J|A|C|S
COMMUNICATIONS

Published on Web 08/21/2008

Intermolecular, Catalytic Asymmetric Hydroamination of Bicyclic Alkenes and Dienes in High Yield and Enantioselectivity

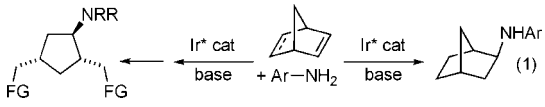
Jianrong (Steve) Zhou and John F. Hartwig*

Department of Chemistry, University of Illinois Urbana−Champaign, 600 South Matthews Avenue, Box 58-6, Urbana, Illinois 61801

Received May 12, 2008; E-mail: jhartwig@uiuc.edu

Asymmetric hydroamination of olefins would be an efficient means to access chiral, nonracemic alkylamines,[1] and development of stereoselective catalysts for these processes has been a long-standing challenge.[2] Only recently have intramolecular, catalytic hydroaminations of alkenes and allenes been reported with a high level of enantioselection.[3] However, no example of *inter*molecular hydroamination of alkenes has been reported with both high yield and high enantioselectivity.[4]

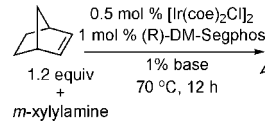
Roughly a decade ago, the beneficial effect of a fluoride anion[5] on the hydroamination of aniline with norbornene[10] was reported. The origin of this effect was never deduced, and additions occurred in either high yield or high enantioselectivity, but not both. Here, we report asymmetric hydroaminations of bicyclic alkenes and dienes with a series of aromatic amines in high yields and enantioselectivities using an organic base in place of the fluoride. This process creates an enantioselective route to 2-norbornylamine, which is a common building block in medicinal chemistry,[6] and to enantioenriched cyclopentylamines containing at least three defined stereocenters and two additional functionalities for further manipulations (eq 1). The effect of base and the reactivity of potential intermediates provide a mechanistic foundation for the hydroamination activities of the iridium catalysts.



Our initial experiments were based on the hypothesis that the fluoride used in previous studies might have served as a base to generate small amounts of arylamide and could be replaced with a soluble organic base. To test this hypothesis, we conducted reactions between *m*-xylylamine and norbornene in the presence of catalysts generated from a combination of $[Ir(cyclooctene)_2Cl]_2$, DM-Segphos, and disilylamide base. These and related data are summarized in Scheme 1. Indeed, added KHMDS base dramatically increased turnover numbers and enantioselectivity for the reactions of a substituted aniline with norbornene.[7] We next considered that KHMDS simply produced catalytic amounts of KNHXylyl. Consistent with this logic, the reaction conducted with 1 mol % of added KNHXylyl occurred with yields and enantioselectivities that were similar to those with added KHMDS.

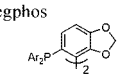
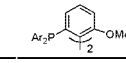
Studies of this reaction catalyzed by complexes of other types of biaryl bisphosphine ligands (Table 1) showed that the backbone dihedral angle and substituents on the *P*-aryl groups both influenced catalyst activity. Reactions conducted with the catalyst containing BINAP or 3,5-xylyl-BINAP occurred with low turnover numbers (Table 1, entries 1 and 2). Complexes of Seg-phos and MeOBIPHEP, which have smaller backbone dihedral angles than BINAP, were more active catalysts (Table 1, entries 3 and 6 vs 1). Catalysts generated from members of these two ligand families containing

Scheme 1



Base	Yield (%)	*ee* (%)
None	6	37
KHMDS	63	96
KNHXyl	61	96

Table 1. Effect of Ligands on the Asymmetric Hydroamination of Norbornene with *m*-Xylylamine under the Conditions of Scheme 1

Entry	Ligand	Ar[a]	Dihedral Angle[b]	Yield (%)	*ee* (%)
1	(*R*)-Ar-BINAP	Ph	86°	2	90
2		DM		26	85
3	(*R*)-Ar-Segphos	Ph	67°	19	99
4		DM		63	96
5	(*R*)-Ar-Segphos= 	DTBM		96	97
6	(*R*)-Ar-MeOBIPHEP	Ph	72°	7	96
7		DM		46	93
8	(*R*)-Ar-MeOBIPHEP= 	DTBM		90	97

[a] DM = 3,5-dimethylphenyl; DTBM = 3,5-di-*tert*-butyl-4-methoxyphenyl. [b] Values from Jeulin, S.; de Paule, S. D.; Ratovelomanana-Vidal, V.; Genet, J. P.; Champion, N.; Dellis, P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5799.

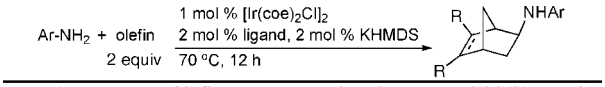
bulky, electron-rich *P*-aryl groups were particularly reactive. A sequential increase in steric bulk and electron donation of the *P*-aryl group led to a smooth increase in yield while maintaining high enantioselectivity (Table 1, entries 3−5 and 6−8). Under similar conditions, reactions catalyzed by complexes generated from Josiphos ligands containing di-*tert*-butyl-, dicyclohexyl-, and diarylphosphino groups[5] formed <15% yield of the product with 22−96% ee.

The scope of the reaction of different aromatic amines with bicyclic olefins is shown in Table 2. In general, both electron-poor and -rich anilines were less reactive than electron-neutral anilines toward this hydroamination catalyzed by the complex of DM-Segphos.[8] Most reactions occurred in high yield and ee using DTBM-Segphos under neat conditions, but in some cases a change in ligand created higher selectivities. X-ray crystallography on the bromoaniline addition product showed that the absolute stereochemistry of the product was (2*S*) when (*R*)-DTBM-Segphos was used as ligand.

These catalysts significantly increase the synthetic utility of this hydroamination by catalyzing additions to norbornadiene. This diene, which often chelates low-valent metals, could be envisioned to poison the catalyst. However, *m*-xylylamine and *p*-anisidine added to norbornadiene in high yield and enantioselectivity in the presence of the catalyst generated from (*R*)-DTBM-Segphos. No product from addition to the second olefin unit was detected by GCMS.[9] Reactions of *p*-anisidine with both olefins also occurred with just 0.5 mol % of iridium, although a longer reaction time was needed. Both benzo-fused and imide-containing bicyclic olefins

10.1021/ja803523z CCC: $40.75

Table 2. Scope of Asymmetric Hydroaminations of Olefins



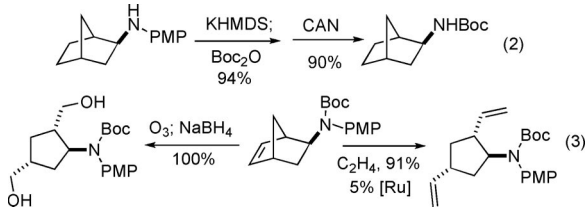
Ar	Olefin	Ligand	Yield (%)	*ee* (%)
p-*t*-BuC_6H_4[a]	norbornene	(*R*)-DM-Segphos	85	92
p-BrC_6H_4		(*R*)-DTBM-Segphos	91	96[b]
p-MeOC_6H_4[a,c]		(*R*)-triMeO-MeOBIPHEP[e]	75	98
p-$CF_3C_6H_4$		(*R*)-DTBM-Segphos	77	91
m-Xylyl[d]	norbornadiene	(*R*)-DTBM-Segphos	94	99
p-MeOC_6H_4[c]		(*R*)-DTBM-Segphos	88	99
m-Xylyl[a,d,f]		(*R*)-DTBM-Segphos	90	99
m-Xylyl[a,d,g]		(*R*)-DTBM-Segphos	84	98

[a] 100 °C, 12 h. [b] *exo*-(2*S*) configuration was determined by X-ray crystallography. [c] 0.5 mol % [Ir]; 40 h. [d] 1 mol % [Ir]; 12 h. [e] triMeO = 3,4,5-trimethoxyphenyl. [f] 1.2 equiv of olefin. [g] 1.2 equiv of *m*-xylylamine.

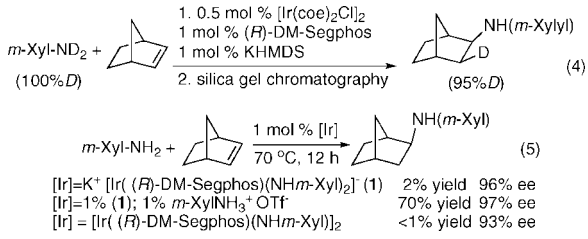
reacted in high yield and enantioselectivity. The product of the latter reaction contains *five new stereocenters*.

Reactions of more hindered and more basic amines formed hydroamination products in lower yields. *o*-Toluidene reacted with norbornene at the ortho methyl group, and *o*-anisidine did not react, even at 100 °C. Alkylamines, such as octylamine or *N*-methylaniline, also did not react with norbornene under these conditions.

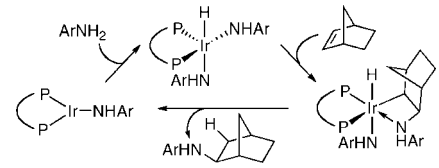
The synthetic manipulations in eqs 2 and 3 illustrate the utility of the addition products. The *p*-methoxyphenyl (PMP) group of the anisidine adduct can be converted in high yield to the Boc-protected norbornylamine. In addition, the unreacted olefin moiety of norbornadiene adducts can be cleaved by ozonolysis or ring-opening cross metathesis to generate stereochemically defined aminocyclopentane derivatives.



Although preliminary, a few pieces of mechanistic data point to the pathway in Scheme 2.[10] First, the reaction of *m*-XylylND_2 with norbornene formed the syn addition product (eq 4).[10] Second, the anionic bisanilide K[Ir(L_2)(NH*m*Xylyl)$_2$] (**1**, L_2 = DM-segphos), formed from [Ir(DM-Segphos)Cl]$_2$[11] and 2 equiv of KNH*m*Xylyl, catalyzed the reaction of XylylNH_2 with norbornene in <5% yield, but this complex in combination with an equimolar amount of *m*-XylylNH_3^+ led to an active catalyst (eq 5). Finally, this reaction catalyzed by the neutral dimeric [Ir(L_2)(NH*m*Xylyl)]$_2$ occurred in <5% yield.



Scheme 2. Proposed Catalytic Cycle for the Hydroamination



The stereochemistry of the addition implies that the reaction occurs by a pathway involving migratory insertion of the alkene, followed by reductive elimination. The data obtained with different catalyst precursors imply that a monomeric, neutral anilide complex catalyzes the reaction. We tentatively postulate that protonation of the anionic anilide complex in the presence of alkene allows entry into the catalytic cycle and that the catalyst deactivates by forming the neutral dimeric [Ir(L_2)(NH*m*Xylyl)]$_2$.[12] If this proposal is correct and the mechanism in Scheme 2 is followed, then each intermediate contains an arylamide ligand. The arylamide would then serve as a reactive *and* ancillary ligand.

In summary, we have reported a series of intermolecular enantioselective hydroaminations that occur in high yield and ee. Studies are underway to design catalysts to improve reaction scope based on the hypothesis that the arylamide serves as both a reactive and ancillary ligand.

Acknowledgment. We thank the DOE for support of this work and Takasago for gifts of chiral phosphines.

Supporting Information Available: Experimental procedures, product characterization, and complete ref 6a (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For general reviews on olefin hydroaminations, see: (a) Muller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (b) Brunett, J. J.; Neibecker, D. In *Catalytic Heterofunctionalization from Hydroamination to Hydrozirconation*; Togni, A., Grützmacher, H., Eds.; Wiley: New York, 2001; pp 91−141.

(2) For reviews on asymmetric olefin hydroaminations, see: (a) Aillaud, I.; Collin, J.; Hannedouche, J.; Schulz, E. *Dalton Trans.* **2007**, 5105. (b) Hultzsch, K. C. *Org. Biomol. Chem.* **2005**, *3*, 1819. (c) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (d) Roesky, P. W.; Müller, T. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 2708.

(3) (a) Gribkov, D. V.; Hultzsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748. (b) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673. (c) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452. (d) Zhang, Z.; Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 14148. (e) Wood, M. C.; Leitch, D. C.; Yeung, C. S.; Kozak, J. A.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 354. (f) Gott, A. L.; Clarke, A. J.; Clarkson, G. J.; Scott, P. *Organometallics* **2007**, *26*, 1729.

(4) For examples of hydroaminations of vinylarenes and conjugated dienes with substantial enantioselectivity, see: (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546. (b) Löber, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366.

(5) Dorta, R.; Egli, P.; Zurcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857–10858.

(6) (a) Wright, S. W.; et al. *J. Med. Chem.* **2006**, *49*, 3068. (b) Perreira, M.; Jiang, J. K.; Klutz, A. M.; Gao, Z. G.; Shainberg, A.; Lu, C.; Thomas, C. J.; Jacobson, K. A. *J. Med. Chem.* **2005**, *48*, 4910.

(7) Reactions conducted with LiHMDS and NaHMDS as base occurred to lower conversions.

(8) A full set of data is provided in the Supporting Information.

(9) The origin of the selectivity for addition of a single amine is unclear.

(10) Additions catalyzed by Ir(PEt_3)$_3$Cl and $ZnCl_2$ occurred with syn stereochemistry: Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738.

(11) (a) Dorta, R.; Togni, A. *Helv. Chim. Acta* **2000**, *83*, 119. (b) Tejel, C.; Ciriano, M. A.; Bordonaba, M.; López, J. A.; Lahoz, F. J.; Oro, L. A. *Chem. Eur. J.* **2002**, *8*, 3128.

(12) Slow addition of [H_3NPh]OTf to a solution of the anionic complex **1** in the absence of alkene generated the neutral dimer [Ir(L_2)(NH*m*Xylyl)]$_2$.

JA803523Z