0.198 mmol, 79%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.74 (s, 3H), 3.06 (d, *J* = 16.5 Hz, 1H), 3.29 (d, *J* = 16.5 Hz, 1H), 3.74 (s, 3H), 6.81 (d, *J* = 8.9 Hz, 2H), 6.92 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.03 (dd, *J* = 8.3, 0.5 Hz, 1H), 7.33 (d, *J* = 8.9 Hz, 2H), 7.45 (ddd, *J* = 8.3, 7.2, 1.6 Hz, 1H), 7.76 (dd, *J* = 7.8, 1.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 30.4, 48.2, 55.4, 82.5, 114.1, 118.5, 121.2, 121.3, 126.7, 126.8, 135.0, 136.3, 159.1, 160.2, 192.1. **HRMS** (ESI) calcd. for $C_{17}H_{17}O_3$+ [M+H]+ 269.1172, found 269.1169.



3c

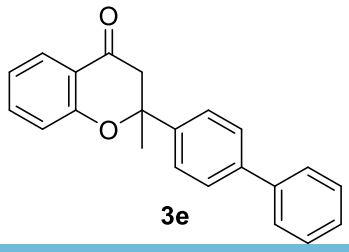
2-(4-(methoxymethyl)phenyl)-2-methylchroman-4-one (3c): Prepared according to the general procedure from 4-methoxymethylphenylboronic acid **1c** (41.5 mg, 0.250 mmol) and 2-

methylchromone **2a** (120 mg, 0.750 mmol). The crude product was purified by flash column chromatography (100:0 to 80:20 hexanes:EtOAc) to yield **3c** (48.0 mg, 0.170 mmol, 68%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.75 (s, 3H), 3.09 (d, *J* = 16.5 Hz, 1H), 3.31 (d, *J* = 16.5 Hz, 1H), 3.36 (s, 3H), 4.38 (s, 2H), 6.92 (dd, *J* = 7.7, 7.4 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.46 (dd, *J* = 8.3, 7.4 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 30.2, 48.2, 58.5, 74.4, 82.6, 118.5, 121.2, 121.3, 125.5, 126.8, 128.1, 136.4, 137.9, 142.6, 160.2, 191.8. **HRMS** (ESI) calcd. for $C_{18}H_{19}O_3$+ [M+H]+ 283.1329, found 283.1325.



3d

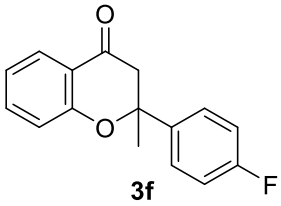
2-methyl-2-(p-tolyl)chroman-4-one (3d): Prepared according to the general procedure from 4-methylphenylboronic acid **1d** (34.0 mg, 0.250 mmol) and 2-methylchromone **2a** (120 mg, 0.750 mmol). The crude product was purified by flash column chromatography (100:0 to 80:20 hexanes:EtOAc) to yield **3d** (48.5 mg, 0.193 mmol, 77%) as a white powder. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.75 (s, 3H), 2.28 (s, 3H), 3.08 (d, *J* = 16.5 Hz, 1H), 3.31 (d, *J* = 16.5 Hz, 1H), 6.92 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.05 (dd, *J* = 8.3, 0.6 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.46 (ddd, *J* = 8.3, 7.2, 1.7 Hz, 1H), 7.76 (d, *J* = 7.8, 1.7 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 21.2, 30.3, 48.2, 82.6, 118.5, 121.2, 121.3, 125.4, 126.8, 129.5, 136.3, 137.6, 140.1, 160.2, 192.0. **HRMS** (ESI) calcd. for $C_{17}H_{17}O_2$+ [M+H]+ 253.1223, found 253.1222.



3e

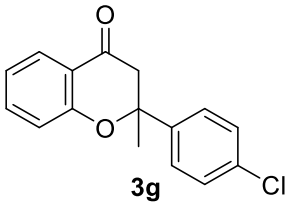
2-([1,1´-biphenyl]-4-yl)-2-methylchroman-4-one (3e): Prepared according to the general procedure from 4-biphenylboronic acid **1e** (49.5 mg, 0.250 mmol) and 2-methylchromone **2a** (120 mg, 0.750

mmol). The crude product was purified by flash column chromatography (100:0 to 80:20 hexanes:EtOAc) to yield **3e** (65.0 mg, 0.208 mmol, 83%) as a white powder. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.81 (s, 3H), 3.13 (d, *J* = 16.5 Hz, 1H), 3.36 (d, *J* = 16.5 Hz, 1H), 6.96 (dd, *J* = 7.7, 7.2 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.41 (appt, *J* = 7.6 Hz, 2H), 7.46-7.56 (m, 7H), 7.80 (d, *J* = 7.7 Hz, 1H). **^{13}C NMR (**$CDCl_3$, 151 MHz) δ 30.1, 48.3, 82.6, 118.5, 121.27, 121.28, 125.9, 126.8, 127.2, 127.5, 127.6, 128.9, 136.4, 140.5, 140.7, 142.1, 160.2, 191.9. **HRMS** (ESI) calcd. for $C_{22}H_{19}O_2$+ [M+H]+ 315.1380, found 315.1374.



3f

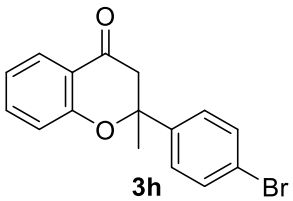
2-(4-fluorophenyl)-2-methylchroman-4-one (3f): Prepared according to the general procedure from 4-fluorophenylboronic acid **1f** (35.0 mg, 0.250 mmol) and 2-methylchromone **2a** (120 mg, 0.750 mmol). The crude product was purified by flash column chromatography (100:0 to 80:20 hexanes:EtOAc) to yield **3f** (33.0 mg, 0.128 mmol, 51%) as a white powder. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.74 (s, 3H), 3.09 (d, *J* = 16.5 Hz, 1H), 3.27 (d, *J* = 16.5 Hz, 1H), 6.92-7.00 (m, 3H), 7.05 (d, *J* = 8.3 Hz, 1H), 7.35-7.42 (m, 2H), 7.47 (dd, *J* = 8.3, 7.2 Hz, 1H), 7.76 (d, *J* = 7.7 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 30.3, 48.3, 82.3, 115.7 (d, *J* = 21.5 Hz), 118.5, 121.2, 121.4, 126.8, 127.3 (d, *J* = 8.2 Hz), 136.5, 139.0 (d, *J* = 3.1 Hz) 160.0, 162.3 (d, *J* = 246.9 Hz), 191.7. **^{19}F NMR** ($CDCl_3$, 565 MHz) δ -114.61. **HRMS** (ESI) calcd. for $C_{16}H_{14}FO_2$+ [M+H]+ 257.0972, found 257.0971.



3g

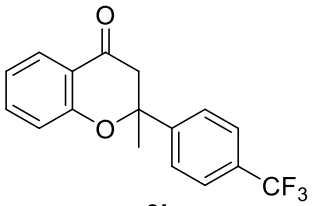
2-(4-chlorophenyl)-2-methylchroman-4-one (3g): Prepared according to the general procedure from 4-chlorophenylboronic acid **1g** (39.1 mg, 0.250 mmol) and 2-methylchromone **2a** (120 mg, 0.750 mmol). The crude product was purified by flash column chromatography (100:0 to 80:20 hexanes:EtOAc) to

yield **3g** (38.5 mg, 0.143 mmol, 57%) as a white powder. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.74 (s, 3H), 3.08 (d, *J* = 16.5 Hz, 1H), 3.26 (d, *J* = 16.5 Hz, 1H), 6.95 (dd, *J* = 7.8, 7.4 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.47 (dd, *J* = 8.3, 7.4 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 30.2, 48.1, 82.3, 118.5, 121.2, 121.5, 126.85, 126.92, 129.0, 133.8, 136.5, 141.8, 159.9, 191.5. **HRMS** (ESI) calcd. for $C_{16}H_{14}ClO_2$+ [M+H]+ 273.0677, found 273.0675.



3h

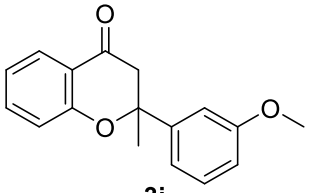
2-(4-bromophenyl)-2-methylchroman-4-one (3h): Prepared according to the general procedure from 4-bromophenylboronic acid **1h** (50.2 mg, 0.250 mmol) and 2-methylchromone **2a** (120 mg, 0.750 mmol). The crude product was purified by flash column chromatography (100:0 to 80:20 hexanes:EtOAc) to yield **3h** (15.0 mg, 0.0480 mmol, 19%) as a white powder. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.74 (s, 3H), 3.08 (d, *J* = 16.5 Hz, 1H), 3.26 (d, *J* = 16.5 Hz, 1H), 6.95 (dd, *J* = 7.8, 7.1 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.48 (ddd, *J* = 8.3, 7.1, 1.0 Hz, 1H), 7.76 (dd, *J* = 7.8, 1.0 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 30.1, 48.1, 82.3, 118.5, 121.2, 121.5, 122.0, 126.9, 127.3, 132.0, 136.5, 142.3, 160.0, 191.5. **HRMS** (ESI) calcd. for $C_{16}H_{14}BrO_2$+ [M+H]+ 317.0172, found 317.0163.



3i

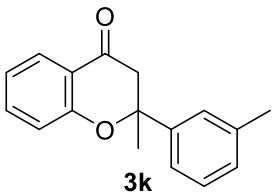
2-methyl-2-(4-(trifluoromethyl)phenyl)chroman-4-one (3i): Prepared according to the general procedure from 4-(trifluoromethyl)phenylboronic acid **1i** (47.5 mg, 0.250 mmol) and 2-methylchromone **2a** (120 mg, 0.750 mmol). The crude product was purified by flash column chromatography (100:0 to 80:20 h2exanes:EtOAc) to yield **3i** (6.1 mg,

0.020 mmol, 8%) as a yellow powder. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.77 (s, 3H), 3.13 (d, *J* = 16.5 Hz, 1H), 3.30 (d, *J* = 16.5 Hz, 1H), 6.97 (dd, *J* = 7.8, 7.4 Hz, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 7.50 (ddd, *J* = 8.3, 7.4, 1.6 Hz, 1H), 7.52-7.60 (m, 4H), 7.77 (dd, *J* = 7.8, 1.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 30.0, 48.2, 82.3, 118.5, 121.2, 121.7, 124.1 (q, *J* = 272.2 Hz), 125.85, 125.92 (q, *J* = 3.7 Hz), 126.9, 130.2 (q, *J* = 32.3 Hz), 136.7, 147.3 (q, *J* = 1.0 Hz), 159.9, 191.3. **^{19}F NMR** ($CDCl_3$, 565 MHz) δ -62.74. **HRMS** (ESI) calcd. for $C_{17}H_{14}F_3O_2$+ [M+H]+ 307.0940, found 307.0938.



3j

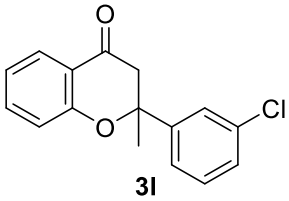
2-(3-methoxyphenyl)-2-methylchroman-4-one (3j): Prepared according to the general procedure from 3-methoxyphenylboronic acid **1j** (38.0 mg, 0.250 mmol) and 2-methylchromone **2a** (120 mg, 0.750 mmol). The crude product was purified by flash column chromatography (100:0 to 70:30 hexanes:EtOAc) to yield **3j** (39.0 mg, 0.170 mmol, 68%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.75 (s, 3H), 3.08 (d, *J* = 16.5 Hz, 1H), 3.29 (d, *J* = 16.5 Hz, 1H), 3.75 (s, 3H), 6.73-6.78 (m, 1H), 6.93 (dd, *J* = 7.8, 7.2 Hz, 1H), 6.95-6.99 (m, 2H), 7.06 (dd, *J* = 8.3. 0.5 Hz, 1H), 7.21 (app t, *J* = 8.0 Hz, 1H), 7.47 (ddd, *J* = 8.3, 7.2, 1.6 Hz, 1H), 7.76 (dd, *J* = 7.8, 1.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 30.1, 48.3, 55.4, 82.6, 111.7, 112.9, 117.8, 118.5, 121.25, 121.27, 126.8, 129.9, 136.4, 144.9, 160.0, 160.2, 191.8. **HRMS** (ESI) calcd. for $C_{17}H_{17}O_3$+ [M+H]+ 269.1172, found 269.1177.



3k

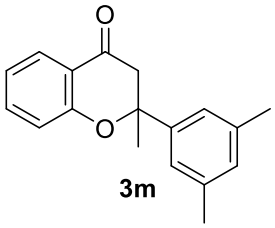
2-methyl-2-(m-tolyl)chroman-4-one (3k): Prepared according to the general procedure from 3-methylphenylboronic acid **1k** (34.0 mg, 0.250 mmol) and 2-methylchromone **2a** (120 mg, 0.750 mmol). The crude

product was purified by flash column chromatography (100:0 to 80:20 hexanes:EtOAc) to yield **3k** (43.5 mg, 0.173 mmol, 69%) as an off-white powder. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.75 (s, 3H), 2.31 (s, 3H), 3.07 (d, *J* = 16.5 Hz, 1H), 3.31 (d, *J* = 16.5 Hz, 1H), 6.93 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.00-7.10 (m, 2H), 7.14-7.25 (m, 3H), 7.47 (ddd, 8.3, 7.2, 1.6 Hz, 1H), 7.77 (dd, *J* = 7.8, 1.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 21.8, 30.1, 48.3, 82.6, 118.5, 121.18, 121.22, 122.5, 126.1, 126.8, 128.65, 128.68, 136.4, 138.4, 143.2, 160.2, 192.0. **HRMS** (ESI) calcd. for $C_{17}H_{17}O_2$+ [M+H]+ 253.1223, found 253.1227



3l

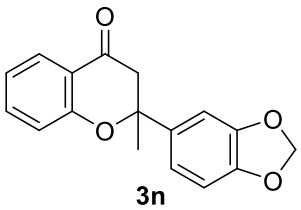
2-(3-chlorophenyl)-2-methylchroman-4-one (3l): Prepared according to the general procedure from 3-chlorophenylboronic acid **1l** (39.1 mg, 0.250 mmol) and 2-methylchromone **2a** (120 mg, 0.750 mmol). The crude product was purified by flash column chromatography (100:0 to 80:20 hexanes:EtOAc) to yield **3l** (14.0 mg, 0.0530 mmol, 21%) as colorless oil. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.74 (s, 3H), 3.08 (d, *J* = 16.5 Hz, 1H), 3.25 (d, *J* = 16.5 Hz, 1H), 6.97 (dd, 7.8, 7.2 Hz, 1H), 7.08 (d, *J* = 8.3 Hz, 1H), 7.18-7.31 (m, 3H), 7.43 (s, 1H), 7.49 (dd, *J* = 8.3, 7.2 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 29.8, 48.2, 82.2, 118.6, 121.1, 121.6, 123.5, 125.8, 126.9, 128.2, 130.2, 135.0, 136.6, 145.5, 159.9, 191.4. **HRMS** (ESI) calcd. for $C_{16}H_{14}ClO_2$+ [M+H]+ 273.0677, found 273.0672.



3m

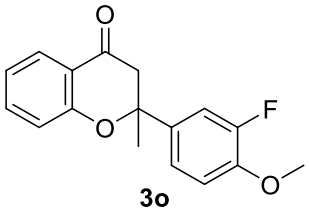
2-(3,5-dimethylphenyl)-2-methylchroman-4-one (3m): Prepared according to the general procedure from 3,5-dimethylphenylboronic acid **1m** (37.5 mg, 0.250 mmol) and 2-methylchromone **2a** (120 mg, 0.750 mmol). The crude product was purified by flash column chromatography

(100:0 to 80:20 hexanes:EtOAc) to yield **3m** (59.0 mg, 0.225 mmol, 90%) as a white solid. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.73 (s, 3H), 2.27 (s, 6H), 3.05 (d, *J* = 16.5 Hz, 1H), 3.30 (d, *J* = 16.5 Hz, 1H), 6.86 (s, 1H), 6.93 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.03 (s, 2H), 7.07 (d, *J* = 8.3 Hz, 1H), 7.47 (ddd, *J* = 8.3, 7.2, 1.6 Hz, 1H), 7.78 (dd, *J* = 7.8, 1.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 21.7, 23.0, 48.3, 82.6, 118.5, 121.1, 121.2, 123.2, 126.8, 129.5, 136.3, 138.3, 143.2, 160.3, 192.0. **HRMS** (ESI) calcd. for $C_{18}H_{19}O_2$+ [M+H]+ 267.1380, found 267.1378.



3n

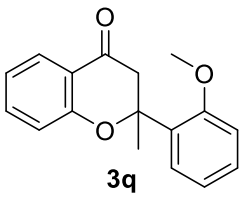
2-(benzo[d][1,3]dioxol-5-yl)-2-methylchroman-4-one (3n): Prepared according to the general procedure from 3,4-methylenedioxyphenylboronic acid **1n** (41.5 mg, 0.250 mmol) and 2-methylchromone **2a** (120 mg, 0.750 mmol). The crude product was purified by flash column chromatography (100:0 to 70:30 hexanes:EtOAc) to yield **3n** (42.4 mg, 0.150 mmol, 60%) as an off-white powder. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.72 (s, 3H), 3.05 (d, *J* = 16.5 Hz, 1H), 3.26 (d, *J* = 16.5 Hz, 1H), 5.89 (d, *J* = 1.4 Hz, 1H), 5.90 (d, *J* = 1.4 Hz, 1H), 6.69 (d, *J* = 8.1 Hz, 1H), 6.82 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.90-6.96 (m, 2H), 7.03 (dd, *J* = 8.3, 0.6 Hz, 1H), 7.45 (ddd, *J* = 8.3, 7.2, 1.6 Hz, 1H), 7.76 (dd, *J* = 7.8, 1.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 30.6, 48.2, 82.5, 101.3, 106.4, 108.2, 118.5, 119.0, 121.26, 121.28, 126.8, 136.4, 137.0, 147.2, 148.2, 160.0, 191.9. **HRMS** (ESI) calcd. for $C_{17}H_{15}O_4$+ [M+H]+ 283.0965, found 283.0960.



3o

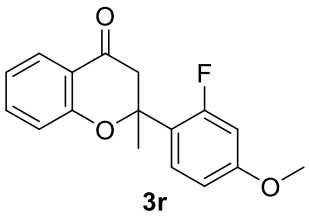
2-(3-fluoro-4-methoxyphenyl)-2-methylchroman-4-one (3o): Prepared according to the general procedure from 3-fluoro-4-methoxyphenylboronic acid **1o** (42.5 mg, 0.250 mmol) and 2-methylchromone **2a** (120 mg, 0.750 mmol). The crude product was

purified by flash column chromatography (100:0 to 70:30 hexanes:EtOAc) to yield **3o** (59.4 mg, 0.208 mmol, 83%) as a light yellow powder. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.72 (s, 3H), 3.06 (d, *J* = 16.5 Hz, 1H), 3.25 (d, *J* = 16.5 Hz, 1H), 3.82 (s, 3H), 6.84 (appt, *J* = 8.6 Hz, 1H), 6.94 (dd, *J* = 7.7, 7.4 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 1H), 7.17 (dd, *J* = 12.5, 2.0 Hz, 1H), 7.46 (dd, *J* = 8.3, 7.4 Hz, 1H), 7.76 (d, *J* = 7.7 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 30.3, 48.1, 56.4, 82.0 (d, *J* = 1.2 Hz), 113.4 (d, *J* = 2.1 Hz), 113.8 (d, *J* = 19.8 Hz) 118.5, 121.2, 121.3 (d, *J* = 3.6 Hz) 121.4, 126.8, 136.2 (d, *J* = 5.4 Hz) 136.5, 147.3 (d, *J* = 10.8 Hz), 152.5 (d, *J* = 246.4 Hz), 160.0, 191.6. **^{19}F NMR** ($CDCl_3$, 565 MHz) δ -133.93. **HRMS** (ESI) calcd. for $C_{17}H_{16}FO_3$+ [M+H]+ 287.1078, found 287.1080.



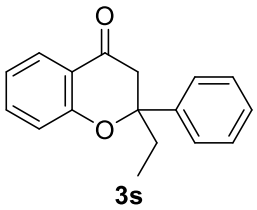
3q

2-(2-methoxyphenyl)-2-methylchroman-4-one (3q): Prepared according to the general procedure from 2-methoxyphenylboronic acid **1q** (38.0 mg, 0.250 mmol) and 2-methylchromone **2a** (120 mg, 0.750 mmol). The crude product was purified by flash column chromatography (100:0 to 70:30 hexanes:EtOAc) to yield **3q** (21.0 mg, 0.0880 mmol, 35%) as a white powder. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.82 (s, 3H), 3.23 (d, *J* = 16.4 Hz, 1H), 3.55 (d, *J* = 16.4 Hz, 1H), 3.86 (s, 3H), 6.86 (dd, *J* = 7.8, 7.2 Hz, 1H), 6.89 (d, *J* = 7.9 Hz, 1H), 6.96 (dd, *J* = 7.8, 7.6 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 1H), 7.21 (ddd, *J* = 7.9, 7.6, 1.6 Hz, 1H), 7.45 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.51 (ddd, *J* = 8.3, 7.2, 1.6 Hz, 1H), 7.77 (dd, *J* = 7.8, 1.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 26.5, 47.1, 55.5, 83.0, 111.9, 118.4, 120.8, 121.1, 121.2, 126.7, 127.0, 129.1, 130.6, 136.3, 156.5, 160.2, 192.8. **HRMS** (ESI) calcd. for $C_{17}H_{17}O_3$+ [M+H]+ 269.1172, found 269.1179.



3r

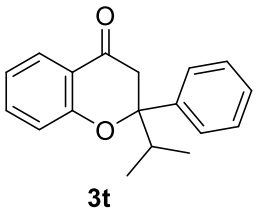
2-(2-fluoro-4-methoxyphenyl)-2-methylchroman-4-one: Prepared according to the general procedure from 2-fluoro-4-methoxyphenylboronic acid **1r** (42.5 mg, 0.250 mmol) and 2-methylchromone **2a** (120 mg, 0.750 mmol). The crude product was purified by flash column chromatography (100:0 to 70:30 hexanes:EtOAc) to yield **3r** (17.9 mg, 0.0630 mmol, 25%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.78 (s, 3H), 3.08 (d, *J* = 16.4 Hz, 1H), 3.34 (d, *J* = 16.4 Hz, 1H), 3.70 (s, 3H), 6.49-6.60 (m, 2H), 6.93 (dd, *J* = 7.7, 7.2 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 7.21-7.26 (m, 1H), 7.47 (ddd, *J* = 8.3, 7.4, 1.3 Hz, 1H), 7.74 (dd, *J* = 7.7, 1.3 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 27.9 (d, *J* = 2.7 Hz), 48.0 (d, *J* = 5.3 Hz), 55.7, 81.6 (d, *J* = 3.9 Hz), 103.0 (d, *J* = 27.1 Hz), 109.9 (d, *J* = 2.8 Hz), 118.4, 121.1, 121.4, 121.6 (d, *J* = 11.9 Hz), 126.8, 128.2 (d, *J* = 5.7 Hz), 136.5, 159.9 (d, *J* = 17.7 Hz), 160.7 (d, *J* = 11.5 Hz), 161.5, 191.9. **^{19}F NMR** ($CDCl_3$, 565 MHz) δ -110.42. **HRMS** (ESI) calcd. for $C_{17}H_{16}FO_3^+$ [M+H]+ 287.1078, found 287.1078.



3s

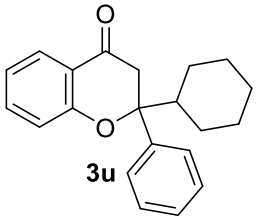
2-ethyl-2-phenylchroman-4-one (3s): Prepared according to the general procedure from phenylboronic acid **1a** (30.5 mg, 0.250 mmol) and 2-ethylchromone **2b** (130 mg, 0.750 mmol). The crude product was purified by flash column chromatography (100:0 to 90:10 hexanes:EtOAc) to yield **3s** (50.0 mg, 0.198 mmol, 79%) as an off-white powder. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 0.86 (t, *J* = 7.4 Hz, 3H), 1.96-2.16 (m, 2H), 3.11 (d, *J* = 16.5 Hz, 1H), 3.27 (d, *J* = 16.5 Hz, 1H), 6.92 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.08 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.18-7.23 (m, 1H), 7.25-7.31 (m, 2H),

7.32-7.38 (m, 2H), 7.46 (ddd, *J* = 8.4, 7.2, 1.7 Hz, 1H), 7.74 (dd, *J* = 7.8, 1.7 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 8.1, 35.4, 46.3, 85.3, 118.5, 121.1, 121.5, 126.1, 126.7, 127.7, 128.6, 136.3, 141.4, 160.2, 192.1. **HRMS** (ESI) calcd. for $C_{17}H_{17}O_2$+ [M+H]+ 253.1223, found 253.1225.



3t

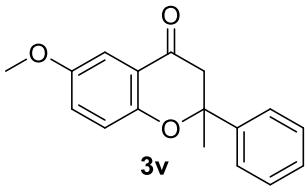
2-isopropyl-2-phenylchroman-4-one (3t): Prepared according to the general procedure from phenylboronic acid **1a** (30.5 mg, 0.250 mmol) and 2-isopropylchromone **2c** (141 mg, 0.750 mmol). The crude product was purified by flash column chromatography (100:0 to 90:10 hexanes:EtOAc) to yield **3t** (28.6 mg, 0.108 mmol, 43%) as a light yellow oil. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 0.87 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 2.27 (sept, *J* = 6.8 Hz, 1H), 3.22 (d, *J* = 16.4 Hz, 1H), 3.29 (d, *J* = 16.4 Hz, 1H), 6.87 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.23 (dd, *J* = 8.0, 7.3 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.43 (ddd, *J* = 8.3, 7.2, 1.6 Hz, 1H), 7.67 (dd, *J* = 7.8, 1.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 17.2, 17.6, 39.1, 42.6, 87.8, 118.5, 121.0, 121.7, 126.7, 127.3, 127.8, 128.3, 136.2, 140.1, 160.5, 192.5. **HRMS** (ESI) calcd. for $C_{18}H_{19}O_2$+ [M+H]+ 267.1380, found 267.1385.



3u

2-cyclohexyl-2-phenylchroman-4-one (3u): Prepared according to the general procedure from phenylboronic acid **1a** (30.5 mg, 0.250 mmol) and 2-cyclohexylchromone **2d** (171 mg, 0.750 mmol). The crude product was purified by flash column chromatography (100:0 to 90:10 hexanes:EtOAc) to yield **3u** (11.5 mg, 0.0380 mmol, 15%) as a light yellow oil. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 1.02-1.31 (m, 5H), 1.62-2.00 (m, 6H), 3.17 (d, *J* = 16.3 Hz, 1H), 3.28 (d, *J* = 16.3 Hz, 1H), 6.86 (dd, *J* = 7.6, 7.4 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 7.17 (t, *J* = 7.0 Hz, 1H), 7.23 (dd, *J* = 7.7, 7.0

Hz, 2H), 7.28 (d, *J* = 7.7 Hz, 2H), 7.42 (dd, *J* = 8.3, 7.4 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 151 MHz) δ 26.5, 26.6, 26.7, 27.2, 27.7, 43.1, 49.2, 87.6, 118.5, 121.0, 121.7, 126.7, 127.3, 127.7, 128.3, 136.2, 140.4, 160.4, 192.6. **HRMS** (ESI) calcd. for $C_{21}H_{23}O_2$+ [M+H]+ 307.1693, found 307.1690.



3v

6-methoxy-2-methyl-2-phenylchroman-4-one (3v): Prepared according to the general procedure from phenylboronic acid **1a** (30.5 mg, 0.250 mmol) and 6-methoxy-2-methylchromone **2e** (142 mg, 0.750 mmol). The crude product was purified by flash column chromatography (100:0 to 70:30 hexanes:EtOAc) to yield **3v** (54.4 mg, 0.203 mmol, 81%) as a tan powder. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.74 (s, 3H), 3.08 (d, *J* = 16.6 Hz, 1H), 3.31 (d, *J* = 16.6 Hz, 1H), 3.73 (s, 3H), 6.99 (d, *J* = 9.0 Hz, 1H), 7.07 (dd, *J* = 9.0, 3.2 Hz, 1H), 7.19 (d, *J* = 3.2 Hz, 1H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.30 (dd, *J* = 7.3, 7.2 Hz, 2H), 7.40 (d, *J* = 7.2 Hz, 2H). **^{13}C NMR** ($CDCl_3$, 101 MHz) δ 30.3, 48.1, 55.9, 82.6, 107.3, 119.8, 121.0, 125.4, 125.5, 127.8, 128.8, 143.2, 153.9, 154.8, 192.0. **HRMS** (ESI) calcd. for $C_{17}H_{17}O_3$+ [M+H]+ 269.1172, found 269.1177.

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CHAPTER 5

CONCLUSIONS

We have shown that cycloadditions of α-substituted azomethine ylides with 3-nitroindoles occur in the presence of a catalyst derived from $Cu(OTf)_2$ and (*R*)-Difluorphos to deliver pyrrolo[3, 4*b*]indoles in moderate-to-good yields (39-85%) with up to 98 : 1 : 1 *exo´*:*exo*:*endo* selectivity and up to 96% yield. A portion of this work demonstrates that the copper-catalyst is involved in an *endo*→*exo´* epimerization process that allows for high *exo´*-selectivity. We obtained data that suggests that D-configured imino esters move through the catalyzed cycloaddition pathway at a rate faster than L-configured imino esters. These reactions set four contiguous stereocenters, two of which are fully substituted.

We have designed a catalyst system that smoothly catalyzes reactions of highly reactive nitrile imines with methyleneindolinones to afford spiro[pyrazolin-3,3´-oxindoles] in up to 98% yield and up to 99% ee. This methodology, which is applicable to a diverse scope of dipoles and dipolarophiles, compliments extant methods which require steric bulk at the β-aryl ring of the methyleneindoline and less reactive hydrazonoyl chlorides in order to achieve high yields and enantioselectivities. Data obtained in competition reactions of dipolarophiles suggests that strength of dipolarophile-catalyst binding plays a role in enantioselectivity in these reactions.

We have demonstrated that conjugate additions of arylboronic acids with 2-substituted chromones occur in aqueous medium in the presence of a catalyst generated from $Pd(TFA)_2$ and 1,10-phenanthroline to deliver 2-alkyl-2-arylchromanones in up to 90% yield. The scope of these reactions includes a variety of arylboronic acids and 2-alkylchromones. These reactions overcome the problems of undesired protodeboronation and arylboronic acid homocoupling and provide a new means to generate a fully substituted carbon center.