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Recent Advances in Iridium-Catalyzed Alkylation of C−H and N−H Bonds

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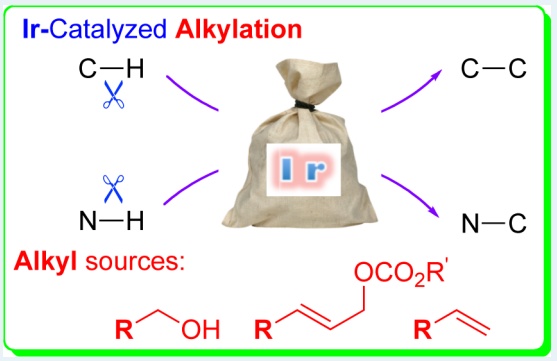
ABSTRACT: Over the past few years, iridium complexes have been widely used in the direct functionalization of unactivated bonds. In the presence of iridium catalysts, inactive C−H and N−H bonds have been transformed into C−C and N−C bonds in dehydrative alkylation using alcohols, allylation using allyl carbonates, and alkylation using alkenes. Enantioselective variants of some reactions have also been reported.



KEYWORDS: *iridium, alkylation, alcohols, carbonates, alkenes*

INTRODUCTION

C−H and N−H bonds are ubiquitous in organic compounds, and their direct functionalization is a fascinating transformation in organic synthesis.[1,2] Thus, synthetic protocols that begin with inactive C−H and N−H bond cleavage have attracted much attention from both academia and industry. To date, various transition-metal catalysts (Pd, Rh, Ru, Cu, Fe, etc.) have been reported to catalyze the direct functionalization of C−H and N−H bonds.[3−6]

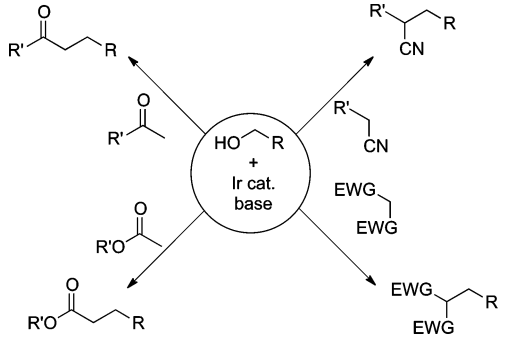
On the other hand, iridium complexes are relative newcomers in this research area.[7] Since Maitlis first reported that an iridium dihydride complex could be prepared from $[Cp^*IrCl_2]_2$ and an alcohol,[8] iridium-catalyzed dehydrative alkylation has played an important role in the area of C−C and N−C bond formation.[9−13] Iridium complexes have also been shown to be efficient catalysts for the allylation of C−H and N−H bonds with allyl carbonates and their analogues. However, many difficulties, such as the control of regio- and enantioselectivity, remain unsolved.[14] More recently, several iridium complexes have been shown to have high catalytic activity in the direct formation of C−C and N−C bonds initiated by the oxidative cleavage of C−H and N−H bonds.

The aim of this perspective is to better understand the recent development of several iridium-catalyzed alkylations for C−C and N−C bond formation.

DEHYDRATIVE ALKYLATION OF C−H AND N−H BONDS WITH ALCOHOLS

The Ir-catalyzed dehydrative alkylation of compounds possessing an acidic proton, such as ketones,[15−19] esters,[20] malonates,[21−25] and benzyl nitriles,[26−30] using alcohols has been comprehensively studied (Scheme 1). However, the direct alkylation of nonacidic C−H bonds, such as aromatic or heteroaromatic C−H bonds, with alcohols has scarcely been reported. In 2007, Grigg observed the high catalytic activity of transition metal complexes, especially $[Cp^*IrCl_2]_2$, in the alkylation of the C3-position of indole (Scheme 2).[31] The reaction proceeded with 2.5 mol % $[Cp^*IrCl_2]_2$ in the presence of KOH (20 mol %). Indole was readily alkylated with benzyl, 3-pyridylmethyl, and isopropyl alcohols to give a variety of 3-alkylindoles in low to good yield. The alkylation of indoles with electron-donating or -withdrawing groups also proceeded.

Scheme 1. Ir-Catalyzed Dehydrative Alkylation Using Alcohols



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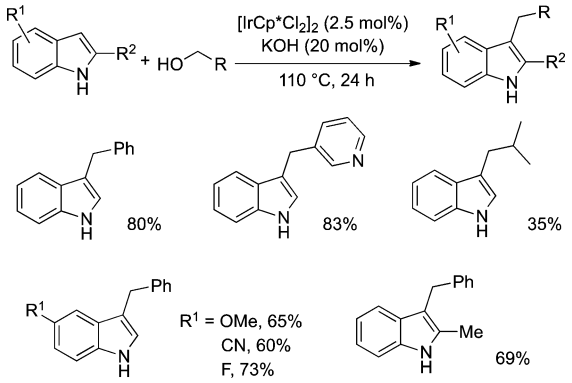
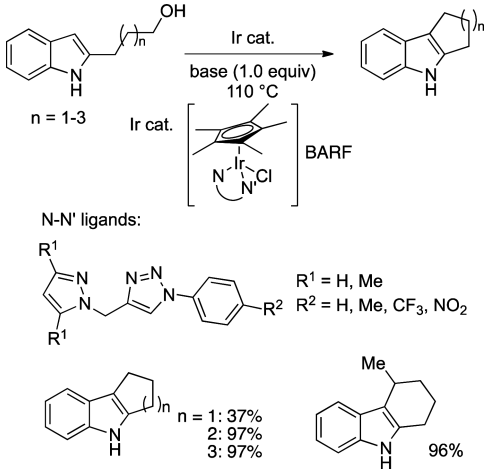
Scheme 2. Intermolecular Alkylation of Indole with Alcohols



Recently, Messerle reported a series of Ir(III) pyrazolyl-1,2,3-triazolyl complexes as catalysts for the intramolecular C3-alkylation of indoles for the synthesis of tricyclic compounds (Scheme 3).[32] The reaction conditions were similar to those of

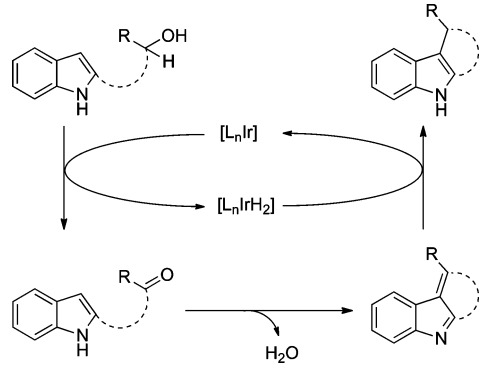
Scheme 3. Intramolecular Alkylation of Indoles with Alcohols



the intermolecular reaction reported by Grigg. Ir(III) pyrazolyl-1,2,3-triazolyl complexes showed higher catalytic activity than $[Cp^*IrCl_2]_2$, and a variety of indole derivatives fused with a five to seven-membered ring system were obtained in high yield.

A possible mechanism for the C3-alkylation of indoles with alcohols by an iridium complex-based system is illustrated in Scheme 4. The dehydrogenative oxidation of an alcohol gives an

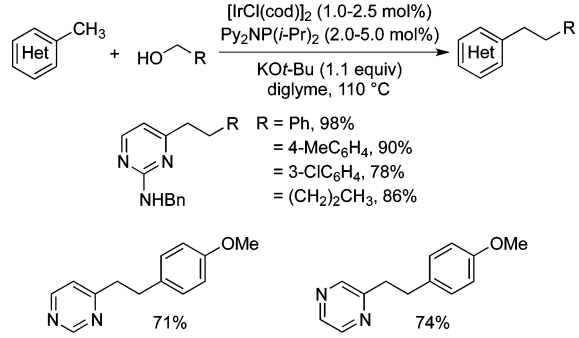
Scheme 4. Mechanism of Alkylation of Indole with Alcohols



aldehyde and an iridium dihydride complex. The subsequent base-mediated cross-aldol condensation and hydrogenation of the double bond provide the 3-alkylindole.

C−C bond-forming reactions along with dehydration catalyzed by iridium complexes have been extended to alkylation of the sp^3 C−H bond. In 2010, Kempe reported the alkylation of a methyl group on pyrimidine and pyrazine using various alcohols (Scheme 5).[33] The reaction was

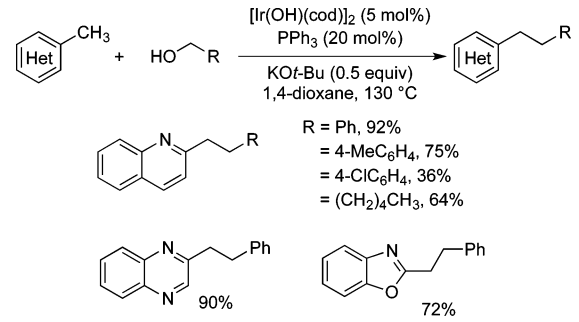
Scheme 5. Alkylation of Methyl-*N*-heteroaromatics Reported by Kempe



examined at 110 °C in the presence of an iridium complex (1.0−2.5 mol %) bearing a P,N-type ligand and KO*t*-Bu (1.1 equiv), and the desired products were obtained in yields of 33−98%. Aliphatic alcohols could also be used as substrates. A range of methyl-substituted heteroaromatic substrates, such as pyrimidine, pyrazines, pyridazines, and pyridines, were tolerated in this transformation.

Recently, Obora reported a more versatile method for the preparation of various alkylquinolines from 2-methylquinoline and alcohols in the presence of an $[Ir(OH)(cod)]_2$-PPh_3 catalyst with a base (Scheme 6).[34] Benzyl alcohols with

Scheme 6. Alkylation of Methyl-*N*-heteroaromatics Reported by Obora



electron-donating and electron-withdrawing groups and aliphatic alcohols were used as alkylating agents. This catalytic system was successfully extended to reactions of various heteroaromatic compounds.

Dehydrative alkylation using alcohols is also a common protocol for the synthesis of N-alkylated amines.[35−41] In 2009, Kempe used a P,N-ligand-coordinated iridium complex as an efficient catalyst for the selective monoalkylation of (hetero)-aromatic amines (Scheme 7).[42] This reaction proceeded under mild reaction conditions, and nearly quantitative conversion was observed at 70 °C, with a catalyst loading as low as 0.05 mol % iridium. The high selectivity of this catalyst for the

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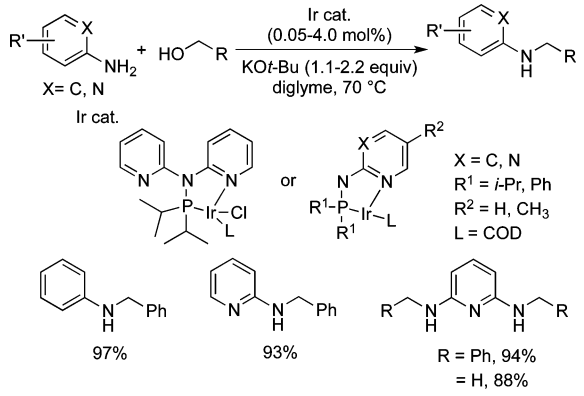
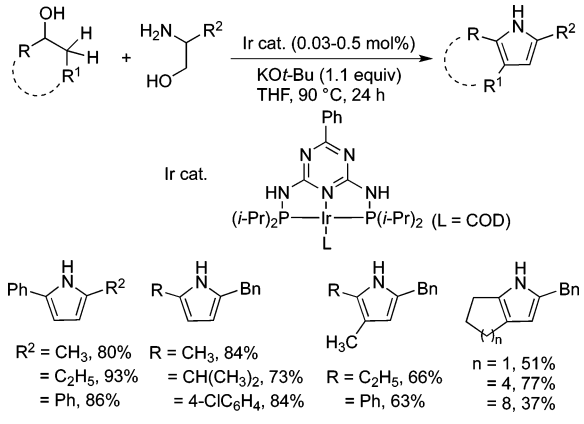
Scheme 7. Alkylation of Amines Using Ir Complex Possessing P,N-Ligands



monoalkylation of aromatic amino functions has been successfully exploited for the alkylation of diamines in both symmetric and unsymmetric fashions, providing a novel and very efficient synthetic tool for the preparation of N,N′-dialkylated aromatic diamines. Encouraged by these results, Kempe further synthesized a series of new iridium complexes containing anionic P,N-ligands.[43,44] These complexes were investigated as efficient catalysts for amine alkylation and resulted in a highly active catalyst for the selective monoalkylation of anilines with primary alcohols under mild reaction conditions.

More recently, Kempe described a new type of P,N-ligand-coordinated iridium complex as an efficient catalyst for the pyrrole synthesis (Scheme 8).[45] The selective dehydrative

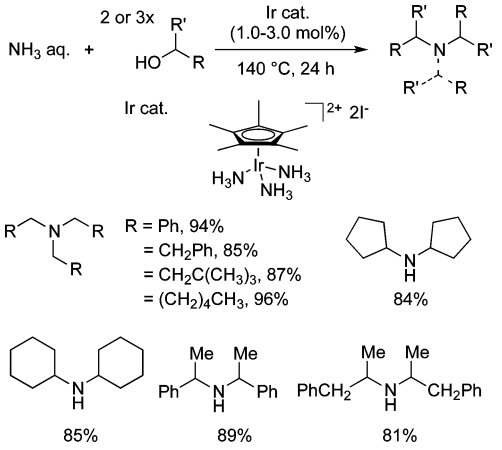
Scheme 8. Consecutive Alkylations of N−H and C−H Bonds for Pyrrole Synthesis



alkylation of N−H bond of amino alcohols with secondary alcohols along with the intramolecular dehydrative C−C bond formation afforded pyrrole derivatives possessing various functional groups.

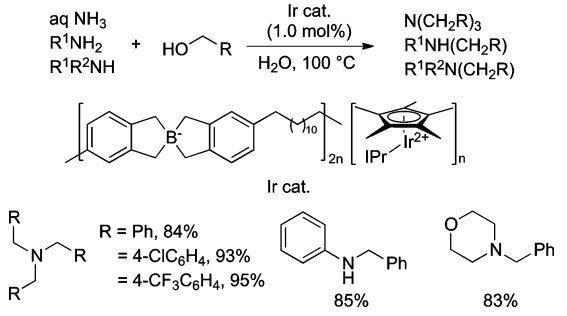
In 2010, Yamaguchi described a novel water-soluble Cp*Ir−ammine complex for the dehydrative alkylation of aqueous ammonia (Scheme 9).[46] A variety of tertiary and secondary amines were obtained in moderate to high yield by the multialkylation of aqueous ammonia with theoretically equivalent amounts of primary and secondary alcohols. This water-soluble iridium catalyst could be easily recovered by extraction and reused without a loss of activity.

Scheme 9. Multialkylation of Ammonia Using Ir−Ammine Complex



In 2011, Uozumi realized a dehydrative alkylation in water using a novel heterobimetallic polymeric boron−iridium catalyst (Scheme 10).[47] The alkylation of ammonia and amines

Scheme 10. Alkylation of Amines Using Heterobimetallic Polymeric Boron−Iridium Catalyst



with alcohols was examined with 1 mol % Ir as a heterogeneous catalyst without the use of organic solvents under aerobic conditions to give the corresponding alkylated products in moderate to high yield. This heterogeneous catalyst could be recovered and reused without a loss of activity.

Very recently, Liu reported a different type of bimetallic iridium complex containing an NHC ligand for the dehydrative alkylation of amines with alcohols (Scheme 11).[48] It was an efficient catalyst for the reductive N,N′-dialkylation of phenylenediamines with alcohols.

Martín-Matute reported cyclopentadienyl Ir catalysts possessing an NHC ligand (Scheme 12).[49] The reaction using a 1:1 ratio of amines and primary or secondary alcohols smoothly proceeded to give a large variety of aromatic amines under base-free conditions.

The mechanism of N-alkylation with alcohol is shown in Scheme 13. The first step of this reaction involves the oxidation of an alcohol to a carbonyl intermediate, accompanied by the generation of an iridium dihydride complex. The carbonyl intermediate then reacts with an amine to afford an imine by dehydration, and subsequent hydrogenation by the iridium dihydride gives the alkylated product.

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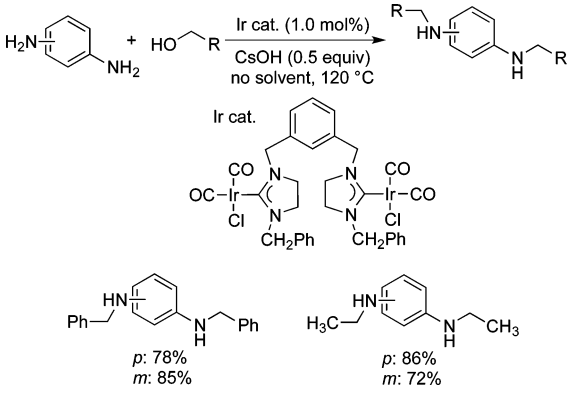
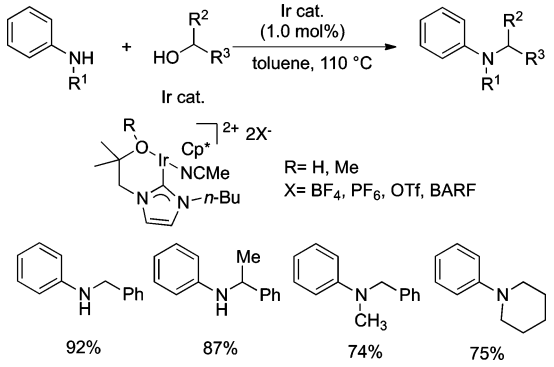
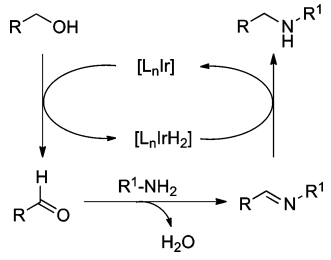
Scheme 11. Alkylation of Amines Using a Bimetallic Iridium Catalyst



Scheme 12. Alkylation of Amines Using Cyclopentadienyl Iridium Catalyst Possessing an NHC Ligand



Scheme 13. Mechanism of N-Alkylation with Alcohol

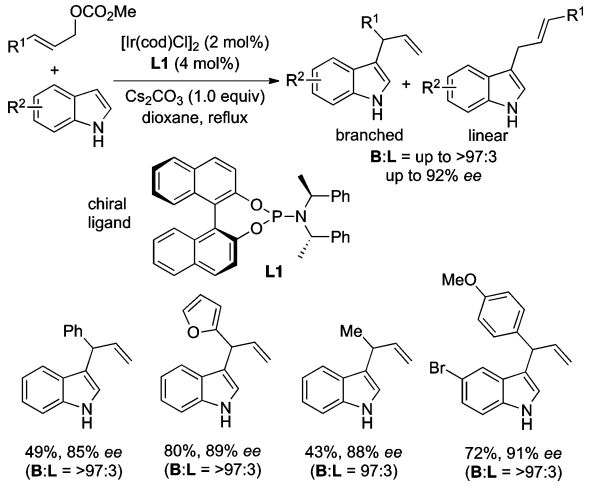


■ ALLYLATION OF C−H AND N−H BONDS WITH ALLYL CARBONATES

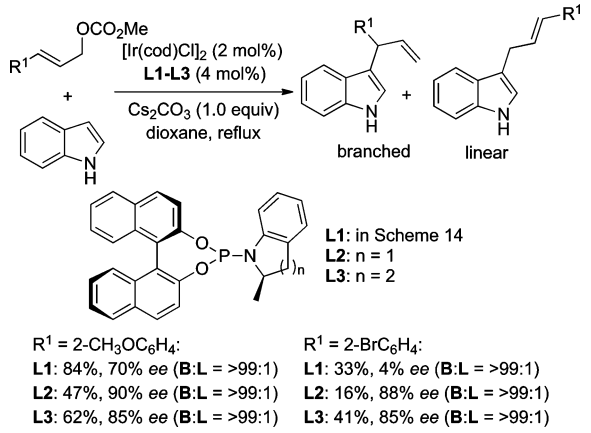
Because of the rapid development in this area, the iridium-catalyzed allylation of C−H and N−H bonds with allyl carbonates now plays an important role in natural product synthesis and medicinal chemistry.[50,51] In 2008, You reported an iridium-catalyzed intermolecular allylation of indole (Scheme 14).[52] The reaction was examined with 2 mol % $[Ir(cod)Cl]_2$ and a chiral phosphoramidite ligand in the presence of Cs_2CO_3 (1.0 equiv) under reflux conditions. The reaction of indole with allyl carbonate with various substituents proceeded smoothly with excellent regio- and enantioselectivity to afford indoles possessing a chiral allylic moiety at the 3-position with high ee.

You synthesized new phosphoramidite ligands (**L2**, **L3**) and used them as chiral ligands in the same transformation (Scheme 15).[53] As a result, **L2** and **L3** were found to be superior to **L1**, especially when the ortho-substituted cinnamyl carbonates were used.

Scheme 14. Intermolecular Enantioselective Allylation of Indoles



Scheme 15. Allylation of Indole with ortho-Substituted Cinnamyl Carbonates



You further reported intramolecular variants of the above-mentioned enantioselective allylation (Scheme 16).[54] In the presence of a chiral iridium catalyst, indole derivatives fused by a seven-membered ring system were obtained in yields of 40−78% with 91−97% ee (see the upper equation in Scheme 16). Meanwhile, when 3-substituted indole substrates were subjected to the reaction using a related chiral iridium catalyst, allylation proceeded at the C5-position of indole to give the corresponding products (see the lower equation in Scheme 16).

Phenols have also been used as C-nucleophiles in an iridium-catalyzed allylation. You reported an enantioselective intramolecular reaction of phenols with a tether containing an allyl carbonate moiety at the 3-position (Scheme 17).[55] The reaction proceeded predominantly or exclusively at the position adjacent to a hydroxy group, and chiral 5-hydroxy-4-vinyl-1,2,3,4-tetrahydroisoquinoline derivatives were obtained in moderate to excellent yields with high enantiomeric excesses.

Chiral Ir catalyst could also realize an enantioselective N-allylation of indoles. Hartwig reported a regio- and enantioselective intermolecular reaction (Scheme 18).[56] In the presence of 2 mol % of the iridium complex, this reaction

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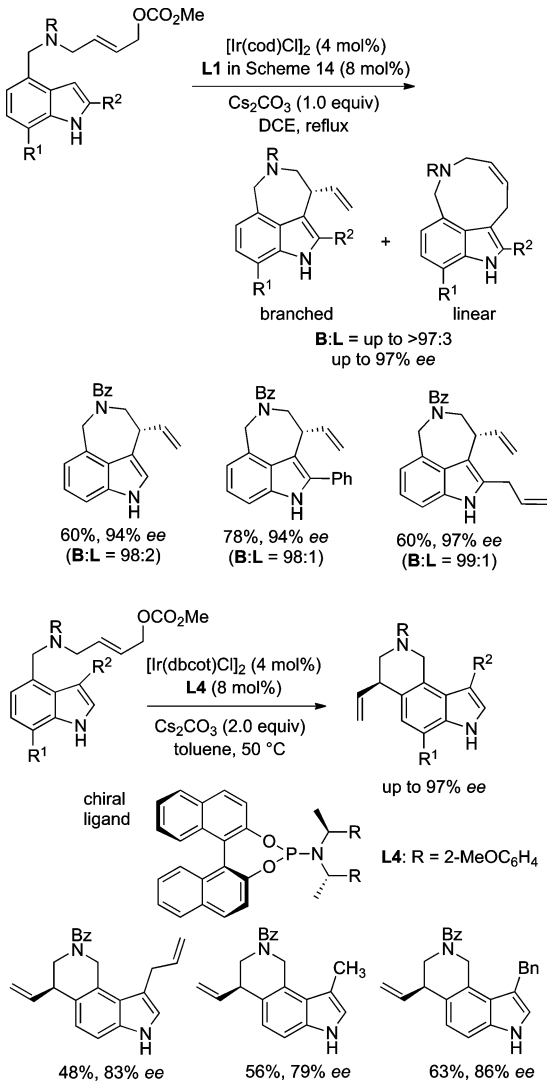
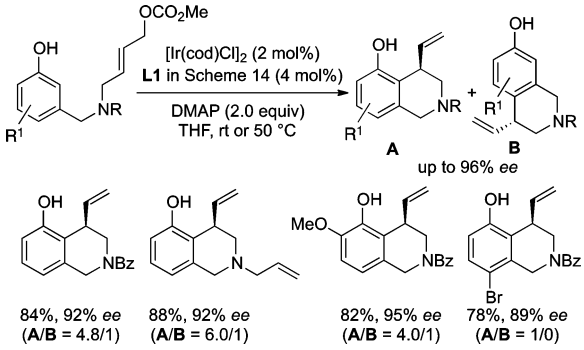
Scheme 16. Intramolecular Enantioselective Allylation of Indoles

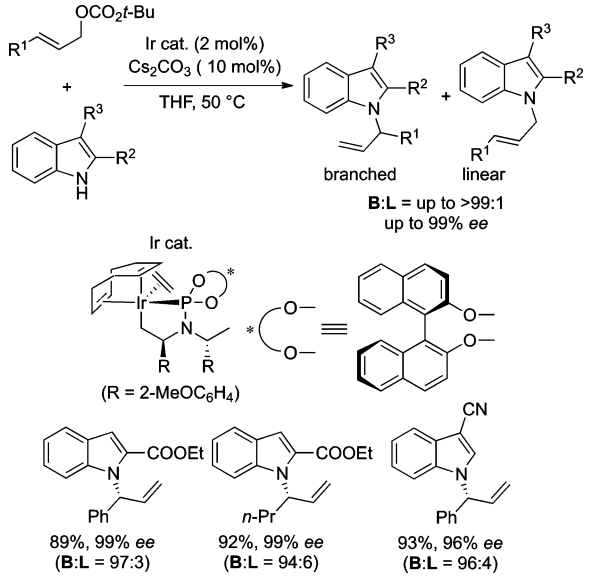


Scheme 17. Intramolecular Enantioselective Allylation of Phenols



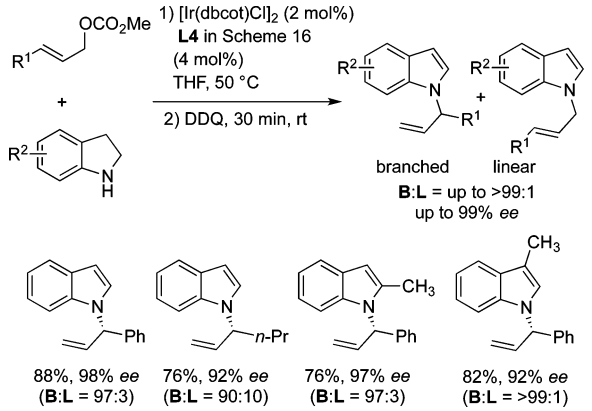
encompassed a broad range of indoles as well as a variety of allyl carbonates with aryl, heteroaryl, and aliphatic substituents or a 1,3-dienyl carbonate. *N*-Allylindoles were formed in a highly enantioselective manner (96–99% ee). However, this reaction generally required an electron-withdrawing group at the C2 or C3 position on the indole ring, which limited the substrate scope.

Scheme 18. Enantioselective N-Allylation of Indoles



Recently, You overcame this limitation through the use of indoline in place of indole as a substrate (Scheme 19).[57] The iridium-catalyzed allylation of indolines followed by oxidation provided a broad range of chiral *N*-allylindoles with excellent enantiomeric excesses.

Scheme 19. Enantioselective N-Allylation of Indolines



DIRECT C–H AND N–H BOND ALKYLATIONS WITH ALKENES

Recently, the transition metal-catalyzed reaction initiated by oxidative cleavage of inactive bonds has attracted increasing attention from both academia and industry.[58−60] Iridium complexes also show potent catalytic activity in C–H and N–H bond activation.

Regarding the direct sp^2 C–H alkylation with alkenes, Togni was the first to report an Ir-catalyzed ortho-alkylation of phenol with norbornene under solvent-free conditions, which led to the formation of one or two C–C bonds.[61] In 2008, we found that norbornene was a good substrate for the alkylation of acetophenone, and enantioselective C–H alkylation was achieved with the use of a chiral iridium catalyst (Scheme 20).[62]

We also reported the direct alkylation of ferrocenes to form various trisubstituted ferrocenes. When a pyridyl or imino group was used as a directing group (DG), the reaction with a

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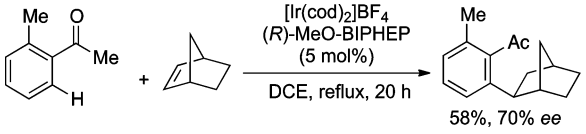
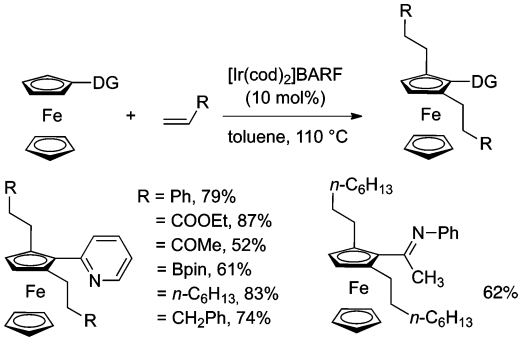
Scheme 20. Enantioselective Alkylation of Acetophenone with Norbornene



variety of terminal alkenes proceeded in the presence of $[Ir(cod)_2]$BARF (10 mol %) (Scheme 21).[63] Functional groups

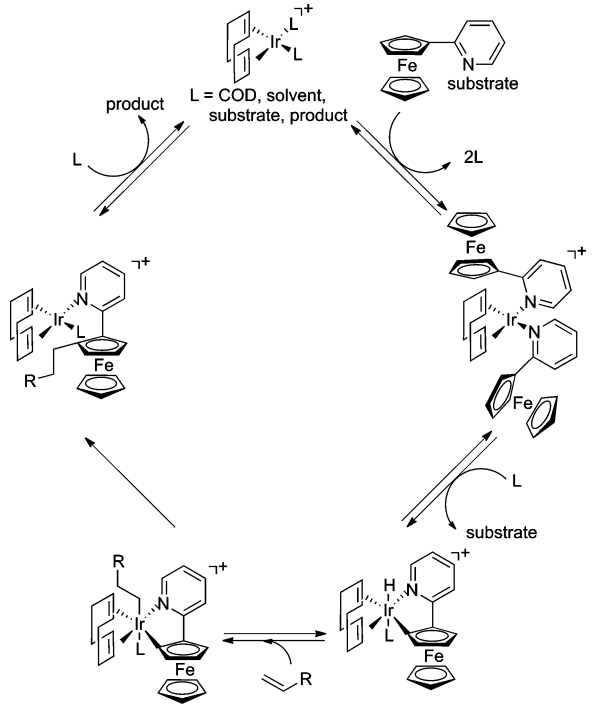
Scheme 21. C−H Alkylation of Ferrocene with Alkenes



such as ester, ketone, and boronic ester groups remained intact under the reaction conditions. This is the first example of the catalytic C−H alkylation of ferrocenes with alkenes.

On the basis of a preliminary mechanistic study, we proposed the mechanism shown in Scheme 22. First, two molecules of the substrate coordinate to the metal center. Oxidative C−H bond cleavage occurs via the release of one of these molecules. Alkene is inserted into the Ir−H bond, and subsequent

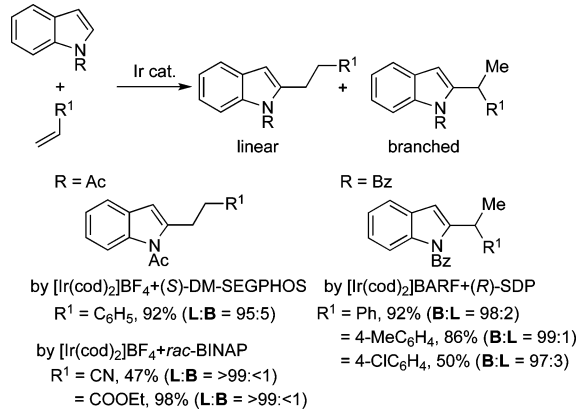
Scheme 22. Proposed Mechanism of C−H Alkylation of Ferrocene Using $[Ir(cod)_2]$BARF



reductive elimination affords the alkylated product along with the regeneration of the catalyst.

Recently, we reported a cationic iridium-catalyzed C2-alkylation of N-substituted indole derivatives with various alkenes, which selectively gave linear or branched 2-alkylindoles in high to excellent selectivity (Scheme 23).[64] In the reaction of

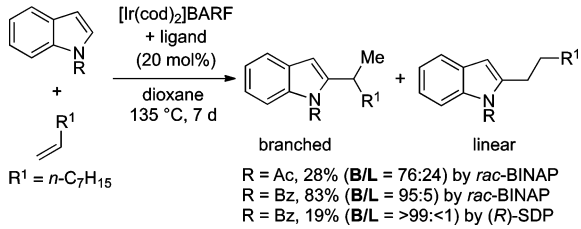
Scheme 23. C2-Alkylation of Indoles with Alkenes



N-acetylindole with alkenes, the corresponding linear 2-alkylindoles were obtained. Functional groups, such as nitrile, ketone, and ester, were tolerated in this reaction. In the case of *N*-benzoylindole, a broad range of branched 2-alkylindoles could be synthesized by reaction with styrene derivatives.

Interestingly, in the reaction of aliphatic alkenes, the branched product was predominant, regardless of the directing group and the ligand of the Ir catalyst (Scheme 24). For

Scheme 24. C2-Alkylation of Indole with 1-Nonene



example, the Ir-BINAP-catalyzed reaction of *N*-acetylindole with 1-nonene predominantly gave the branched product, albeit in low yield. When a benzoyl group was used as a directing group, the products were obtained in high yield with excellent selectivity under the same reaction conditions. The Ir-SDP catalyst realized almost perfect branch selectivity.

More recently, Hartwig reported an iridium-catalyzed asymmetric alkylation of C−H bond of heteroarenes with norbornene in high yield with high enantiomeric excess (Scheme 25).[65] The present C−H alkylation selectively proceeded adjacent to a heteroatom of indole, benzofuran, pyrrole, etc.

Compared with sp^2 C−H bond activation, sp^3 C−H bond activation has been relatively unexplored. In 2009, we reported a cationic Ir-catalyzed sp^3 C−H bond activation using amide as a directing group, but it was limited to the activation of a primary sp^3 C−H bond.[66] The direct functionalization of a secondary sp^3 C−H bond is more difficult, but also much more fascinating because it can create a chiral center. In 2011, we realized the first example of a highly enantioselective alkylation

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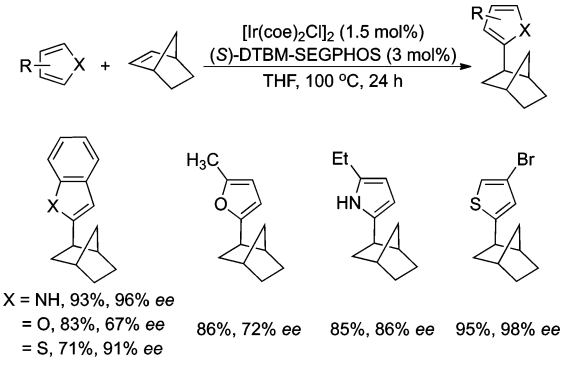
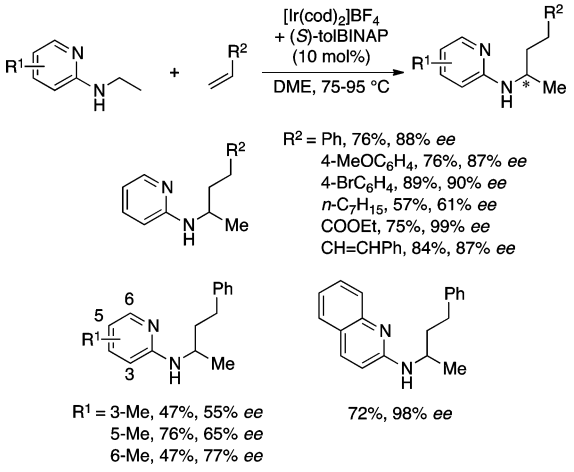
Scheme 25. Asymmetric Alkylation of C−H Bond Adjacent to Heteroatom



of an sp^3 C−H bond of 2-(alkylamino)pyridines with alkenes using a chiral cationic iridium catalyst (Scheme 26).[67,68] In the

Scheme 26. Enantioselective Alkylation of Secondary sp^3 C−H Bonds

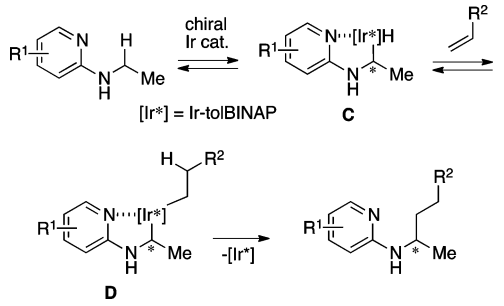


presence of $[Ir(cod)_2]BF_4$ (10 mol %) and (*S*)-tolBINAP, a wide variety of chiral amines were obtained. In particular, the reaction of 2-(ethylamino)pyridine with ethyl acrylate gave the corresponding amine in almost perfect enantiomeric excess (99% ee). 1,3-Diene was also a favorable substrate, and high ee was achieved in this transformation. Interestingly, the yield and ee varied depending on the position of methyl group on the pyridine. When a quinolyl group was used as a directing group, excellent enantiomeric excess was achieved in the reaction with styrene.

We have proposed the following mechanism (Scheme 27). Cleavage of the C−H bond adjacent to the nitrogen atom gives the intermediate **C**, subsequent hydroiridation to alkene gives intermediate **D**, and reductive elimination gives a chiral amine. The enantioselectivity depends on the alkenes, which means that the first two steps are reversible, and only the final step is irreversible.

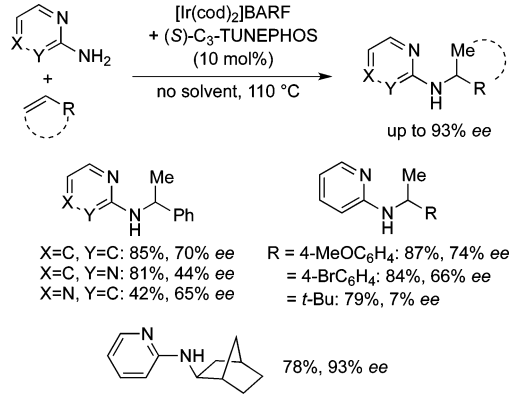
The hydroamination to alkene is a form of N−H alkylation.[69,70] Intermolecular and enantioselective hydroamination remains a challenging but desirable strategy for the synthesis of chiral amines.[71,72] Togni first reported an Ir-catalyzed reaction of norbornene,[73] which was further improved by Hartwig.[74] Recently, we reported that a chiral cationic Ir(I)-C_3-TUNEPHOS complex catalyzed an intermolecular hydro-

Scheme 27. Proposed Mechanism of C−H Bond Alkylation



amination of styrene derivatives with various heteroaromatic amines under solvent-free conditions (Scheme 28).[75] The

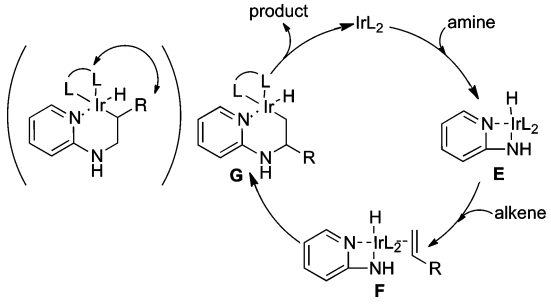
Scheme 28. Hydroamination of Alkenes with Heteroaromatic Amines



regioselectivity was perfect, and branched amines were the only products, even in the reaction of a bulky alkene (R = *t*-Bu). Norbornene was also a good coupling partner, and high enantioselectivity was achieved.

A proposed mechanism for the above reaction is shown in Scheme 29. Pyridine-directed N−H bond activation of 2-

Scheme 29. Proposed Mechanism of Regioselective Hydroamination



aminopyridine is an initial step to give intermediate **E**. An alkene inserts into the Ir−N bond to give the more favored intermediate **G** to avoid steric repulsion between the substituent on the alkene (R) and the bulky ligand on the metal center.

Recently, Hartwig reported an iridium-catalyzed intermolecular hydroamination of amides and sulfonamides to simple alkenes (Scheme 30).[76] A large variety of N-branched alkyl

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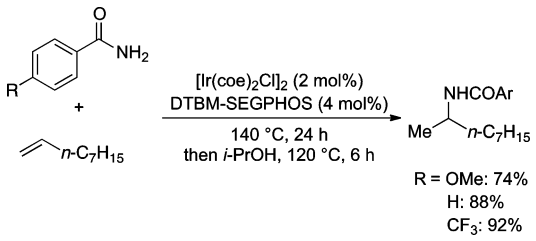
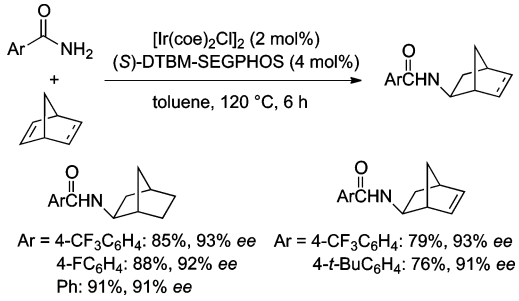
amides could be obtained via the addition of N−H bonds to unactivated alkenes.

Scheme 30. N-Alkylation of Amides Using an Unactivated Alkene



This methodology could encompass the enantioselective addition of N−H bonds of amides. In the reaction of norbornene and norbornadiene, the desired products were formed in high yields with excellent enantiomeric excesses (Scheme 31). These results represent the first intermolecular and highly enantioselective hydroamination using amides.

Scheme 31. Enantioselective N-Alkylation of Amides Using Bicycloalkenes



OUTLOOK

Overall, remarkable progress has been achieved in the iridium-catalyzed alkylation of C−H and N−H bonds over the past few years. Iridium complexes exhibit excellent catalytic performance in a variety of dehydrative alkylations of C−H and N−H bonds with alcohols. These reactions can be carried out under mild conditions with a low loading of catalysts. Notably, the dehydrative alkylation reaction can be extended to the alkylation of a methyl group. The allylation of C−H and N−H bonds with allylic carbonates is also an important transformation in organic synthesis. Compared with counterpart palladium catalysts, which give linear products, iridium catalysts give branched products with excellent regio- and enantioselectivity. Certainly, the direct functionalization of C−H and N−H bonds is much more attractive, since this makes it possible to eliminate the preactivation of substrates and to reduce waste byproducts. Ir catalysis has realized the sp^2 C−H bond alkylation of ferrocene and indole. In particular, chiral iridium catalysts have achieved asymmetric alkylation initiated by enantioselective cleavage of a secondary sp^3 C−H bond. Hence, we should expect to see the further development of useful protocols in this rapidly evolving research area.

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Notes

The authors declare no competing financial interest.

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