

Iridium-Catalyzed Intermolecular Asymmetric Hydroheteroarylation of Bicycloalkenes

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Supporting Information

ABSTRACT: Catalytic hydroarylation of alkenes is a desirable process because it can occur under neutral conditions with regioselectivity complementary to that of acid-catalyzed reactions and stereoselectivity derived from the catalyst. We report an intermolecular asymmetric addition of the C–H bonds of indoles, thiophenes, pyrroles, and furans to bicycloalkenes in high yield with high enantiomeric excess. These heteroarene alkylations occur ortho to the heteroatom. This selectivity is observed even with unprotected indoles, which typically undergo alkylation at the C3 position. Initial mechanistic studies revealed that oxidative addition of a heteroarene C–H bond to a neutral Ir^I species occurs within minutes at room temperature and occurs in the catalytic cycle prior to the turnover-limiting step. Products from syn addition of the C–H bond across the olefin were observed.

Arene and heteroarene alkylation is one of the most fundamental transformations in synthetic chemistry. The Friedel–Crafts reaction is the most common method for arene alkylation, but this reaction often generates stoichiometric quantities of waste, forms byproducts from isomerization of intermediate carbocations, and occurs without control of the stereochemistry of the product.¹ Metal-catalyzed additions of aromatic C–H bonds across alkenes to form alkyl arenes can occur under conditions that are milder than those of classical methods² with site selectivity complementary to that of acid-catalyzed reactions and with enantioselectivity.³ Thus, many groups have sought catalysts for regioselective and enantioselective hydroarylation of alkenes.

Additions of heteroaryl C–H bonds are particularly valuable because of the importance of heteroarenes in biologically active structures⁴ and materials applications.⁵ Recently, the Shibata group reported the hydroarylation of *N*-acyl indoles, which is one of the few cases of intermolecular alkene hydroheteroarylation with selectivity complementary to that of Friedel–Crafts alkylation.⁶ However, the reactions reported by Shibata require a directing group on the indole nitrogen and occur with low enantioselectivities. No systems for asymmetric intermolecular hydroheteroarylation of unconjugated alkenes with high enantioselectivity have been reported.⁷

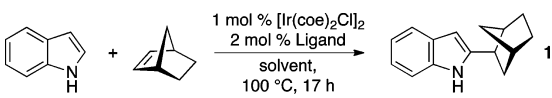
Here we report enantioselective, Ir-catalyzed additions of the C–H bonds of indoles, thiophenes, pyrroles, and furans across bicycloalkenes. These reactions form a single constitutional isomer in both high yield and high enantioselectivity.

Mechanistic studies showed that the addition of the heteroaryl C–H bond to Ir is rapid and occurs before turnover-limiting insertion of the alkene.

Our observation of asymmetric hydroheteroarylation of bicycloalkenes stemmed from our recent work on Ir-catalyzed additions of N–H bonds of amides and sulfonamides to alkenes.⁸ While investigating potential hydroaminations involving alkenes and heteroaryl N–H bonds, we observed the addition of heteroaryl C–H bonds across alkenes. We then evaluated a range of Ir catalysts for potential asymmetric hydroheteroarylations.

The results of reactions of indole with norbornene (nbe) catalyzed by combinations of [Ir(coe)₂Cl]₂ (coe = cyclooctene) with a series of bisphosphine ligands under a range of conditions are summarized in Table 1. Ir complexes of Segphos were more

Table 1. Development of the Ir-Catalyzed Enantioselective Addition of Indole to Norbornene^a



entry	Ligand	[indole] (M), solvent	equiv NBE	%conv ^b	%yield ^b	%ee ^c
1	(<i>R</i>)-Binap	0.75, PhMe	1.2	23	22	43
2	(<i>R</i>)-MeOBiphep	0.75, PhMe	1.2	33	30	56
3	(<i>S</i>)-Segphos	0.75, PhMe	1.2	53	48	60
4	(<i>S</i>)-DTBM-MeOBiphep	0.75, PhMe	1.2	65	63	90
5	(<i>S</i>)-DTBM-Segphos ^c	0.75, PhMe	1.2	80	70	96
6	dcpm ^d	0.75, PhMe	1.2	64	60	—
7	(<i>S</i>)-DTBM-Segphos	0.75, Heptane	1.2	100	85	97
8	(<i>S</i>)-DTBM-Segphos	0.75, MTBE	1.2	100	87	96
9	(<i>S</i>)-DTBM-Segphos	0.75, THF	1.2	100	94	96
10	(<i>S</i>)-DTBM-Segphos	0.75, <i>m</i> -Xylene	1.2	87	79	96
11	(<i>S</i>)-DTBM-Segphos	1.50, THF	1.2	62	44	93
12	(<i>S</i>)-DTBM-Segphos	0.60, THF	1.2	100	97	96
13	(<i>S</i>)-DTBM-Segphos	0.75, THF	2.2	61	58	94
14	(<i>S</i>)-DTBM-Segphos	0.75, THF	4.0	38	33	90

^aReactions were performed with 0.2 mmol of indole. ^bDetermined by GC analysis. ^cDetermined by HPLC analysis using a chiral stationary phase. ^ddcpm = bis(dicyclohexylphosphino)methane.

reactive than complexes of MeOBiphep and Binap (entries 1–3), suggesting that a small dihedral angle in the ligand is important for generating a more active and selective catalyst. In a similar vein, substantial yields were obtained from reactions catalyzed by Ir complexes of one-carbon methylene-bridged bisphosphines (entry 6), whereas no addition product was observed from

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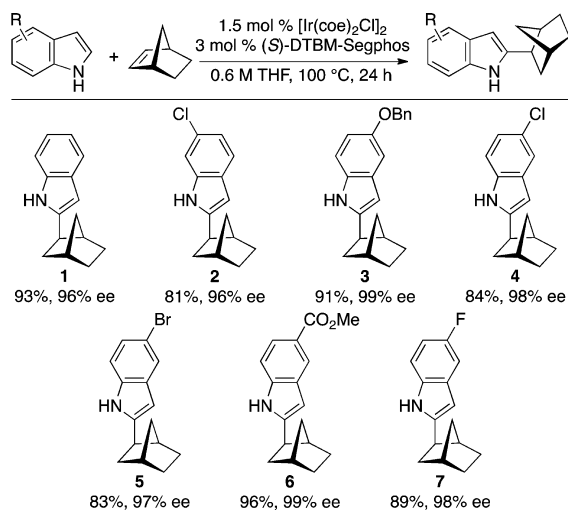
reactions catalyzed by complexes containing analogous two- or three-carbon-bridged phosphines. An increase in the steric bulk from the parent Segphos ligand to the DTBM-Segphos (DTBM = 3,5-di-*tert*-butyl-4-methoxy) derivative led to an increase in the yield and enantiomeric excess (ee) of **1** (entry 5). These reactions constitute the first enantioselective intermolecular additions of indoles across alkenes at the non-nucleophilic C2 position with high ee.

The solvent had a pronounced effect on the yields of the reaction of indole with nbe catalyzed by $[\text{Ir}(\text{coe})_2\text{Cl}]_2$ and (*S*)-DTBM-Segphos. Reactions conducted in relatively nonpolar aliphatic solvents proceeded with complete consumption of the starting material (Table 1, entries 7 and 8). However, the reaction yields were lower than the conversions by 10–15% in these solvents because of the formation of a side product from oxidative dimerization of the heteroarene starting material.⁹ The reactions conducted in coordinating solvents (e.g., acetonitrile, dimethylformamide, and dimethyl sulfoxide) did not occur, presumably because of competitive binding of these solvents to the Ir catalyst. However, full conversion and high product yields were observed when the reaction was conducted in the moderately polar solvent tetrahydrofuran (THF) (entry 9).

The amount of nbe and indole affected the rate and enantioselectivity of the reaction. Reactions conducted with an excess amount of nbe were significantly slower than those conducted with 1.2 equivalents of nbe (entries 14 vs 9), and the ee of the product of the reaction with 4 equiv of nbe was lower (90% ee) than that of the reaction conducted with 1.2 equiv of nbe. Reactions with a lower 0.6 M concentration of indole formed the hydroarylation product **1** in 97% yield with no detectable amount of product from indole homocoupling (entry 12).

The scope of the Ir-catalyzed addition of indoles to nbe by this procedure is summarized in Chart 1. High yields and ee's were obtained from the reactions of indoles possessing electron-donating or electron-withdrawing substituents. Halides, protected alcohols, and esters were tolerated under the reaction conditions. The 2-substituted indole located at the exo position

Chart 1. Ir-Catalyzed Enantioselective Addition of Indoles to Norbornene^a



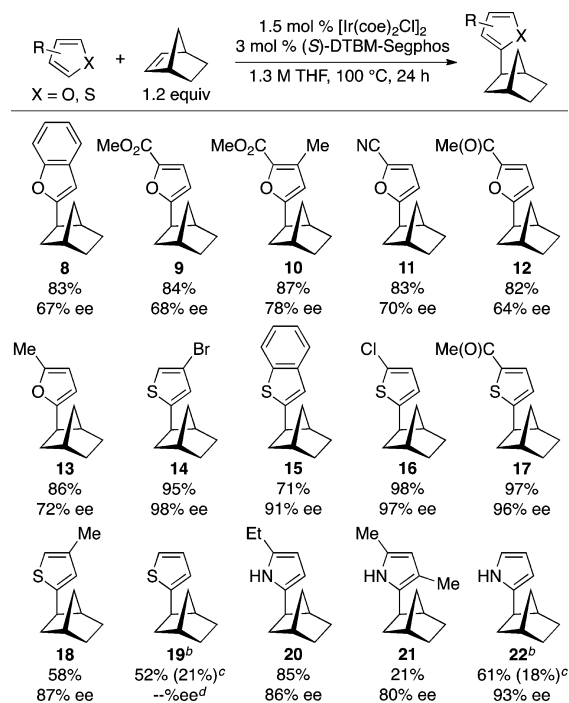
^aReactions were performed with 0.5 mmol of indole and 1.2 equiv of nbe. Isolated yields are reported. The ee's were determined by HPLC analysis using a chiral stationary phase.

of the bicycloalkane was the exclusive isomer formed. Indoles bearing chloride and bromide substituents underwent oxidative homocoupling to a greater extent than did the other indoles studied, but the yields of the addition products remained high.

The absolute stereochemistry of ester-substituted **6** was determined to be 2*R* by single-crystal X-ray analysis with a copper radiation source. The solid-state analysis also confirmed that the indole was connected at C2. Thus, these reactions occur at the C2 position of the indole without a protecting or directing group on nitrogen.

The scope of the hydroheteroarylation process extends to furans, thiophenes, and pyrroles, as summarized in Chart 2.

Chart 2. Ir-Catalyzed Enantioselective Addition of Furans, Thiophenes, and Pyrroles to Norbornene^a



^aReactions were performed with 0.4 mmol of heteroarene and 1.2 equiv of nbe. Isolated yields are reported. The ee's were determined by HPLC analysis using a chiral stationary phase. ^bThe reaction was performed with 0.9 equiv of nbe relative to heteroarene. ^cYield of the 2,5-dialkylated product. ^dThe ee could not be determined because the signals of the mono- and dialkylated products overlapped.

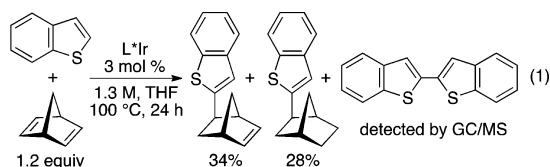
These heteroarenes did not undergo oxidative homocoupling reactions under the catalytic conditions. Therefore, the rates could be increased without a reduction in yield by running the reactions at concentrations higher than those for the reactions of indoles (see the Supporting Information for reaction development).

The reactions of substituted thiophenes and pyrroles formed products from alkylation at the 2-position in high yield with excellent ee. Reactions of thiophenes substituted at the 2- or 3-position with alkyl groups or ketone and halogen functionality occurred in high yield and ee. Reactions of pyrrole and a 2-alkylpyrrole occurred in high yield and enantioselectivity. However, the reactions of 2-acetylpyrrole or methyl pyrrole-2-carboxylate did not form detectable amounts of product, most likely because the substrate or product chelates to the Ir center through the nitrogen and oxygen atoms. The reactions of *N*-

methyl- and *N*-phenylpyrrole also formed the corresponding products in only trace amounts, in this case because the substituent leads to steric hindrance at the 2-position. This steric influence also leads to a lower yield for the reaction of 2,4-dimethylpyrrole (**21**) than for 2-ethylpyrrole.

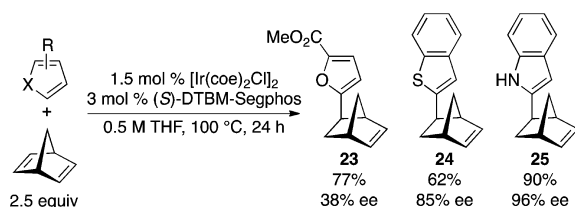
The reactions of furans also formed products in good yield. Although the enantioselectivity was lower than in the reactions of thiophenes and pyrroles, a broad range of functional groups that can undergo further transformations (e.g., esters, ketones, and nitriles) were tolerated by the hydroheteroarylation reaction.^{10,6}

The scope of the hydroheteroarylation also encompasses the addition of the C–H bonds of heteroarenes to norbornadiene (nbd). However, some modification of the reaction conditions was needed to obtain good yields of the product from addition to the diene. The reactions of nbd conducted under the same conditions as the reactions of nbe with thiophenes and furans gave a significant amount of product from heteroarene oxidative homocoupling. Moreover, the equivalent of hydrogen formed by oxidative coupling led to the formation of substituted norbornanes via reduction of the substituted norbornenes, and the two classes of products could not be separated (eq 1).



Thus, the reaction conditions were modified to reduce the amount of product formed by homocoupling of the heteroarene. The reactions were conducted at a heteroarene concentration of 0.5 M instead of 1.3 M, and 2.5 equiv of the alkene was used instead of 1.2 equiv (Chart 3). Under these modified conditions,

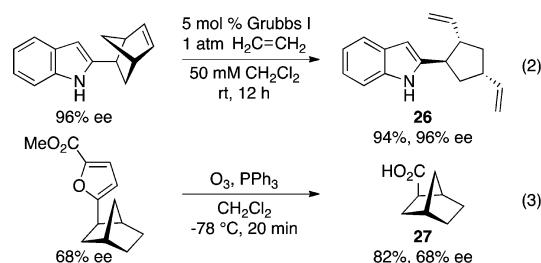
Chart 3. Ir-Catalyzed Enantioselective Addition of Heteroarenes to Norbornadiene^a



^aReactions were performed with 1.0 mmol of heteroarene and 2.5 equiv of nbd. Isolated yields are reported. The ee's were determined by HPLC analysis using a chiral stationary phase.

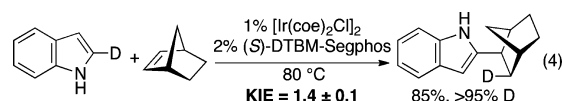
the products of the addition of indoles and thiophenes to nbd were formed in high yields with excellent ee. Like the reactions of furans with nbe, the reaction of methyl 2-furoate with nbd occurred in high yield but with low ee. The origin of the low enantioselectivity in the reactions of furans is unknown at this time. No products from additions of the heteroarenes to α -olefins such as 1-octene or styrene were obtained under the conditions for the additions to nbe and nbd.

The products of asymmetric hydroheteroarylation of bicycloalkenes can be elaborated to chiral, enantioenriched building blocks. Ring-opening metathesis of **26** with ethylene formed the highly functionalized cyclopentane **27** as a single diastereomer with no erosion of ee (eq 2). Oxidation of the furan in **9** led to the alkyl carboxylic acid, also with no erosion of ee (eq 3). Finally, the compatibility of the catalyst with a broad range of



halides, ketones, esters, and nitriles allows further transformations to be conducted on the addition products.

Initial mechanistic studies of the addition reactions of heteroarenes across bicycloalkenes were conducted by deuterium labeling and by studying the individual steps of the process. The reaction of nbe with 2-D-indole formed *syn*-deutero-(indolyl)norbornane (eq 4). This relative stereochemistry



implies that the hydroheteroarylation occurs by a mechanism involving olefin insertion into an Ir–C or Ir–H bond. Comparison of the initial rates for the addition of 2-H- and 2-D-indole to nbe in separate vessels revealed a kinetic isotope effect (KIE) of 1.4. This small but greater than unity KIE could result from reversible addition of the indole C–H bond to the Ir center prior to the turnover-limiting step.

To probe whether cleavage of the C2–H bond occurs prior to the turnover-limiting step, reactions of 2-H- and 2-D-indole with nbe under the catalytic conditions were followed by ¹H and ²H NMR spectroscopy. Illustrative spectra are shown in Figure 1.

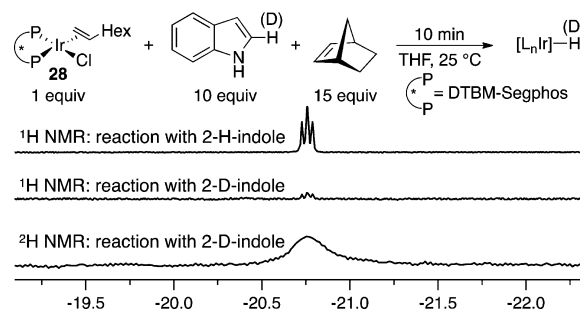


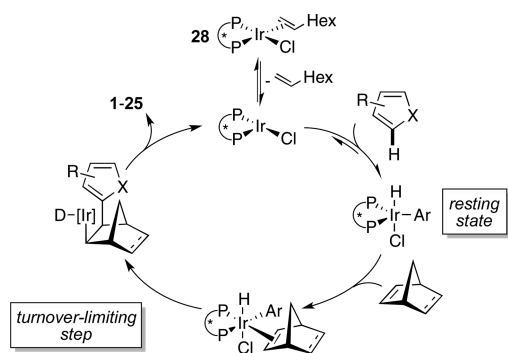
Figure 1. Comparison of the hydride regions of the ¹H and ²H NMR spectra of the resting-state Ir complex under catalytic conditions with 2-H-indole and 2-D-indole.

The combination of indole, nbe, and Ir–bisphosphine complex **28**, which was formed from 1-octene, DTBM-Segphos, and [Ir(coe)₂Cl]₂, formed a light-yellow solution (from the initial red solution) within 10 min at room temperature. A doublet-of-doublets hydride resonance at –20.8 ppm was observed by ¹H NMR spectroscopy. A similar experiment with 2-D-indole gave rise to an Ir–deuteride resonance at –20.8 ppm in the ²H NMR spectrum and a much smaller hydride resonance in the ¹H NMR spectrum. No hydroheteroarylation products were detected after 24 h at room temperature. These data indicate that C–H activation occurs at the 2-position of indole at temperatures below those required for catalytic turnover.

Because oxidative addition at the C2 position of indole occurs much faster than the overall catalytic cycle, the turnover-limiting

step likely follows the C–H cleavage process. Because reductive eliminations to form carbon–carbon bonds from an Ir center are rare or unknown, we propose that the C–H bond addition reaction is followed by insertion of the alkene into the Ir–C bond and C–H bond-forming reductive elimination, as illustrated in Scheme 1. For the product to form by insertion of the alkene into the Ir–H bond, C–C bond-forming reductive elimination must occur from an alkyliridium aryl intermediate.

Scheme 1. Proposed Catalytic Cycle



In summary, we have reported examples of intermolecular asymmetric additions of the C2–H bonds of indoles, thiophenes, pyrroles, and furans to bicycloalkenes. The additions of indoles, thiophenes, and pyrroles occurred in high yields with high ee's. Alkylation of the heteroarene occurs at the C–H bond adjacent to the heteroatom by the transition-metal catalyst, even for indoles, which typically undergo alkylation at C3. The neutral catalyst that we have developed for this reaction tolerates a broad range of functional groups, which can be elaborated to form additional enantioenriched products. Initial mechanistic studies of the identity of the catalyst resting state and the measured KIE demonstrated that heteroarene C–H bond oxidative addition to an Ir^I species occurs prior to the turnover-limiting step. Efforts to extend the scope of the enantioselective reactions to encompass unstrained alkenes are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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