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Authors

Sevov, Christo S.
Zhou, Jianrong (Steve)
Hartwig, John F.

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Iridium-Catalyzed Intermolecular Hydroamination of Unactivated Aliphatic Alkenes with Amides and Sulfonamides

Christo S. Sevov,[‡,§] Jianrong (Steve) Zhou,[§] and John F. Hartwig*[,‡,§]

[‡]Division of Chemical Sciences, Lawrence Berkeley National Laboratory, and Department of Chemistry, University of California, Berkeley, California 94720, United States

[§]Department of Chemistry, University of Illinois, 600 South Matthews Avenue, Urbana, Illinois 61801, United States

Supporting Information

ABSTRACT: The intermolecular addition of N−H bonds to unactivated alkenes remains a challenging, but desirable, strategy for the synthesis of *N*-alkylamines. We report the intermolecular amination of unactivated α-olefins and bicycloalkenes with arylamides and sulfonamides to generate synthetically useful protected amine products in high yield. Mechanistic studies on this rare catalytic reaction revealed a resting state that is the product of N−H bond oxidative addition and coordination of the amide. Rapid, reversible dissociation of the amide precedes reaction with the alkene, but an intramolecular, kinetically significant rearrangement of the species occurs before this reaction with alkene.

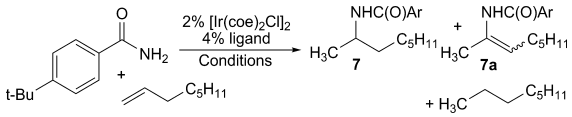
Amine functionality is ubiquitous in biologically active and industrially useful molecules. Many strategies to form C−N bonds provide access to this functional group in fine chemical building blocks, pharmaceuticals, agrochemicals, solvents, and surfactants. Classical methodologies for C−N bond formation involve reductive aminations of carbonyl compounds or substitution reactions of prefunctionalized aliphatic starting materials. An alternative, more synthetically efficient route to construct C−N bonds is the addition of an N−H bond across an unsaturated C−C bond, a transformation formally known as hydroamination. A majority of metal-catalyzed hydroaminations are *intra*molecular cyclizations of aminoalkenes to form amine heterocycles. Few complexes catalyze *inter*molecular hydroamination of alkenes.[1]

With few exceptions,[2] intermolecular hydroaminations are limited to reactions of activated alkenes, such as bicycloalkenes,[3] 1,3-dienes,[4] allenes,[5] and vinylarenes,[2b,6] or the unsubstituted ethylene.[7] Examples of intermolecular additions of N−H bonds across unactivated alkenes are rare, and additions of amides and sulfonamides to higher α-olefins are particularly unusual.[8] Here, we report a well-defined transition-metal complex that catalyzes the intermolecular hydroamination of unactivated alkenes with amides and sulfonamides to form *N*-alkylamides and sulfonamides. The same system catalyzes additions of amides to norbornene (nbe) and norbornadiene (nbd) that are highly enantioselective. Mechanistic studies on these additions to unstrained and strained alkenes reveal the resting state of the catalyst and the turnover-limiting steps of the hydroamination processes.

Recent work in our laboratory has demonstrated the high activity and selectivity of bisphosphine-ligated iridium complexes for the intermolecular hydroamination of bicycloalkenes with arylamines.[3a] On the basis of this observation, we sought to develop the catalytic addition of N−H bonds to unactivated alkenes with more versatile nitrogen donors, such as amides and sulfonamides, than had been added to unstrained alkenes previously.[2b,c,e]

The combination of $[Ir(coe)_2Cl]_2$ and a series of bisphosphine ligands was tested as catalyst for the addition of 4-*tert*-butylbenzamide to 1-octene. The results are summarized in Table 1. Ir complexes of aryl bisphosphines containing ethyl, propyl, and ferrocenyl backbones did not form active catalysts for the desired transformation (see SI for full ligand set). A small amount of product was observed for reactions catalyzed by complexes of methylene-bridged bisphosphines (entry 1),

Table 1. Reaction Development for Ir-Catalyzed Intermolecular Addition of 4-*tert*-Butylbenzamide to 1-Octene[a]



entry	ligand	equivs of 1-octene	temp (°C)	% yield of 7 + 7a[b]	ratio 7:7a
1	dcpm[c]	5	120	8	12:1
2	(*R*)-DM-BINAP	5	120	2	4.1:1
3	(*R*)-DM-MeOBIPHEP	5	120	12	1.8:1
4	(*S*)-DM-SEGPHOS[d]	5	120	18	2.0:0
5	(*R*)-DTBM-MeOBIPHEP	5	120	28	1.9:1
6	(*S*)-DTBM-SEGPHOS[e]	5	120	44	1.9:1
7	(*S*)-DTBM-SEGPHOS	1	120	13	3.3:1
8	(*S*)-DTBM-SEGPHOS	20	120	74	1.3:1
9	(*S*)-DTBM-SEGPHOS	20	100	47	1.8:1
10	(*S*)-DTBM-SEGPHOS	20	140	96	1.4:1

[a]Reactions were performed neat in 1-octene with 0.1 mmol of 4-*tert*-butylbenzamide. [b]Yields and conversions were determined by GC analysis with dodecane as an internal standard. [c]dcpm = bis-(dicyclohexylphosphino)methane. [d]DM = 3,5-dimethylphenyl. [e]DTBM = 3,5-di-*tert*-butyl-4-methoxyphenyl.

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suggesting that a small bite angle in the ligand was important for generating an active catalyst.

A similar effect of the ligand bite angle on the yield of the catalytic reaction was observed for reactions catalyzed by Ir complexes of bisphosphine ligands containing biaryl backbones, and a survey of commercially available bisphosphines containing biaryl backbones led to a system that formed *N*-alkylamide and enamine products in high combined yield. Studies of ligands with varied dihedral angles of the ligand backbone showed that the yields were higher for reactions conducted with ligands having smaller dihedral angles (entries 2−4). 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 yield of addition products. Furthermore, the lipophilicity of the *tert*-butyl groups imparted greater solubility of the catalyst in the alkene. An excess of the α-olefin was required to effect the transformation in high yield. Low conversion to the alkylamide and alkyl enamide products was observed with 1 equiv of 1-octene to the amide catalyzed by the Ir catalyst ligated by DTBM-Segphos. Ultimately, reaction of the benzamide with 20 equiv of the alkene formed the hydroamination product in 56% yield and the corresponding enamide in 40% yield. The alkene is the terminal reductant for the enamide side product; the corresponding alkane was also formed in 40% yield.

To generate a single amination product, the enamide was reduced to the alkylamide by subjecting the crude reaction mixture to 1 atm of H_2 or an excess of isopropanol after the amination process. Thus, a one-pot reaction workup with isopropanol formed the saturated product exclusively and in high yield. The alkylamide products were formed with low 10−19% ee, but these measurable values do rule out hydroamination of the alkene by a proton-catalyzed process alone.[8] Moreover, the enamide product was found to be stable to the catalytic conditions, indicating that the stereogenic center of the *N*-alkylamide is set by the C−N bond-forming step rather than asymmetric hydrogenation of an enamide intermediate.

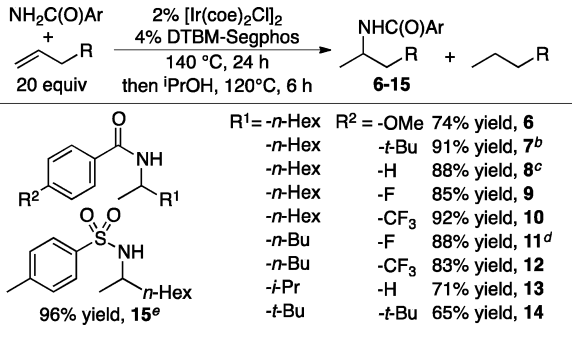
The scope of the Ir-catalyzed addition of amides to unactivated α-olefins by this procedure is summarized in Table 2. Following a one-pot reductive workup, high yields were obtained from reactions of the arylamides possessing electron-donating and electron-withdrawing aryl substituents. Products of more hindered alkenes were formed in yields that were slightly lower than those of less hindered alkenes, but still substantial. Finally, additions of sulfonamides occurred without alkene isomerization to form the Markovnikov product in high yield.

The scope of this methodology also encompasses the addition of N−H bonds of amides and sulfonamides to bicycloalkenes. As shown in Table 3, products of the reactions of norbornadiene and norbornene with arylamides and tosylamide were formed in high yield and ee. These types of amides added to nbd in slightly lower yields than to nbe, but with ee's that were similar to those for the reactions with nbe. The catalytic process proceeds with excellent diastereoselectivity to form the monoalkylated *exo* product. Hydrolysis of the amide led to the 2-norbornylamine building block with no erosion of the ee. Much effort has been spent to form norbornylamine by a catalytic process in enantioenriched form,[10] and this hydroamination provides the most direct route. The absolute stereochemistry of the amide was determined by optical rotation of the 2-aminonorbornane to be 2*R*. These results constitute the first intermolecular asymmetric hydroamination of an alkene with amides and sulfonamides in high yield and ee.

This catalytic process proved amenable to mechanistic studies. The combination of $[Ir(coe)_2Cl]_2$, 4-CF_3-benzamide, and DTBM-Segphos formed a clear solution (from the initial orange solution) within 15 min at room temperature (Figure 1a). A similar color change was observed at the start of the catalytic reaction. This finding suggested that the catalyst resting state did not contain an alkene.

The structure of the complex formed from the amide, ligand, and Ir was determined by X-ray diffraction (Figure 1b) and solution NMR spectroscopy. This complex results from oxidative addition of the N−H bond of the amide and coordination of a second amide to Ir through an unusual M−N dative bond. The assignment of the amide and amidate ligands of **1** was based on the difference between the two Ir−N bond lengths (2.076 Å for the amidate and 2.117 Å for the amide) and the Ir−N−C−O dihedral angle. The group assigned as a bound amide has a larger Ir−N−C−O dihedral angle (22°) than that of the nearly planar amidate (5°) because of the absence of a free lone pair to interact with the carbonyl group. The ^{31}P and ^{19}F NMR resonances of **1** matched the respective resonances of the complex that was formed in the catalytic

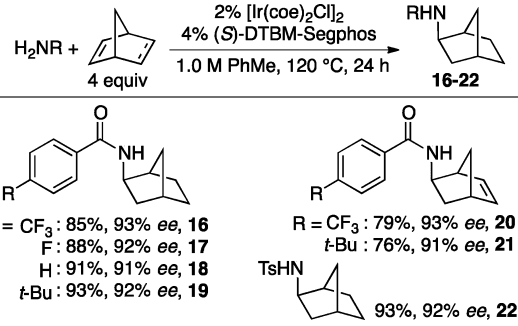
Table 2. Ir-Catalyzed Intermolecular Addition of Amides and Sulfonamides to Unactivated α-Olefins[a]



R^1 = -*n*-Hex	R^2 = -OMe	74% yield, **6**
-*n*-Hex	-*t*-Bu	91% yield, **7**[b]
-*n*-Hex	-H	88% yield, **8**[c]
-*n*-Hex	-F	85% yield, **9**
-*n*-Hex	-CF_3	92% yield, **10**
-*n*-Bu	-F	88% yield, **11**[d]
-*n*-Bu	-CF_3	83% yield, **12**
-*i*-Pr	-H	71% yield, **13**
-*t*-Bu	-*t*-Bu	65% yield, **14**

[a]Reactions were performed neat in 20 equiv of alkene with 0.3 mmol of amide or sulfonamide. Reported yields are isolated yields following a reductive workup with isopropanol. ee was determined by chiral HPLC analysis prior to reductive workup. [b]12% ee. [c]13% ee. [d]19% ee. [e]12% ee.

Table 3. Ir-Catalyzed Enantioselective Intermolecular Addition of Amides and Sulfonamides to Bicycloalkenes[a]



[a]Reactions were performed with 0.3 mmol of amide or sulfonamide and 4.0 equiv of nbe or 1.2 equiv of nbd. Reported yields are isolated yields. ee was determined by chiral HPLC analysis.

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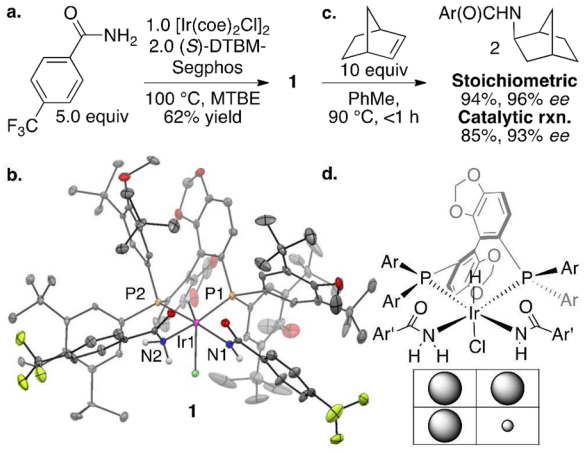


Figure 1. (a) Synthesis and (b) X-ray structure of **1**. (c) Stoichiometric reaction of **1** with nbe. (d) Structure and quadrant diagram of the coordination sites of **1**. Ar = 3,5-di-*tert*-butyl-4-methoxyphenyl; Ar′ = 4-trifluoromethylphenyl.

reaction at room temperature and 50 °C. Thus, **1** is the resting state of the catalyst in these additions of amides to alkenes.

To determine if the observed complex is competent to be an intermediate in the catalytic reaction, a stoichiometric amount of **1** was subjected to a 10-fold excess of nbe (Figure 1c). After 1 h at 90 °C—a time that is much shorter and a temperature that is lower than those of the catalytic process—complete consumption of the complex was observed. *N*-Norbornylamide **16** was formed in 94% yield, based on consumption of both amides in the complex. The ee of **16** was similar to those of the catalytic processes. Therefore, complex **1** is kinetically competent to be an intermediate in the catalytic cycle.

Kinetic measurements of the catalytic reaction as a function of the concentration of substrates were performed. The reactions were conducted with 2 mol % of isolated **1** at 100 °C, and initial rates (to 15% conversion) were measured by GC (see the Supporting Information). An inverse first-order dependence of the rate on the concentration of amide was observed. This order implies that the amide ligand dissociates reversibly prior to the turnover-limiting step (TLS). This system is, therefore, an unusual example of a catalytic process that is inverse-order in a reactant.[11] A first-order dependence of the rate on the concentration of 1-octene was observed, indicating that olefin coordination occurs before the TLS.

In contrast, the rate of the reaction was independent of the concentration of nbe under the standard catalytic conditions. A plot of the initial rate vs the concentration of nbe shows that the value of the rate saturates at high [nbe] (Figure 2). The reaction is first-order in nbe at low concentrations and zero-

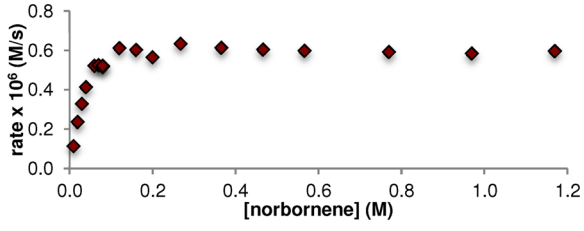
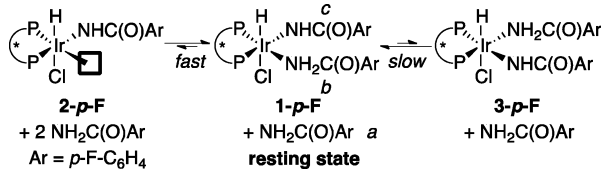


Figure 2. Plot of initial rate vs [nbe] for the addition of 4-trifluoromethylbenzamide to nbe catalyzed by **1**. Data for reactions with varied [trifluoromethylbenzamide] are included in the SI.

order at high concentrations of the alkene. No intermediate that might contain the alkene was observed during these reactions. At high [nbe] (0.5 M), under which conditions the reaction is zero-order in alkene, the reaction is inverse first-order in amide. These data indicate that the amide amidate complex **1** undergoes reversible dissociation of the amide, followed by an intramolecular rearrangement before reacting with the alkene.

To gain information on the dynamics of complex **1**, we conducted variable-temperature (VT) NMR spectroscopy on a *p*-fluorobenzamide analogue of **1** (**1-*p*-F**). Spectra with added amide were most informative. The ^{19}F NMR spectrum of the combination of **1-*p*-F** and 1 equiv of added amide contained three distinct ^{19}F NMR resonances for the amide and amidate ligands and for the free amide. Exchange between the free amide (signal *a*) and the datively bound amide (signal *b*) was observed between room temperature and 60 °C; the resonance for amidate ligand *c* remained unchanged (Figure 3) in this

Scheme 1. Dynamic Ligand Exchange Processes for 1-*p*-F



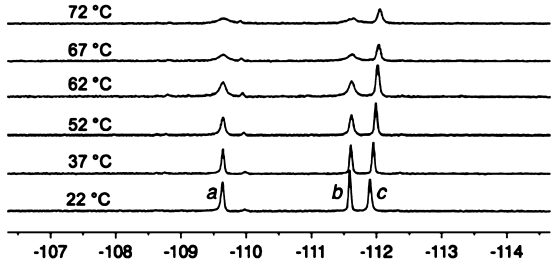


Figure 3. VT ^{19}F NMR spectroscopy of complex **1-*p*-F** (resonances *b* and *c*) with 1 equiv of 4-F-benzamide (resonance *a*) in toluene.

regime. The lack of exchange of the amide and amidate indicates that the five-coordinate intermediate **2-*p*-F** formed by amide dissociation is stereochemically rigid on the NMR time scale below 60 °C. Above 60 °C, the resonance for the amidate ligand (signal *c*) broadened, and VT NMR EXSY experiments confirmed that exchange occurred between the amide and amidate ligands as illustrated in Scheme 1 (see SI for further discussion). The reversible dissociation of the amide is consistent with the inverse first-order dependence of the rate on the amide. Line-shape analysis on resonance *a* showed that the activation parameters for ligand dissociation from **2-*p*-F** are $\Delta H^{\ddagger}$ = 20.7 kcal/mol and $\Delta S^{\ddagger}$ = 12.4 eu. This positive entropy is consistent with a dissociative process.

Consideration of the steric effects of the DTBM-Segphos ligand on the sites of amide and amidate ligands helps rationalize the preference for ligation of the amidate to one of the two diastereotopic coordination sites. The bulky aryl groups on the phosphorus atom in the chiral, C_2-symmetric ligand that is cis to the dative amide ligand (P2) both project toward the coordination site. This steric demand of one phosphino group contrasts the antipodal orientation of the aryl groups on the other phosphorus atom, which is located cis to the covalent amidate ligand (P1). One aryl substituent of this group projects

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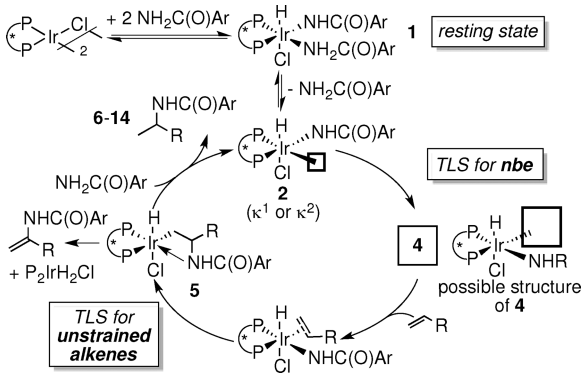
toward the coordination site of the amidate ligand, whereas the other aryl group occupies space away from the amide and amidate ligands. The C_1-symmetric quadrant diagram for **1** (Figure 1d) deviates from the classical C_2-symmetric quadrant diagram for BINAP-ligated complexes.[12] This difference in ligand coordination can be attributed to the different steric properties of the axial ligands (H vs Cl).

Scheme 2. Proposed Catalytic Cycle for the Ir-Catalyzed N−H Bond Addition of Arylamides to α-Olefins



These conclusions are summarized as a proposed catalytic cycle in Scheme 2. Oxidative addition of the N−H bond of an arylamide to a bisphosphine Ir(I) complex forms the catalyst resting state. Reversible dissociation of the dative amide ligand occurs to generate a complex in which the amidate ligand occupies the most open coordination site. An intramolecular reorganization then precedes coordination of the alkene. This reorganization likely involves either migration of the amidate ligand to form the less stable isomer **4** containing a more open coordination site or a shift of the amidate from a κ^2 binding mode in an 18-electron intermediate to a κ^1 binding mode in a 16-electron intermediate. Coordination and insertion of the alkene into the Ir−N bond would then occur to form the alkyliridium hydride **5**. This complex undergoes competitive C−H bond-forming reductive elimination to form the *N*-alkylamide and *β*-hydride elimination to form the enamide.

In conclusion, we have discovered a rare example of a catalytic process for the addition of amides and sulfonamides to unactivated alkenes and have identified the resting state of the catalyst and the components in the intermediate that adds the alkene. This methodology includes Ir-catalyzed reactions of bicycloalkenes with amides and sulfonamides to form products in high yield and ee. The resting state of the Ir-catalyzed hydroamination reaction was determined to result from oxidative addition of an N−H bond and coordination of an amide. Finally, kinetic data indicate that a kinetically detectable reorganization of the species formed by amide dissociation precedes alkene binding and insertion. Studies to increase the reaction scope further and to develop enantioselective additions to unstrained alkenes are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of all new compounds, including NMR spectroscopy data, conditions for chiral HPLC separations, optical rotations, kinetic studies, optimization data, and CIF data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

jhartwig@berkeley.edu

Notes

The authors declare no competing financial interest.

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