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Transition-Metal-Catalyzed Asymmetric Allylic Dearomatization Reactions

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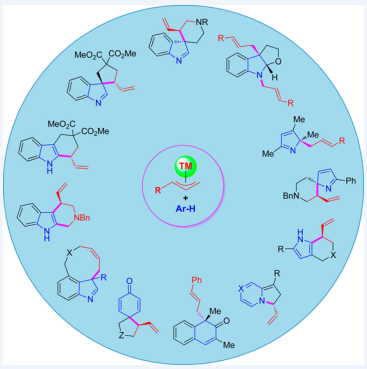
CONSPECTUS: Dearomatization reactions serve as powerful methods for the synthesis of highly functionalized, three-dimensional structures starting with simple planar aromatic compounds. Among processes of this type, catalytic asymmetric dearomatization (CADA) reactions are attractive owing to the large number of aromatic compounds that are readily available and the fact that they enable direct access to enantiopure polycycles and spirocycles, which frequently are key structural motifs in biologically active natural products and pharmaceuticals. However, as a consequence of their high stabilities, arenes only difficultly participate in dearomatization reactions that take place with high levels of enantioselectivity.



Transition-metal-catalyzed asymmetric allylic substitution reactions have been demonstrated to be powerful methods for enantioselective formation of C−C and C−X (X = O, N, S, etc.) bonds. However, the scope of these processes has been explored mainly using soft carbon nucleophiles, some hard carbon nucleophiles such as enolates and preformed organometallic reagents, and heteroatom nucleophiles. Readily accessible aromatic compounds have been only rarely used directly as nucleophiles in these reactions.

In this Account, we present the results of studies we have conducted aimed at the development of transition-metal-catalyzed asymmetric allylic dearomatization reactions. By utilizing this general process, we have devised methods for direct dearomatization of indoles, pyrroles, phenols, naphthols, pyridines, and pyrazines, which produce various highly functionalized structural motifs bearing all-carbon quaternary stereogenic centers in a straightforward manner. In mechanistic investigations of the dearomatization process, we found that the five-membered spiroindolenines serve as intermediates, which readily undergo stereospecific allylic migration to form corresponding tetrahydro-1*H*-carbazoles upon treatment with a catalytic amount of TsOH. It is worth noting that no notable loss of the enantiomeric excess of the spiroindolenine derivatives takes place during the rearrangement process as a consequence of the intervention of a "three-center−two-electron"-type transition state, a proposal that has gained support from the results of DFT calculations. Equally intriguing, upon tuning of the electronic nature of the tethers, pyrroles or indoles undergo unprecedented Ir or Ru catalyzed intramolecular allylic alkylation promoted dearomatization/migration reactions. The operation of this novel reaction pathway provides additional information leading to a greater mechanistic understanding of the transition-metal-catalyzed enantioselective intramolecular functionalizations of pyrroles and indoles. The combined results of this effort provide not only methods for the efficient synthesis of highly enantioenriched fused and spiro polycycles but also novel strategies in the field of asymmetric catalysis.

1. INTRODUCTION

Transition-metal-catalyzed asymmetric allylic substitution reactions are among the most important and reliable methods for enantioselective construction of C−C and C−X bonds.[1] The diverse types of nucleophiles that can be employed in these reactions include various alcohols, amines, and α-electron-withdrawing group substituted carbanions. The direct utilization of electron-rich arenes as nucleophiles in this process has attracted much attention. In 1999, Kočovský and co-workers[2] reported the first Mo(II)-catalyzed allylic substitution reaction of electron-rich arenes including phenols, indoles, and furans. Over the past decade, several Pd-catalyzed Friedel−Crafts-type allylic substitution reactions of indoles have been described.[3] When variants of chiral Pd complexes are employed, high enantioselectivities attend both intra-[4] and intermolecular[5] versions of this reaction. In addition, other transition metals such as Au[6] and Ru[7] are also effective in promoting asymmetric allylic alkylation reactions of indoles.

In addition, significant progress has been made in recent years in studies aimed at the development of Ir-catalyzed asymmetric allylic substitution reactions.[8] Complementary to Pd-catalyzed reactions, those promoted by Ir catalysts can be used to prepare compounds with branched allylic stereogenic centers from monosubstituted allylic substrates (Scheme 1). Excellent levels of enantioselectivity accompany these processes when chiral phosphoramidite ligands[9] are employed. However, to the best of our knowledge, electron-rich arenes were not used directly as nucleophiles in Ir-catalyzed asymmetric allylic substitution reactions before 2008.[10]

Aromatic compounds widely exist in nature, and as a result, they serve as basic starting materials for reactions developed in

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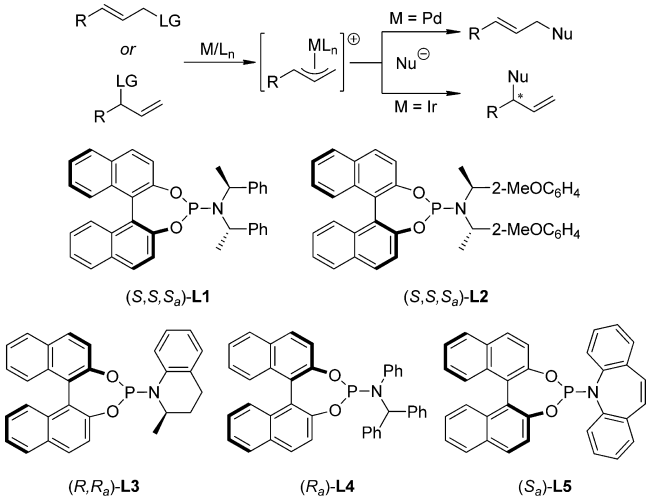
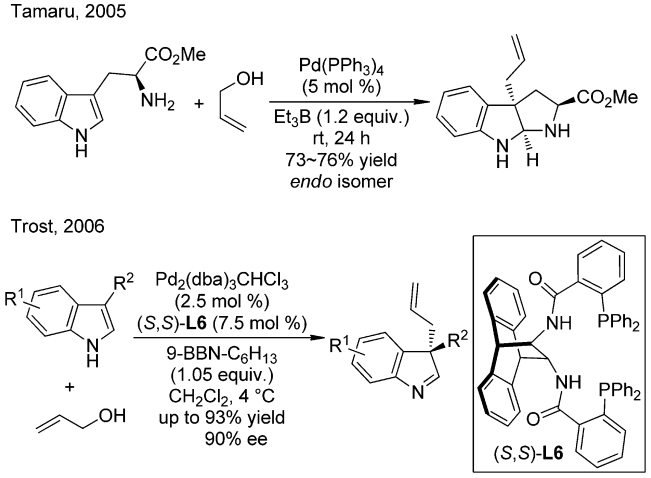
Scheme 1. Ir-Catalyzed Allylic Substitution Reactions and Phosphoramidite Ligands Used in This Study



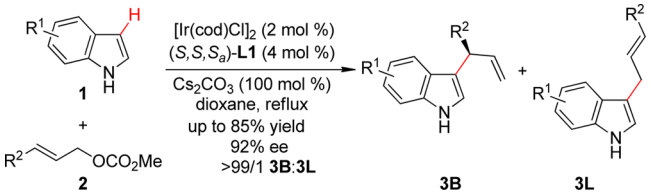
Scheme 2. Pioneering Work Leading to the Development of Transition-Metal-Catalyzed Allylic Dearomatization Reactions



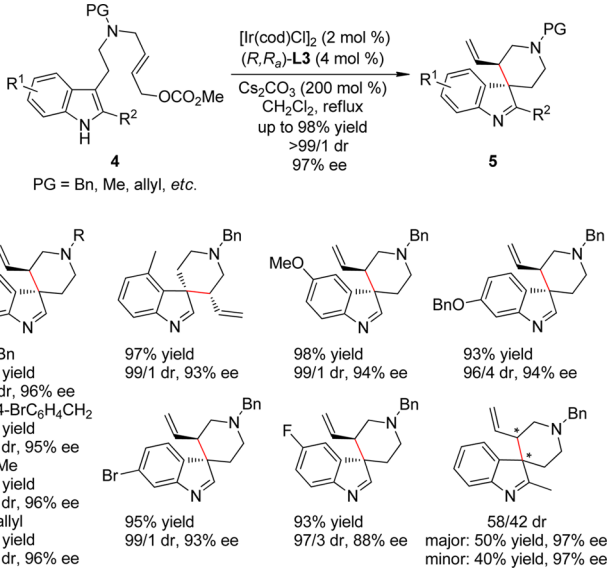
research carried out in both academic and industrial organizations. Notably, most of the known reactions of arenes lead to products that retain the characteristic planar aromatic structure. However, dearomatization[11] reactions of arenes, which represent another extremely important class of transformations, directly convert planar aromatics into three dimensionally more complex ring structures. Dearomatization reactions represent very attractive strategies in organic synthesis given the fact that the corresponding dearomatized products, particularly those arising from heteroarenes, are frequently observed key ring motifs in biologically active natural products and pharmaceuticals.

Despite the enormous synthetic interest that exists in these processes, enantioselective versions of dearomatization reactions have been nearly neglected. This is mainly a result of the harsh conditions that are generally required to overcome loss of aromaticity derived stabilization, which impedes subtle factors involved in the control of enantioselection. Recent progress has been made in the development of catalytic asymmetric dearomatization reactions, including oxidative dearomatizations with chiral hypervalent iodine reagents, Diels–Alder and

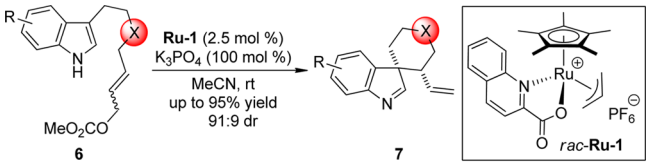
Scheme 3. Ir-Catalyzed Intermolecular Asymmetric Allylic Substitution of Indoles



Scheme 4. Enantioselective Construction of Six-Membered Aza-spiroindolenines by Ir-Catalyzed Intramolecular Allylic Dearomatization of Indoles



Scheme 5. Ru-Catalyzed Intramolecular Allylic Dearomatization Reactions



related cycloaddition reactions, Reissert-type nucleophilic addition reactions, organocatalytic dearomatization reactions, and dearomatization reactions catalyzed by transition-metal complexes.[12] Especially in the case of indoles, dearomatization reactions provide unique opportunities for the construction of many privileged polycyclic structural motifs. In 2004, MacMillan and co-workers[13] reported the synthesis of pyrroloindoline architectures by using the organocatalytic dearomatization of tryptamine derivatives and applied this method to the enantioselective synthesis of (−)-flustramine B. In this regard, transition-metal-catalyzed allylic substitution reactions also are potentially applicable to asymmetric dearomatizations of indoles (Scheme 2). In 2005, Tamaru and co-workers[14] reported the first example of Pd-catalyzed C3-selective allylation of indoles with allylic alcohols in the presence of Et_3B. Interestingly, reaction of a C3-substituted indole was observed to generate the corresponding indolenine product. Also, exclusive *endo* selectivity is observed when L-tryptophan methyl ester is used as the substrate. Soon after Tamaru's report, Trost

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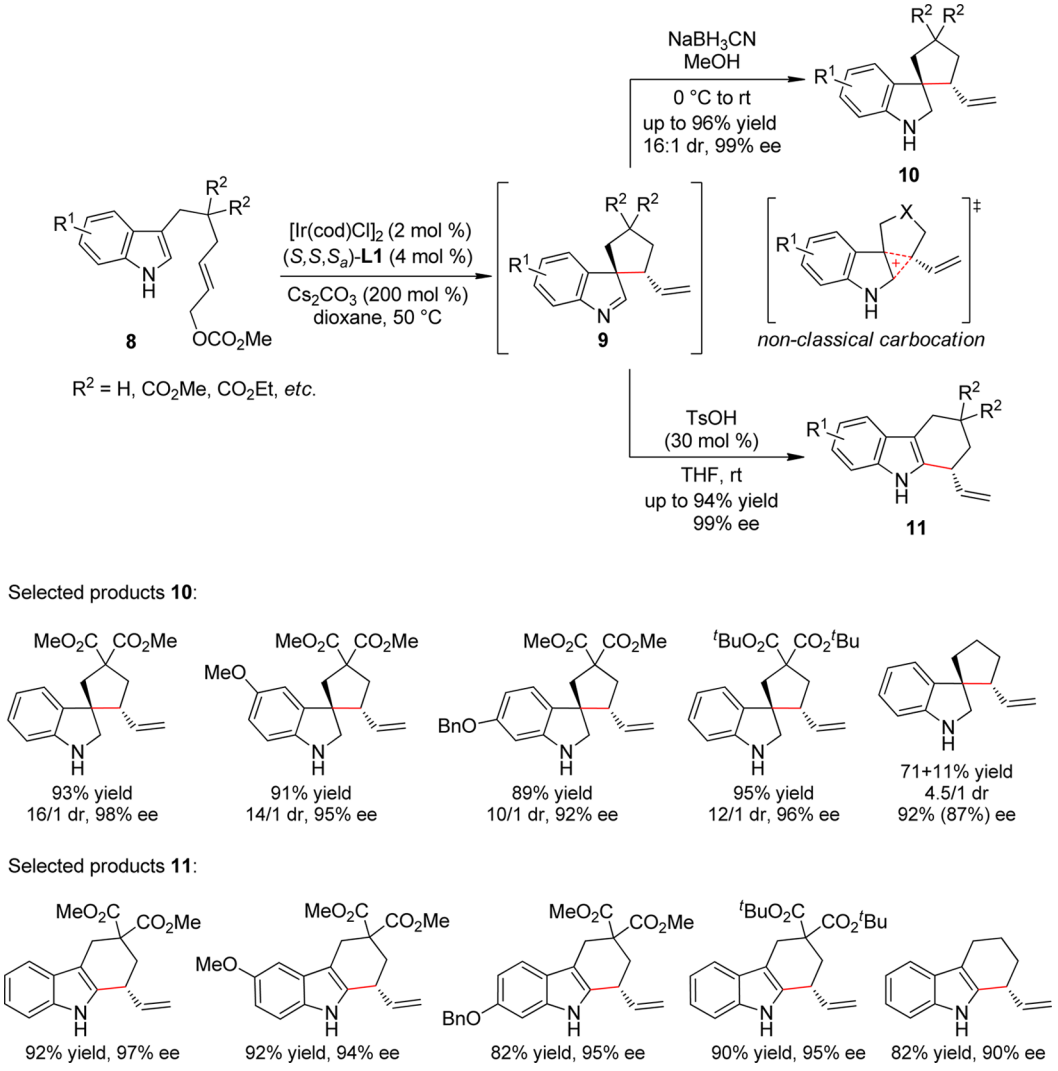
Scheme 6. Enantioselective Construction of Cyclopentane-1,3′-indolines and Tetrahydro-1*H*-carbazoles by Ir-Catalyzed Intramolecular Allylic Dearomatization and Acid-Catalyzed Migration



and Quancard[15] described the catalytic enantioselective variant of this reaction employing a chiral bisphosphine ligand and modified 9-BBN as the promoter. Later, Rawal and co-workers[16] reported Pd-catalyzed allylic substitution reactions of various 2,3-disubstituted indoles with allylic carbonates.

In recent years, studies in our group have focused on the development of transition-metal-catalyzed asymmetric allylic dearomatization reactions. An array of indole, pyrrole, phenol, β-naphthol, and even electron-deficient heteroarenes, such as pyridine and pyrazine, participate as nucleophiles in intra- or intermolecular versions of this reaction and, by doing so, enable the highly enantioselective synthesis of a variety of spiro and fused polycyclic scaffolds. In addition, some spiroindolenine ring systems produced in this way undergo novel, highly stereoselective rearrangement reactions to form functionalized indoles. In this Account, we summarize the contributions to this field made in studies carried out by our research group.

2. ASYMMETRIC ALLYLIC DEAROMATIZATION REACTIONS OF INDOLE DERIVATIVES

In 2008, we reported the first example of an Ir-catalyzed regio- and enantioselective Friedel−Crafts-type allylic substitution reaction of indoles.[10] Specifically, we observed that in the presence of a catalytic amount of $[Ir(cod)Cl]_2$ and phosphoramidite ligand (S,S,S_a)-**L1**, reactions of indoles **1** and monosubstituted allylic carbonates **2** form highly enantioenriched branched products **3** (Scheme 3). Later it was found that reactions with well-designed tryptamine derived indol-3-yl allylic carbonates **4** as substrates lead to enantioselective production of the six-membered aza-spiroindolenines **5**, which serves as the first example of an Ir-catalyzed intramolecular allylic dearomatization reaction (Scheme 4).[17] The novel N-aryl phosphoramidite (R,R_a)-**L3** developed in our laboratory[18] is the optimal ligand for this reaction. Notably, the results of extensive mechanistic studies along with density functional theory (DFT) calculations and X-ray crystallographic analyses of the (π-allyl)−Ir complexes derived from ligand (R,R_a)-**L3** show that when (R,R_a)-**L3** is employed as the ligand the active catalytic species is formed via a $C(sp^2)$−H bond activation rather than $C(sp^3)$−H bond activation in the case of the iridacycle derived from ligand **L1**. This reaction enables the synthesis of chiral spiro compounds from readily available starting materials and the construction of two contiguous stereogenic centers. Excellent yields and levels of enantioselectivity are observed for reactions of most substrates except for those containing substituents at C2 position of the indole. In addition, only electron-donating

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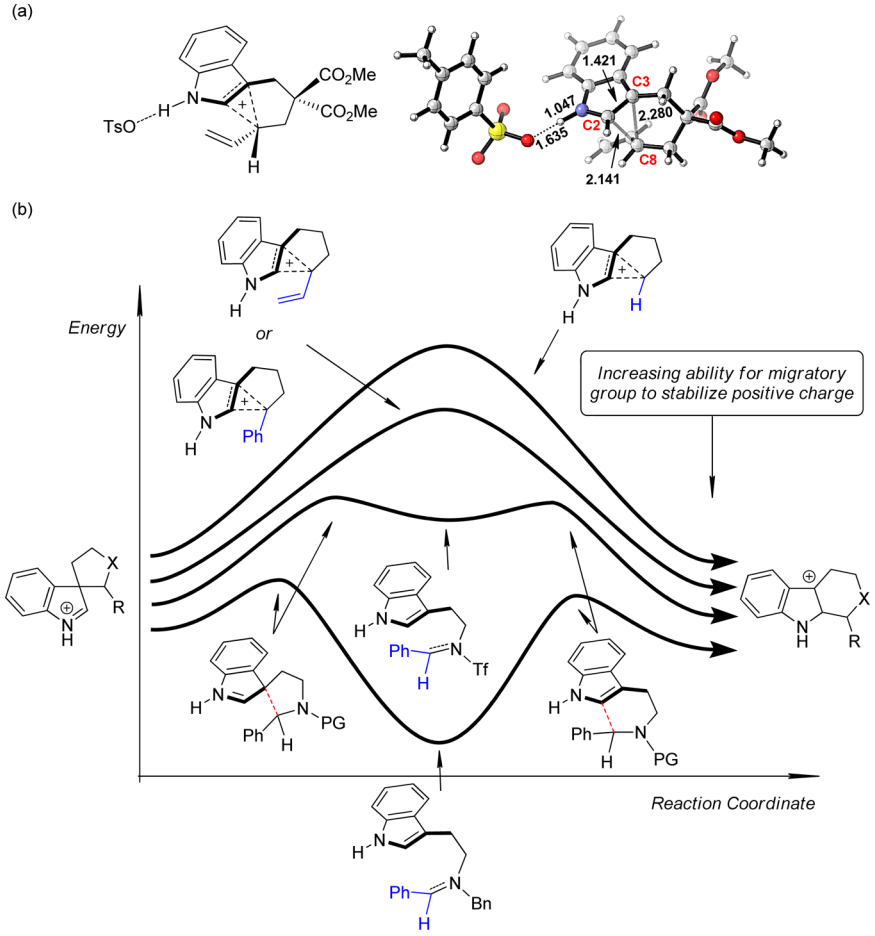
Scheme 7. (a) Calculated Transition State for the Allyl Migration (PBE1PBE/6-311+G(d,p) Level of Theory) and (b) Influence of Electronic Properties of the Migratory Groups on the Reaction Profile

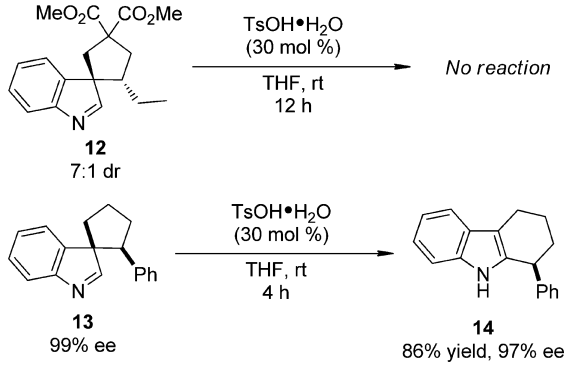


groups such as benzyl, allyl, and methyl on nitrogen linkage are tolerated in this reaction.

Interestingly, the substrate scope for the process leading to spiroindolenines is greatly expanded when Ru is employed as the catalyst.[19] The ruthenium complex *rac*-**Ru-1** was found to be an efficient catalyst for the intramolecular allylic dearomatization reaction of indol-3-yl allylic carbonates **6** (Scheme 5).[20] Compared with the case of Ir-catalysis mentioned above,[17] the Ru-catalyzed process has a relatively broader substrate scope, employs a cheaper and more easily prepared catalyst, and is carried out under mild conditions and with great operational simplicity. N-Tethered substrates bearing either an electron-donating or electron-withdrawing group as well as the C-tethered substrates participate in this reactions. The allylic carbonate moieties were not limited to be *trans* configuration. In addition, the products can be formed from the corresponding allylic alcohol substrates under slightly modified reaction conditions.

The next question addressed in this effort was whether other types of spiroindolenine compounds could be synthesized employing the newly established methodology. By changing the nature of the linkage between the indole core and allylic carbonate, we were able to synthesize spiro cyclopentane-1,3′-indolines **10** by Ir-catalyzed asymmetric allylic dearomatization of substrates **8** followed by $NaBH_3CN$ reduction (Scheme 6).[21] The desired products were typically generated with moderate to high levels of diastereoselectivity and excellent enantioselectivity.

Scheme 8. Experimental Validation



More intriguing was the observation that upon treatment with a catalytic amount of TsOH, the spiroindolenine intermediates **9** undergo stereospecific allylic migration to form the corresponding tetrahydro-1*H*-carbazoles **11**. The ee of the products as well as the absolute configuration of the allylic stereogenic center are preserved in this process, which is proposed to take place through a nonclassical carbocation intermediate.

Information about the mechanism of the allylic migration reaction was gained from the results of DFT calculations,[22] which show that the allylic migration is concerted and occurs through a "three-center−two-electron" type transition state. This is the reason for the observed high levels of stereoselectivity

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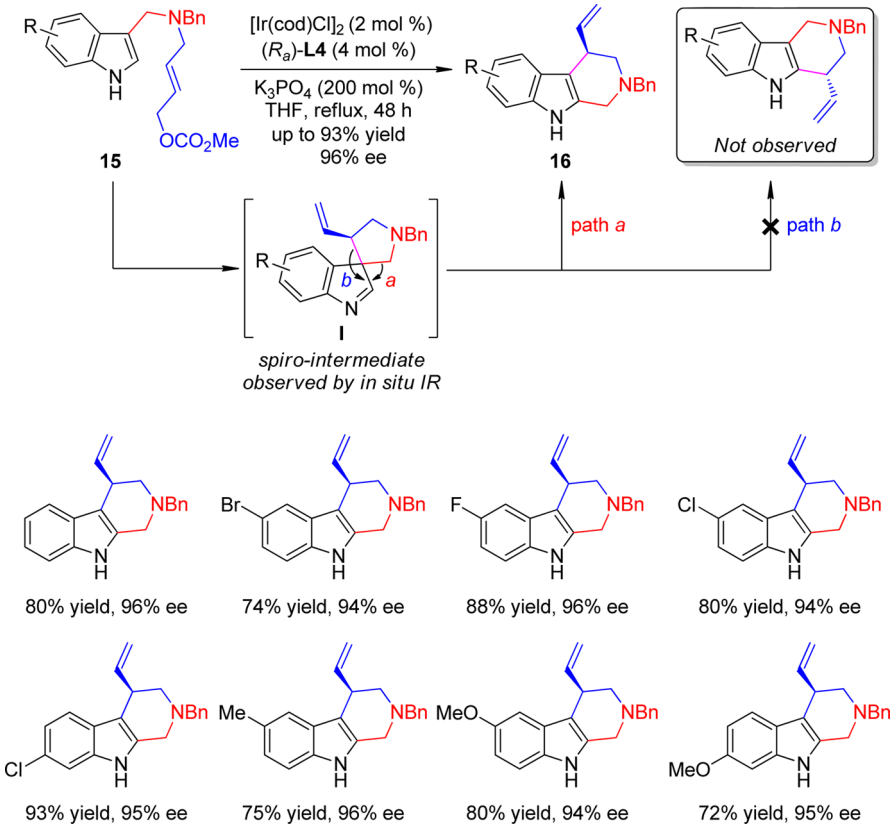
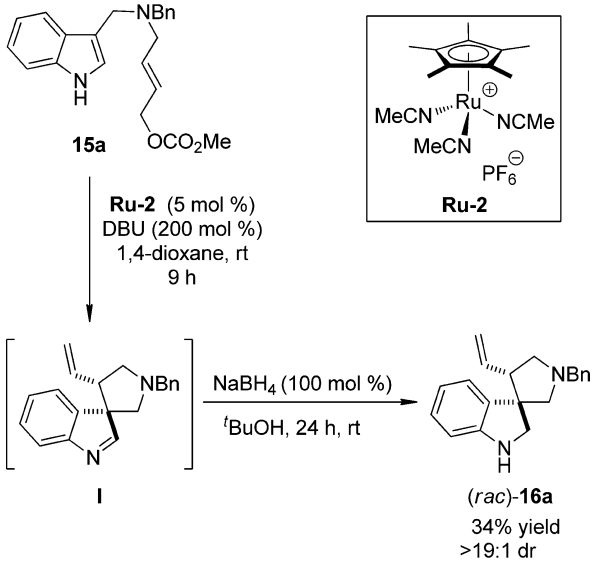
Scheme 9. Enantioselective Synthesis of Polycyclic Indole Derivatives via the *in Situ* Formation and Migration of Spiroindolenine Intermediates

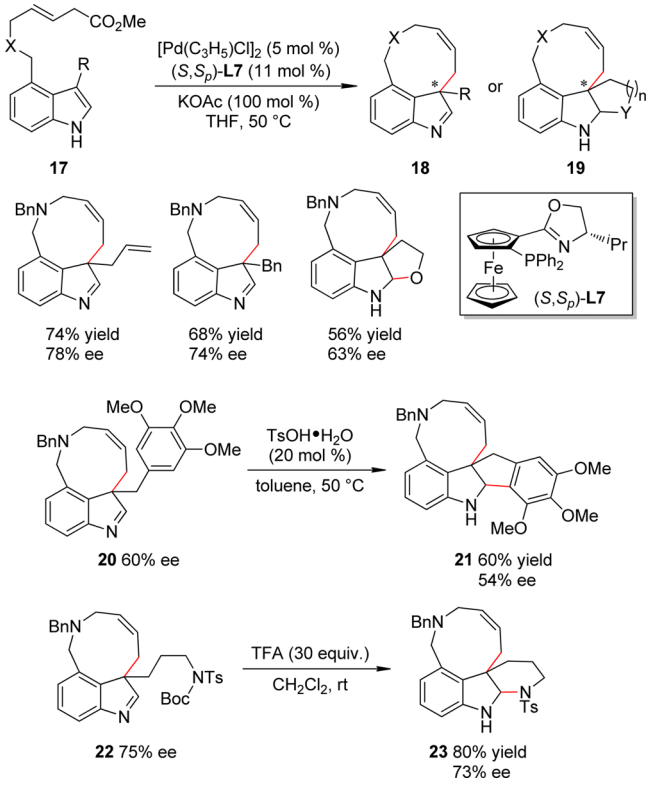


Scheme 10. Capture of the Key Intermediate I by *in Situ* Reduction



(Scheme 7). In addition, the electronic properties of the migrating groups were found to have a significant influence on the profile of the migration reaction. Generally, the group that possesses the greater ability to stabilize positive charge has greater aptitude to migrate. Also, the reaction mechanism shifts from concerted to stepwise as the migratory ability of the group increases. Two additional observations were made in studies of

Scheme 11. Pd-Catalyzed Asymmetric C4-to-C3 Dearomatization Reactions of Indoles



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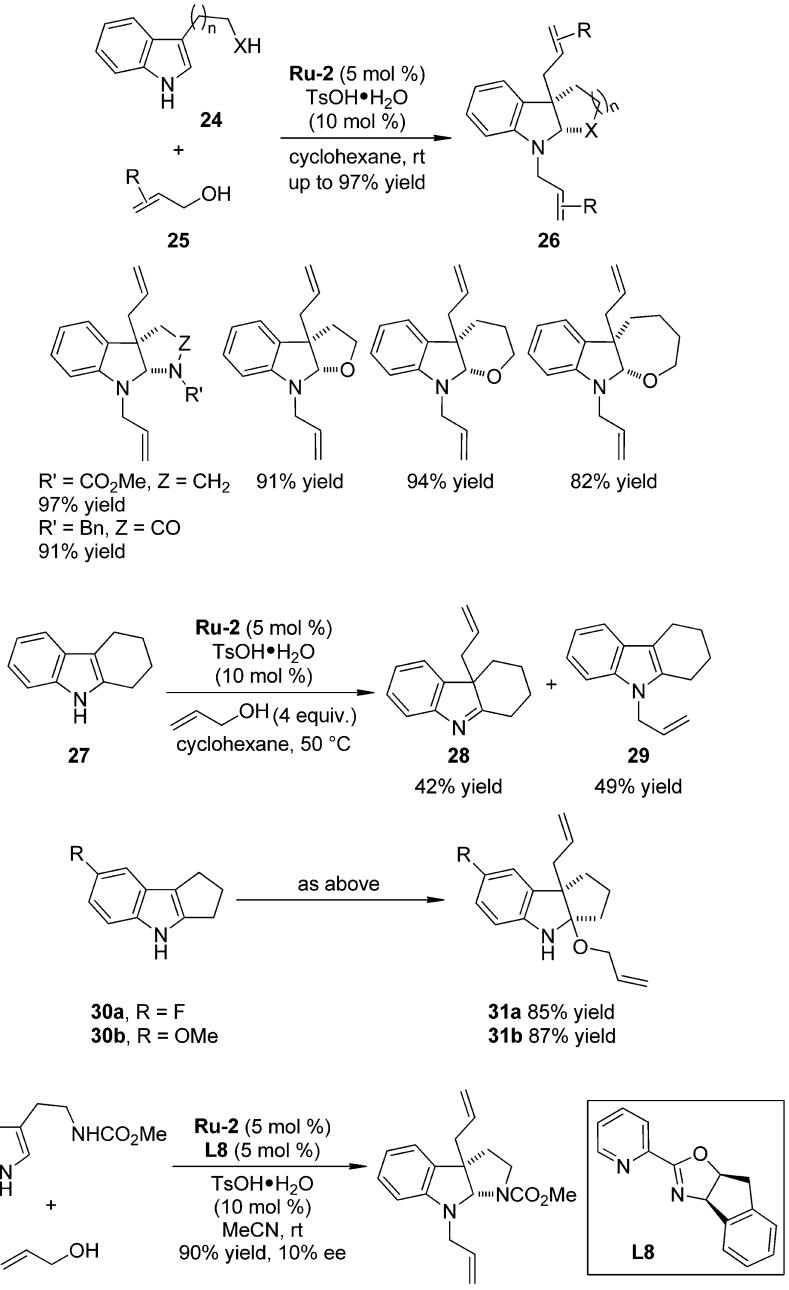
Scheme 12. Ru-Catalyzed Intermolecular Dearomatization Reactions of C3-Substituted Indoles



reactions of designed substrates (Scheme 8). First, no reaction occurs when the ethyl substituted five-membered spiroindolenine **12** is used as the substrate. Second, enantiopure spiroindolenine **13** bearing a benzylic stereogenic center is smoothly converted to the corresponding tetrahydrocarbazole **14** without notable loss of enantiopurity. The results are in full accord with those anticipated based on the mechanistic conclusion stated above.

Based on the above mechanistic foundation, we envisioned that the migration site of the spiroindolenine species could be changed to the methylene moiety by enhancing its migratory aptitude. Employing this proposal, we recently developed a tandem dearomatization/migration reaction that produces chiral polycyclic indole scaffolds (Scheme 9).[23] By utilizing substrates **15** with an *N*-Bn group as the tether, the process yields enantioenriched tetrahydro-β-carboline derivatives **16** through a route involving *in situ* formation and rearrangement of the spiro intermediate **I** by an Ir catalyst derived from a readily accessible phosphoramidite ligand (R_a)-**L4**. During the reaction, the substituent attached to the indole C3 position in the starting material migrates to the C2 position of the indole ring in the product. The existence of the key intermediate **I** in the pathway gains support from observation made by *in situ* IR spectroscopy monitoring of the reaction process. Furthermore, we recently found that similar transformation of **15** to **16** can be carried out using Ru catalysis and that intermediate **I** can be captured by *in situ* sodium borohydride reduction to form the corresponding spiroindoline **16a** with a high level of diastereoselectivity (Scheme 10).[25] The capture of spiroindolenine **I** provides solid evidence for the proposed dearomatization/migration pathway.

The pathway involving formation and rearrangement of spiroindolenine intermediates has been overlooked in many

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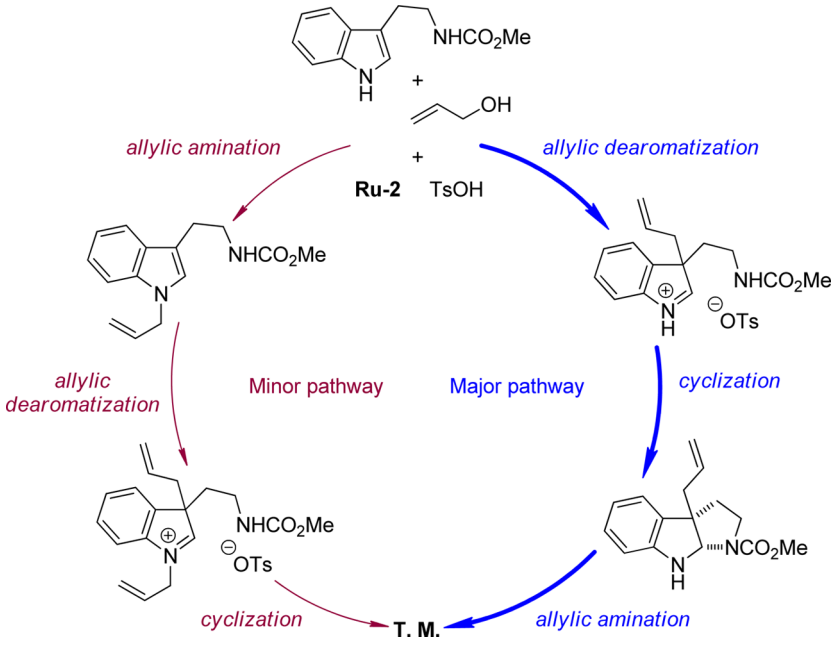
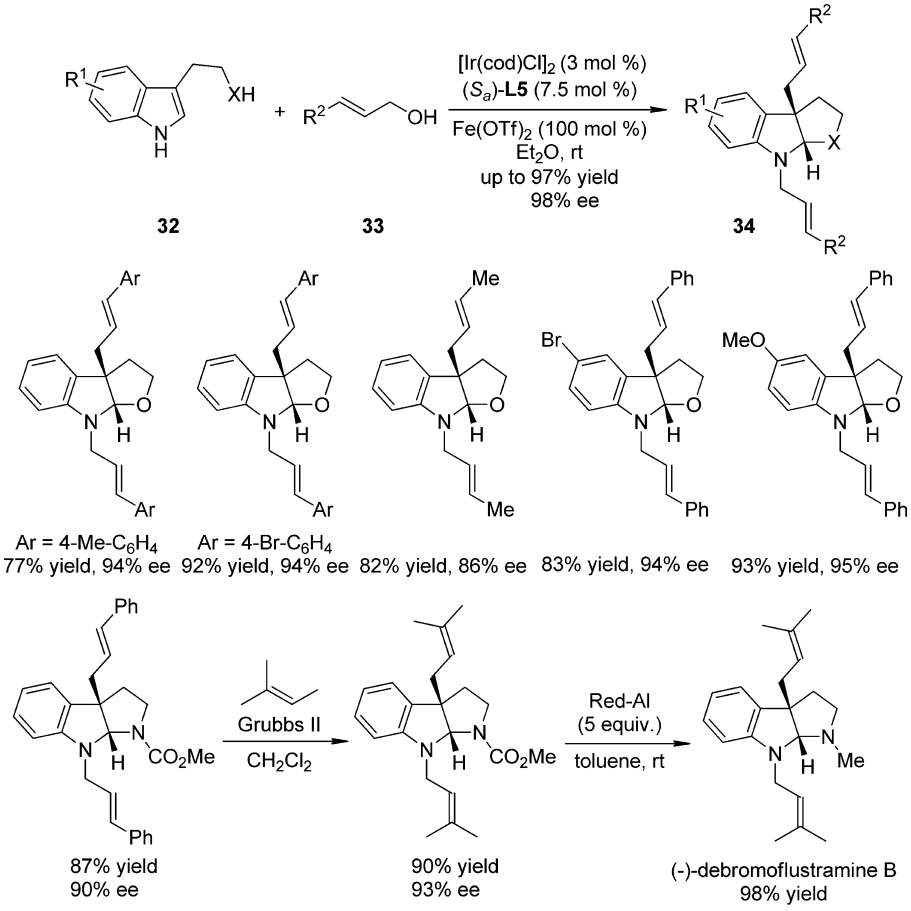
Scheme 13. Plausible Reaction Pathways



Scheme 14. Ir-Catalyzed Asymmetric Intermolecular Allylic Dearomatization of Indoles



reactions studied in the past, and as a result, incorrect structural assignments have been made.[4] Specifically, the results of this study clearly demonstrate the importance of spiroindolenine intermediates in asymmetric Pictet–Spengler[24] and related intramolecular indole C3-to-C2 functionalization reactions. Moreover, they suggest a novel approach for the enantioselective synthesis of polycyclic indole derivatives.

The installation of the side chain of the allylic moiety on the C4 position of the indole core allows the synthesis of various indole-based peri-annulated compounds.[26] As shown in Scheme 11,

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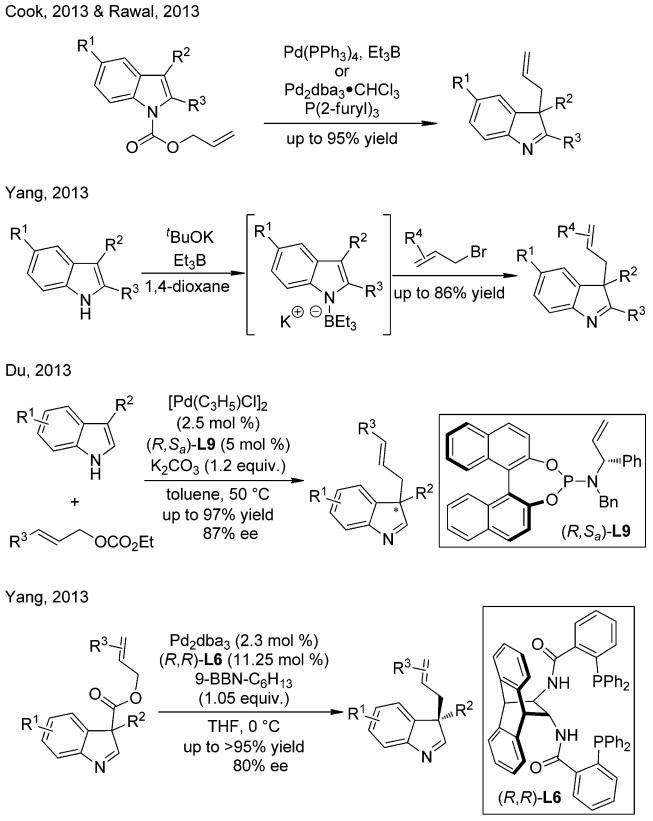
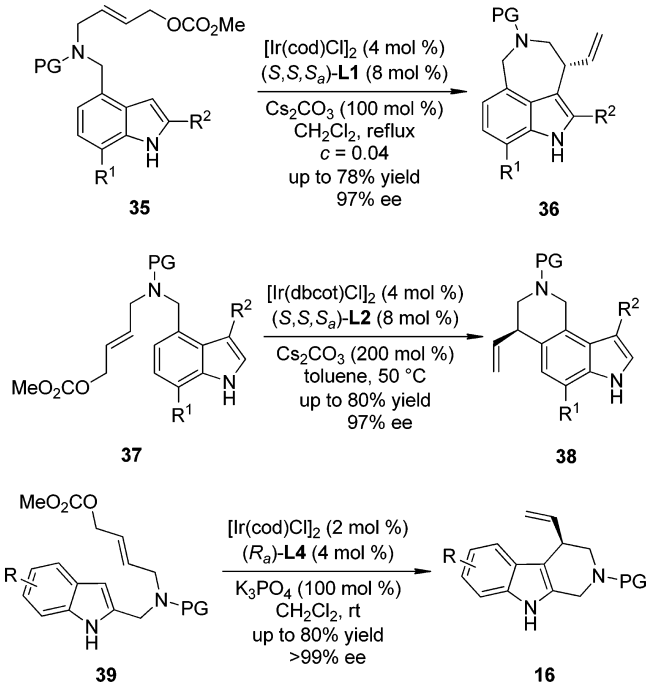
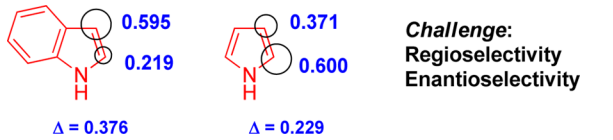
Scheme 15. Pd-Catalyzed Allylic Dearomatization Reactions of Indoles



Scheme 16. Ir-Catalyzed Asymmetric Friedel–Crafts-Type Allylic Substitution Reactions of Indoles



Scheme 17. Comparison of the HOMO Electron Density Distribution of Indole and Pyrrole



Pd-catalyzed asymmetric allylic dearomatization reactions of indoles **17** take place with moderate enantioselectivity when planar-chiral ferrocene-based ligand (S,S_p)-**L7** is used. Enantioenriched tricyclic indolenines **18** are typically formed in these reactions. In some cases, the imine functionality is captured by a nucleophile attached at the C3 position of indole to yield tetracyclic compounds **19**. For example, treatment of **20** with 20 mol % of TsOH·H_2O leads to production of the Friedel-Crafts-type cyclization product **21** in 60% yield. The formation of these types of tetracyclic compounds could be achieved using a stepwise route in the case of substrates bearing masked nucleophiles. This is exemplified by formation of the dearomatized product **22** followed by its reaction with an excess amount of TFA leading to removal of the Boc protecting group and cyclization to generate **23** in 80% yield.

The pyrroloindoline moiety is the core structural feature of interesting alkaloid natural products that have received the interest of synthetic organic chemists. Intermolecular dearomatization reactions of indole derivatives that contain nucleophilic side chains at the C3 position provide a convenient method to prepare this heterocyclic scaffold. Recently, we found that the catalytic system of Ru-complex **Ru-2** and TsOH·H_2O allows the synthesis of pyrroloindolines **26** from C3-substituted indoles **24** and allylic alcohols **25** via a cascade sequence including allylic dearomatization, cyclization, and N-allylation (Scheme 12).[27] Reactions of 2,3-disubstituted indoles under these optimized conditions were also explored. In reaction of tetrahydrocarbazole **27**, the corresponding dearomatized product **28** was obtained in 42% yield together with the N-alkylation product **29** in 49% yield. Moreover, interesting observations were made in studies with the tetrahydrocyclopenta[*b*]indoles **30a** and **30b**. Following the occurrence of the expected allylic dearomatization reactions, the allylic alcohol undergoes nucleophilic addition to C2 of the indolenium intermediates to produce indolines **31**. The difference in the reactivities of **27** and **30** is likely a consequence of ring strain of the [3.3.0]-bicyclic system in the substrates that is better released by intermolecular nucleophilic addition of the allylic alcohol. In addition, the results of preliminary investigations of asymmetric variants of this process show that relatively low enantioselectivities (up to 10% ee) occur when chiral pyridine-oxazoline ligand **L8** is employed. Monitoring the reaction (**24**, n = 1, X = NCO_2Me; **25**, R = H) by using HPLC demonstrated that two plausible reaction pathways are followed in the Ru-catalyzed intermolecular dearomatization reactions of tryptamine derivatives. The major pathway involves a cascade sequence consisting of allylic dearomatization/cyclization/allylic amination reaction, while a minor amount of the substrate undergoes allylic amination before the allylic dearomatization/cyclization sequence (Scheme 13).

Highly enantioselective intermolecular allylic dearomatization reactions of indoles were observed to take place utilizing Ir catalysis.[28] Tryptophol and tryptamine derivatives **32** were found to react with various allylic alcohols **33** in the presence of the Carreira catalytic system {[Ir(cod)Cl]$_2$ + (S_a)-**L5**},[29] generating the corresponding furoindoline and pyrroloindoline products **34** (Scheme 14). The results of a systematic evaluation of the effects of additives revealed that Fe(OTf)$_2$ is the optimal Lewis

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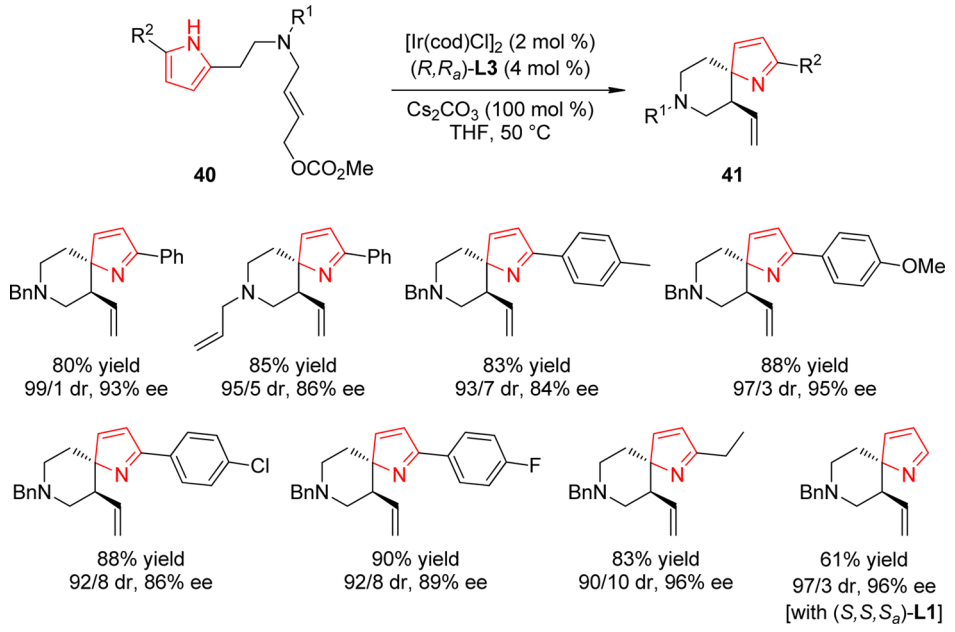
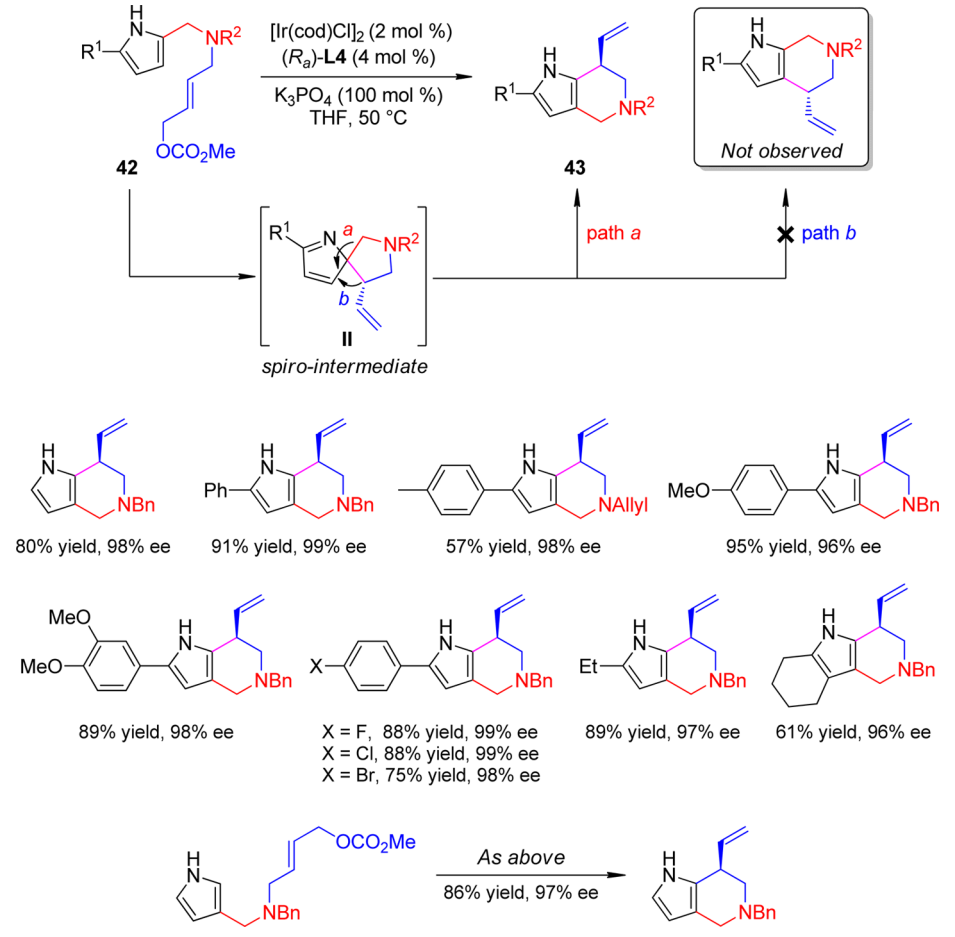
Scheme 18. Ir-Catalyzed Asymmetric Allylic Dearomatization Reaction of Pyrroles



Scheme 19. Ir-Catalyzed Asymmetric Sequential Dearomatization/Migration Reaction of Pyrroles



acid, perhaps owing to its ability to promote departure of the allylic alcohol hydroxyl group. This process is among the only limited number of examples where Ir-catalyzed asymmetric allylic substitution reactions proceed via discrimination of the enantiotopic faces of prochiral nucleophiles.[30] Remarkably different from the regular pattern seen in Ir-catalyzed asymmetric allylic substitution reactions, nucleophile attack takes place at the terminal allylic position probably as a result of steric congestion at the C3 position of **32**. In addition, the practicality and synthetic utility of this transformation was

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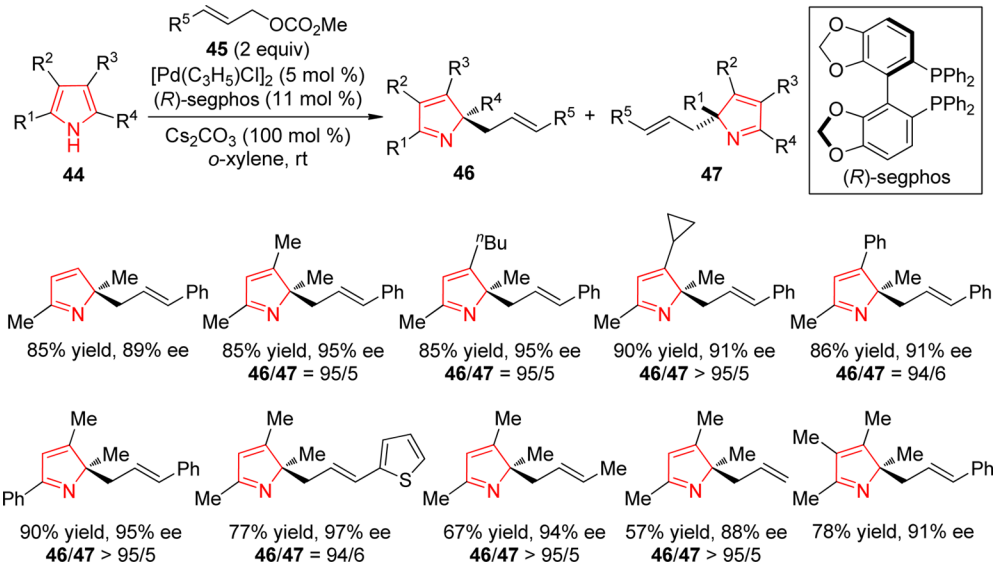
Scheme 20. Pd-Catalyzed Intermolecular Asymmetric Allylic Dearomatization Reaction of Pyrroles



demonstrated by its application in an asymmetric total synthesis of (−)-debromoflustramine B.

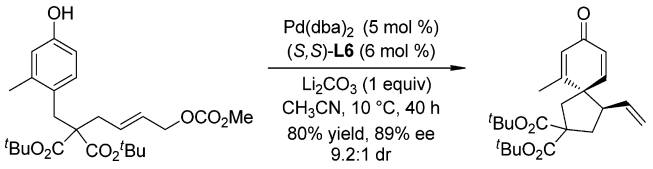
Recently, groups headed by Cook[31] and Rawal[32] have developed Pd-catalyzed allylic dearomatization reactions of indoles. Yang and co-workers[33] uncovered similar reactions that employ Et_3B as a stoichiometric promoter. High levels of enantioselectivity attend reactions promoted by using a palladium complex bearing a chiral P−olefin ligand by Liu and Du.[34] Kaiser and Yang[35] also reported an elegant example of a Pd-catalyzed enantioconvergent decarboxylative allylic alkylation reaction of allyl indolenin-3-carboxylates (Scheme 15).

Apart from studies of Ir-catalyzed asymmetric allylic dearomatization reactions of substituted indoles described above, we recently carried out an investigation that led to the development of asymmetric intramolecular Freidel−Crafts-type allylic substitution reactions of indole derivatives catalyzed by Ir complexes.[26,36] Governed by the rational design of substrates, different cyclization patterns such as C4-to-C3, C4-to-C5, and C2-to-C3, which lead to diverse polycyclic systems, were accomplished. Importantly, high to excellent regio- and enantioselectivities typically accompany reactions of a large array of substrates (Scheme 16), which produce in the case of C2-to-C3 cyclization reactions products that are identical to those obtained from the allylic dearomatization/cyclization sequences starting with indol-3-yl allyl carbonates **15**.[23]

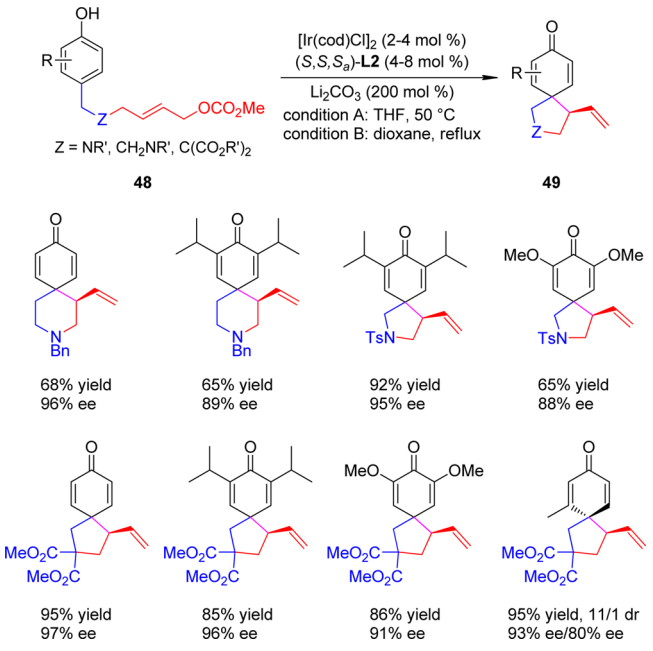
3. ASYMMETRIC ALLYLIC DEAROMATIZATION REACTIONS OF PYRROLE DERIVATIVES

As another important class of electron-rich heterocycles, pyrroles occur widely as a structural unit in biologically active natural products and pharmaceutical agents. However, owing to regioselectivity issues caused by the fact that the C2- and C3-positions of these heterocycles display similar reactivity with electrophiles,[37] relatively few regio- and enantioselective functionalization reactions of pyrroles have been devised (Scheme 17). By taking advantage of the intramolecular design strategy, we uncovered the first example of an Ir-catalyzed asymmetric allylic dearomatization reaction of pyrroles. Observations made in that effort show that highly functionalized spiro-2*H*-pyrroles **41** are formed with excellent levels of diastereoselectivity and enantioselectivity (Scheme 18).[38]

Scheme 21. Pd-Catalyzed Intramolecular Asymmetric Allylic Dearomatization Reaction of Phenols



Scheme 22. Ir-Catalyzed Intramolecular Asymmetric Allylic Dearomatization Reaction of Phenols



Recently, we found that the pyrroles **42** containing one carbon shortened tethers undergo sequential dearomatization/migration reactions to generate chiral polycyclic pyrroles **43**, which have served as popular structure cores in medicinal chemistry (Scheme 19).[23] Like analogous reactions of indoles described earlier, a novel dearomatization/migration cascade reaction pathway has been proposed for these processes.

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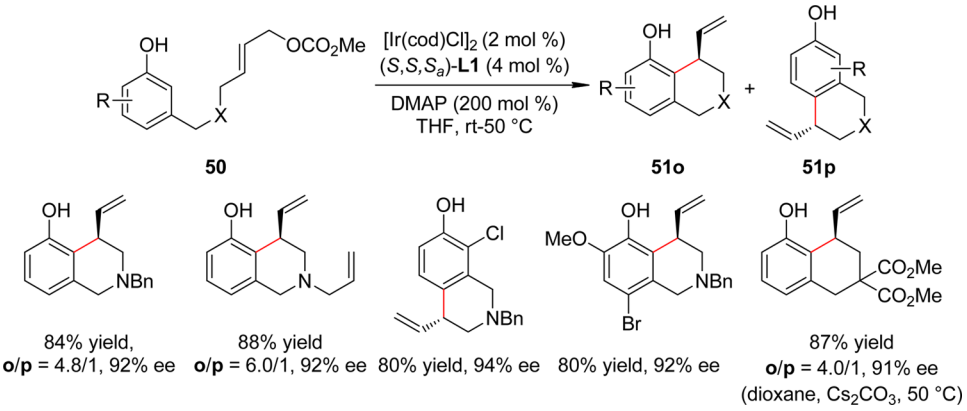
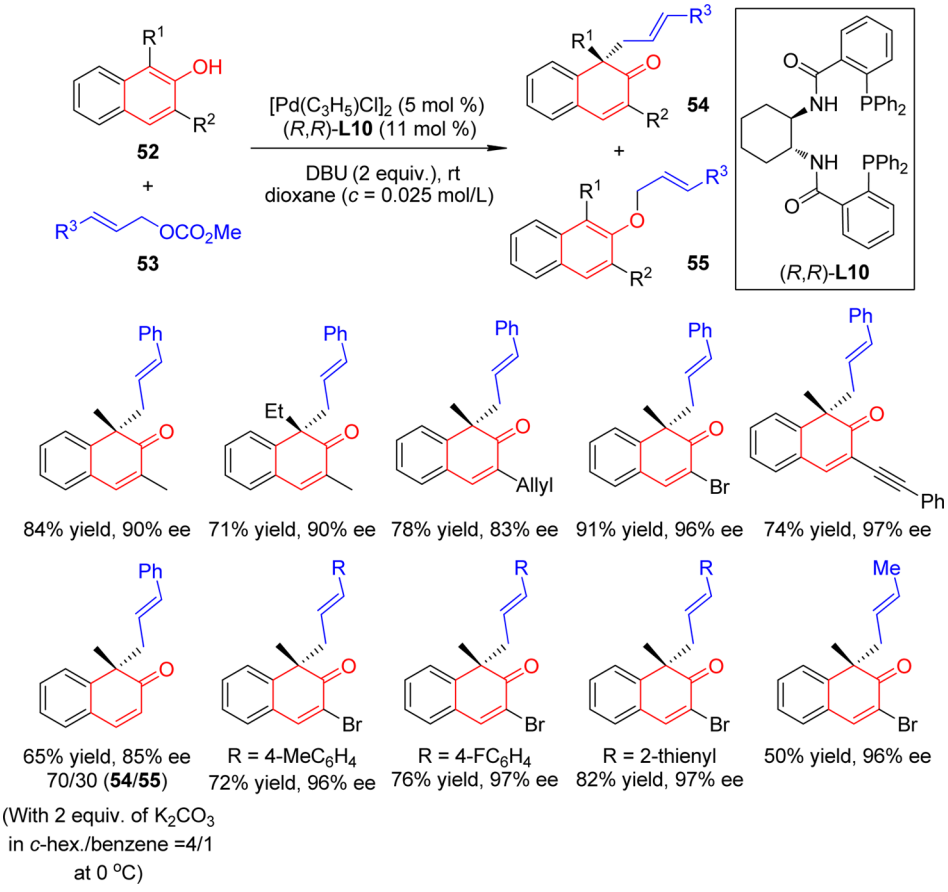
Scheme 23. Ir-Catalyzed Intramolecular Asymmetric Friedel–Crafts-Type Allylic Alkylation Reaction of Phenols



Scheme 24. Pd-Catalyzed Intermolecular Asymmetric Allylic Dearomatization Reaction of Naphthols



Notably, when the allylic carbonate tether is located at the C3 position of the pyrrole backbone, reaction occurs to form the same product that is generated by direct asymmetric allylic alkylation reaction at the C2 position.

Owing to the similar reactivities of the C2- and C3-position of pyrroles, the design of direct intermolecular asymmetric dearomatization reactions of simple substituted pyrroles is challenging and has rarely been explored. Recently, we uncovered a highly regio- and enantioselective method for the synthesis of polysubstituted 2*H*-pyrroles via Pd-catalyzed intermolecular asymmetric allylic dearomatization reactions of multisubstituted pyrroles (Scheme 20).[39] With use of commercially available palladium precursor and chiral ligand, the substituted 2*H*-pyrroles **46**, containing a chiral quaternary carbon center, are regioselectively produced in up to 97% ee and >95/5 regioselectivity. Interestingly, the reactions occur smoothly with excellent regioselectivities when the di-, tri-, and tetra-substituted pyrrole derivatives **44** are used as substrates.

4. ASYMMETRIC ALLYLIC DEAROMATIZATION REACTIONS OF PHENOL DERIVATIVES

Phenols are readily available chemical feedstocks, and as a result, they are widely used as starting materials in organic synthesis. However, the development of allylic dearomatization reactions of phenols that take place with high levels of chemoselectivity and stereoselectivity is difficult because of competition

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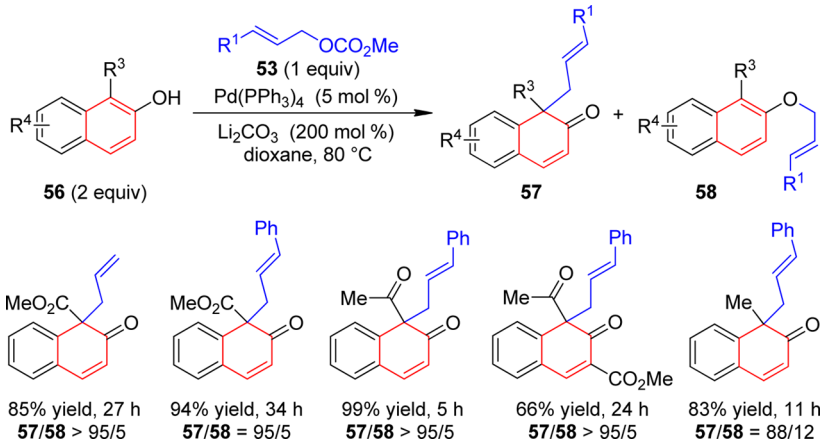
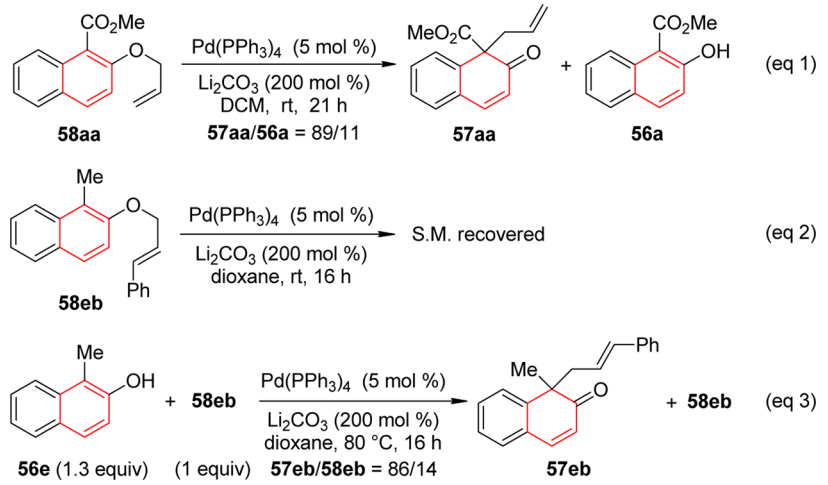
Scheme 25. Pd-Catalyzed Intermolecular Allylic Dearomatization Reactions of Simple α-Substituted β-Naphthols



Scheme 26. Mechanistic Studies



that occurs between O- and the Friedel–Crafts-type-alkylation. Compared with recently developed asymmetric dearomatization reactions of phenols that involve the use of oxidative protocols, catalytic asymmetric dearomatization reactions of these substrates under nonoxidative conditions are rare.[40]

In transition-metal-catalyzed allylic substitution reactions, phenols usually serve as oxygen nucleophiles, and only a limited number of examples of C-allylation have been observed. In 2010, Hamada and co-workers reported examples of Pd-catalyzed intramolecular dearomatization reactions of phenols.[41] This effort also uncovered an interesting and elegant example of an enantioselective process promoted by using $Pd(dba)_2$/(*S*,*S*)-**L6** as the catalyst (Scheme 21).

At the same time, we discovered that Ir-catalyzed asymmetric allylic dearomatization reactions of *para*-substituted phenol derivatives tethered with an allylic carbonate take place to form spirocyclohexadienone derivatives **49**, containing both five- and six-membered-rings, in excellent yields and enantioselectivity (Scheme 22).[42]

Interestingly, by relocating the tethered allylic carbonate to the *meta*-position of the phenol core, Ir-catalyzed asymmetric Friedel–Crafts-type allylic alkylation reactions take place[43] to give chiral tetrahydroisoquinolines **51** in moderate to excellent yields and enantioselectivity and high regioselectivity (Scheme 23).

As demonstrated by the examples presented above, taking advantage of the intramolecular design strategy enables avoidance of competitive O-alkylation reactions of phenols. Despite this feature, intermolecular asymmetric allylic dearomatization reactions of phenol derivatives are highly challenging because of chemo-, regio-, and enantioselectivity issues. Recently, the first intermolecular palladium-catalyzed asymmetric allylic dearomatization reaction of naphthols has been developed in our group.[44] By this process, β-naphthalenones **54** bearing all-carbon quaternary stereogenic centers are readily produced starting with simple aromatic naphthol derivatives **52** in good to excellent yields and excellent levels of chemo- and enantioselectivity (Scheme 24). The results show that introduction of substituents at the γ-positions of β-naphthols leads to significant increases in both chemo- and enantioselectivities of the process. The compatibility of the process with bromo-substituents enables diverse transformations.

It should be noted that the chemoselectivity displayed in reactions of substrates that do not have a substituent at the γ-position of β-naphthols is low. In addition, the allylic substituent R^1 is limited to alkyl groups, and electron-deficient substituents are not tolerated in reactions occurring under the previously developed conditions. However, we recently discovered a new catalytic system that enables the dearomatization reaction to have a larger substrate scope. Specifically, we observed that $Pd(PPh_3)_4$ is an efficient catalyst for the allylic dearomatization reactions of a wider variety of α-substituted-β-naphthol substrates **56** (Scheme 25).[45]

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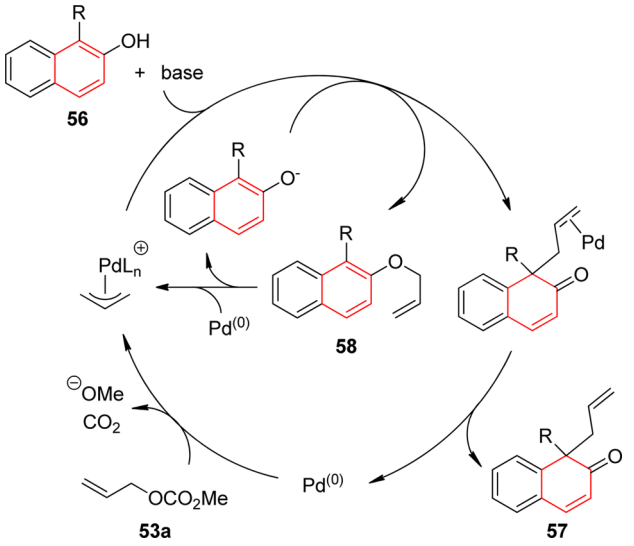
Scheme 27. A Plausible Mechanistic Pathway



Observations made in mechanistic studies of this process show that the etherification product **58aa** is converted to **57aa** and **56a** in the presence of the palladium catalyst (eq 1, Scheme 26). In addition, enone **58eb** is not transformed to **57eb** under the reaction conditions, and under more forcing reaction conditions, **58eb** is converted to **57eb** in 86% conversion (eqs 2 and 3, Scheme 26).

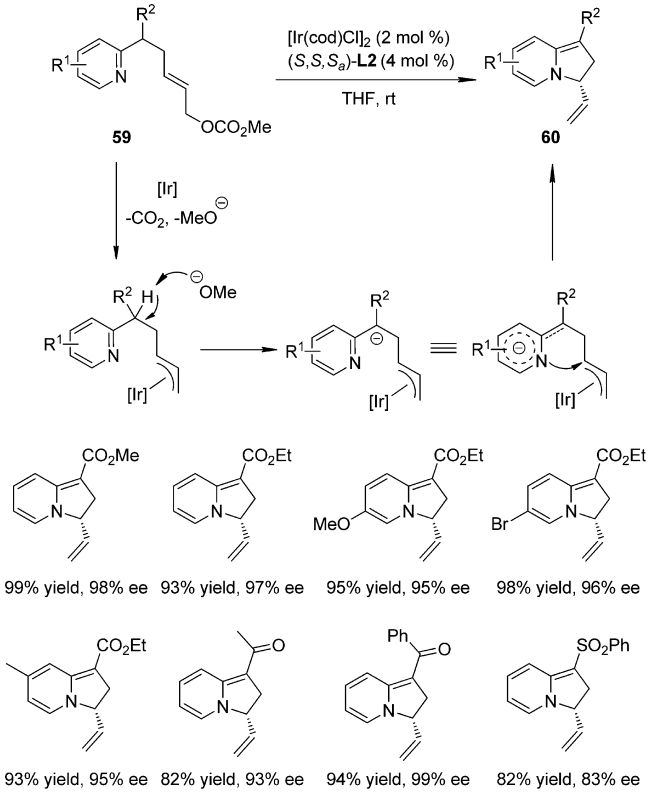
On the basis of the findings arising from these experiments, we have proposed a plausible mechanism for this reaction outlined in Scheme 27. In the pathway, the π-allyl palladium species initially formed via oxidative addition of allylic carbonate **53a** to Pd(0) undergoes nucleophilic attack of **56** to form **57** and **58**. The allyl ether **58** formed in this manner is then converted to π-allyl palladium species through oxidative addition to Pd(0), which then undergoes nucleophilic attack of **56** to form **57**.

5. ASYMMETRIC ALLYLIC DEAROMATIZATION REACTIONS OF PYRIDINE AND PYRAZINE DERIVATIVES

In addition to electron-rich arenes such as indole, pyrrole, and phenol derivatives, electron-deficient heteroarenes such as pyridines and pyrazines also serve as nucleophiles in Ir-catalyzed asymmetric allylic dearomatization reactions (Scheme 28).[46] In reactions of pyridine substrates **59**, deprotonation of the acidic α-H of the formed π-allyl iridium intermediate gives an enamine type species that serves as an N nucleophile in the allylic substitution reaction. Alternatively, the reaction could also proceed by initial N-alkylation followed by isomerization to generate an enamine that reacts to produce the dearomatized product. By using this strategy, we designed various pyridine tethered allylic carbonates that undergo dearomatization reaction to produce dihydroindolizine derivatives in excellent yields and levels of enantioselectivity. Notably, no additional base is required in this reaction. The dearomatization products **60** generated in these reactions can be employed in Diels–Alder reactions as part of routes for the synthesis of enantioenriched multifunctionalized bridge–ring compounds **61** (Scheme 29).

Utilizing a similar substrate design, Ir-catalyzed asymmetric allylic dearomatization reactions of pyrazines have also been developed. These processes produce 6,7-dihydropyrrolo[1,2-*a*]-pyrazine derivatives in excellent yields and levels of enantioselectivity

Scheme 28. Ir-Catalyzed Asymmetric Allylic Dearomatization Reaction of Pyridines



(Scheme 30). These observations have not only expanded the scope of the allylic dearomatization reaction but also opened a new avenue for the design of new dearomatization reactions of electron-deficient nitrogen-containing heteroarenes.

6. SUMMARY

As can be seen by viewing the results presented above, we have developed novel direct asymmetric allylic dearomatization reactions of various types of aromatic compounds. The overall process serves as a straightforward method for the construction of various enantioenriched and highly functionalized ring structures. Ir, Pd, and Ru complexes are found to be suitable catalysts for the process and the compatible arenes uncovered thus far include indoles, pyrroles, phenols, naphthols, pyridines, and pyrazines. The process serves as a step-economical and powerful method to convert readily available planar aromatic compounds to three-dimensionally complex products. The catalytic systems discovered that promote the transition-metal-catalyzed allylic substitution reactions provide an excellent platform for the introduction of chiral ligands that direct asymmetric variants of dearomatizations process. This is a significant feature because, despite the great potential of catalytic asymmetric allylic dearomatization reactions, developments in this field are still in their infancy. For example, until now the Ir/phosphoramidite ligand system was still the most widely used catalyst to promote asymmetric allylic dearomatization reactions because it provides a structurally well-defined chiral environment in the key transition state in the catalytic cycle. However, the catalytic activity is not sufficiently high for synthetic purposes, especially in the case of intermolecular reactions. In a complementary manner, although the number of examples is limited, Pd-based catalytic systems exhibit

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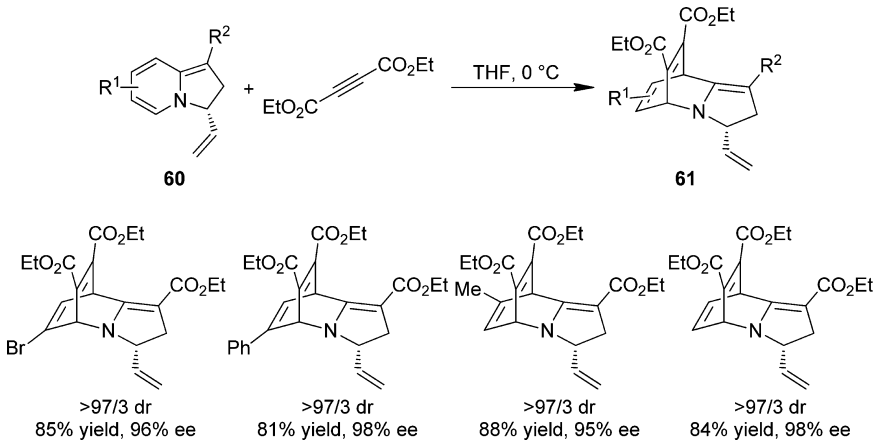
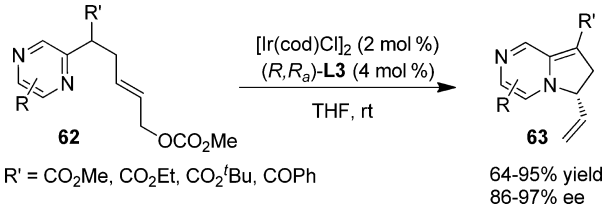
Scheme 29. Diels–Alder Reactions of Dearomatized Products



Scheme 30. Ir-Catalyzed Asymmetric Allylic Dearomatization Reaction of Pyrazines



enhanced activity and levels of stereochemical control in intermolecular asymmetric allylic dearomatization reactions. On the other hand, Ru complexes have been recently identified to be highly effective catalysts for the allylic dearomatization reactions in which allylic alcohols can be employed as the starting materials, water being the sole byproduct. Despite the fact that highly enantioselective reactions have not been developed, the use of Ru catalysts is a potential direction for future developments in this area if appropriate chiral ligands can be uncovered. It should be noted that related propagylic dearomatization reactions have been disclosed very recently.[47] Therefore, the development of highly enantioselective variants of these reactions also represents a significant future goal. With the addition of more catalytic systems to the list of promoters of asymmetric allylic dearomatization reactions, it is quite reasonable to believe that these processes will evolve into reliable and routine organic synthetic methods.

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Notes

The authors declare no competing financial interest.

Biographies

Chun-Xiang Zhuo was born in Fujian, China, in 1986. He graduated from Hunan University in 2009 with a B.Sc. in chemistry. Then he joined Professor Shu-Li You's group at the Shanghai Institute of Organic Chemistry (SIOC) as a Ph.D. student. His current work focuses on transition-metal-catalyzed allylic dearomatization reactions.

Chao Zheng was born in 1985 in Hubei, China, and received his B.Sc. degree in chemistry from Shanghai Jiao Tong University in 2007. He obtained his Ph.D. degree at the Shanghai Institute of Organic Chemistry under the supervision of Prof. Shu-Li You and Prof. Yu-Xue Li in 2012. Then he joined Prof. Shu-Li You's group as an Assistant Professor. His current work is focused on understanding reaction mechanisms through computational methods.

Shu-Li You received his B.Sc. in chemistry from Nankai University in 1996 and a Ph.D. from the Shanghai Institute of Organic Chemistry (SIOC) in 2001 under the supervision of Prof. Li-Xin Dai. He carried out postdoctoral studies with Prof. Jeffery W. Kelly at The Scripps Research Institute, and from 2004 he worked at the Genomics Institute of the Novartis Research Foundation as a Principal Investigator before returning to SIOC in 2006. His research interests include asymmetric catalysis, synthetic methodology, natural product synthesis, and medicinal chemistry.

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