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Ir(I)-Catalyzed Intermolecular Regio- and Enantioselective Hydroamination of Alkenes with Heteroaromatic Amines

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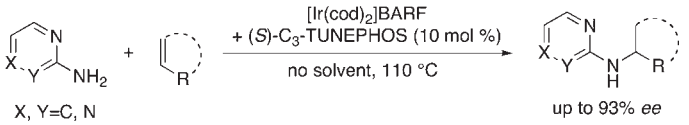
ABSTRACT



A cationic Ir(I)-C_3-TUNEPHOS complex catalyzed an intermolecular hydroamination of styrene derivatives with various heteroaromatic amines. The reaction gave Markovnikov products with perfect regioselectivity and good enantioselectivity under solvent-free conditions.

The hydroamination reaction of alkenes with amines is a highly atom economical and facile method for the preparation of substituted amines that are attractive targets for organic synthesis and the pharmaceutical industry.[1] In extensive studies using various metal catalysts over the last two decades,[2] regioselective intermolecular reactions were reported, which selectively gave Markovnikov adducts[3] or anti-Markovnikov ones.[4] Regarding the intermolecular enantioselective reaction,[5] Togni pioneeringly reported an Ir-catalyzed reaction of norbornene,[6a] which was further improved by Hartwig.[6b] The enantioselective hydroamination to electron-deficient alkenes was achieved by chiral Ni and Pd catalysts.[7,8] However, there have been relatively few studies of intermolecular regio- and enantiocontrolled hydroaminations of unactivated alkenes without

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(1) Reviews: (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (b) Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795. (c) Beller, M.; Breindl, C.; Eichberger, M.; Hurtung, C. G.; Seayad, J.; Thiel, O. R.; Tillack, A.; Trauthwein, H. *Synlett* **2002**, 1579. (d) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368. (e) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673. (f) Hartwig, J. F. *Nature* **2008**, *455*, 314. (g) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (h) Nugent, T., Ed. *Chiral Amine Synthesis: Methods, Developments and Applications*; Wiley-VCH: Weinheim, Germany, 2010. (i) Hesp, K. D.; Stradiotto, M. *ChemCatChem* **2010**, *2*, 1192. Review of asymmetric reactions: (j) Roesky, P. W.; Müller, T. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 2708. (k) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (l) Hultzsch, K. C. *Org. Biomol. Chem.* **2005**, *3*, 1819.

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(3) For selected examples: (a) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14286. (b) Li, K.; Horton, P. N.; Hursthouse, M. B.; Hii, K. K. *J. Organomet. Chem.* **2003**, *665*, 250. (c) Kaspar, L. T.; Fingerhut, B.; Ackermann, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 5972. (d) Qian, H.; Widenhoefer, R. A. *Org. Lett.* **2005**, *7*, 2635. (e) Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828.

(4) For selected examples: (a) Beller, M.; Eichberger, M.; Trauthwein, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2225. (b) Utsunomiya, M.; Kuwano, R.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 5608. (c) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 2702. (d) Zhang, X.; Emge, T. J.; Hultzsch, K. C. *Angew. Chem., Int. Ed.* **2011**, *51*, 394.

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(6) (a) Dorta, R.; Egli, P.; Zürcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857. (b) Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220.

(7) (a) Fadini, L.; Togni, A. *Chem. Commun.* **2003**, 30. (b) Fadini, L.; Togni, A. *Tetrahedron: Asymmetry* **2008**, *19*, 2555.

(8) (a) Li, K.; Hii, K. K. *Chem. Commun.* **2003**, 1132. (b) Gischig, S.; Togni, A. *Eur. J. Inorg. Chem.* **2005**, 4745.

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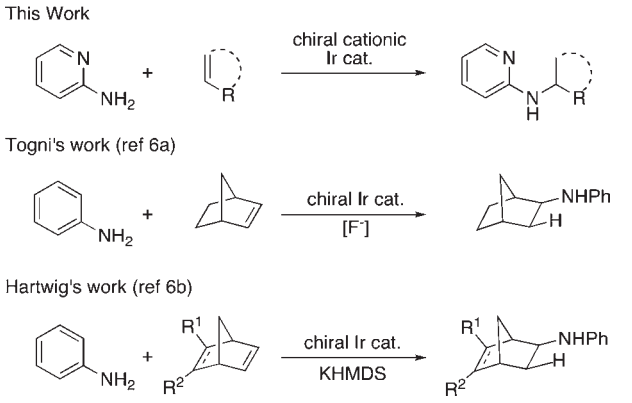
an electron-deficient group, which gave chiral branched amines by Markovnikov selectivity. Chiral Pd catalysts realized the regio- and enantioselectivity in the reaction of styrene derivatives.[9] Recently chiral gold and lanthanide catalysts made it an open possibility to use aliphatic alkenes.[10,11]

We here disclose a regio- and enantioselective hydroamination of unactivated alkenes with heteroaromatic

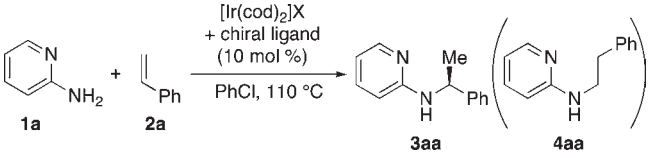
Scheme 1. Examples of Iridium-Catalyzed Intermolecular Enantioselective Hydroamination of Alkenes



amines using a chiral cationic Ir catalyst. Perfect Markovnikov selectivity was achieved by various nitrogen-containing heteroaromatic amines (Scheme 1). In previous reactions,[6] an intermolecular reaction of norbornene derivatives with anilines proceeded using chiral neutral Ir catalysts.

We have focused on the development of cationic iridium-catalyzed reactions initiated by C−H bond activation[12] and recently developed an enantioselective sp^3 C−H bond activation of 2-(alkylamino)pyridine with alkenes.[13] Based on the reported protocol, we studied a cationic Ir-catalyzed N−H bond activation using pyridyl as a directing group. The reaction of 2-aminopyridine (**1a**) with excess amounts of styrene (**2a**) (8 equiv) was investigated in the presence of cationic Ir catalysts using chlorobenzene as a solvent (Table 1). But the formation of a hydroaminated product was not observed under ligand-free conditions (entry 1). When BINAP was used as a chiral ligand, the desired product **3aa** was obtained with moderate *ee* (entry 2), and an *S* isomer was a major enantiomer.[14] The yield was low, but the Markovnikov adduct was exclusively formed, and the anti-Markovnikov linear amine **4aa** could not be detected. Among the BINAP derivatives, tolBINAP realized good yields, but the *ee* was moderate (entry 3).

Table 1. Optimization of the Reaction Conditions[a]



entry	X	chiral ligand	time (h)	yield (%)[b]	*ee* (%)
1[c]	BF_4	none	18	ND	–
2	BF_4	(*S*)-BINAP	6	35	56
3	BF_4	(*S*)-tolBINAP	6	70	47
4	BF_4	(*S*)-Cy-BINAP	6	<5	33
5	BF_4	(*S*)-H_8−BINAP	6	29	59
6	BF_4	(*S*)-SYNPHOS	6	9	73
7	BF_4	(*S*)-SEGPHOS	6	<5	72
8	BF_4	(*S*)-C_3-TUNEPHOS	6	19	74
9	OTf	(*S*)-C_3-TUNEPHOS	6	15	71
10	BARF[d]	(*S*)-C_3-TUNEPHOS	6	52	74
11	BARF[d]	(*S*)-C_3-TUNEPHOS	18	83	68
12[e]	BARF[d]	(*S*)-C_3-TUNEPHOS	18	27	78
13[f]	BARF[d]	(*S*)-C_3-TUNEPHOS	12	85	70
14[f,g]	BARF[d]	(*S*)-C_3-TUNEPHOS	24	82	69
15[f,h]	BARF[d]	(*S*)-C_3-TUNEPHOS	72	90	72

[a] Conditions: 2-aminopyridine (**1a**) (0.1 mmol), styrene (**2a**) (0.8 mmol), PhCl (0.2 mL), unless otherwise noted. [b] Isolated yield. [c] The reaction was examined at 135 °C. [d] Tetrakis(3,5-bis(trifluoromethyl)phenyl)-borate. [e] The reaction was examined at 90 °C. [f] The reaction was examined without solvent. [g] The catalyst loading was 5 mol %. [h] The catalyst loading was 2 mol %.

SYNPHOS and SEGPHOS achieved good enantioselectivity, but the yields were poor (entries 6 and 7). When C_3-TUNEPHOS was utilized, **3aa** was obtained with the highest *ee* in promising yield (entry 8). As a result of counteranion screening, we were pleased to find that BARF dramatically improved the yield without loss of *ee*, but the substrate **1a** was not completely consumed (entry 10).[15] The prolonged reaction time enabled a further increase of yield along with a slight decrease of *ee* (entry 11).[16] At a lower temperature of 90 °C, the reaction sluggishly proceeded and the yield was low, but the *ee* was sigificantly improved (entry 12). The present reaction

(9) (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. (c) Li., K.; Phua, P. H.; Hii, K. K. *Tetrahedron* **2005**, *61*, 6237. (d) Hu, A.; Ogasawara, M.; Sakamoto, T.; Okada, A.; Nakajima, K.; Takahashi, T.; Lin, W. *Adv. Synth. Catal.* **2006**, *348*, 2051.

(10) Reznichenko, A. L.; Nguyen, H. N.; Hultzsch, K. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 8984.

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(12) (a) Tsuchikama, K.; Kasagawa, M.; Hashimoto, Y.; Endo, K.; Shibata, T. *J. Organomet. Chem.* **2008**, *693*, 3939. (b) Tsuchikama, K.; Hashimoto, Y.; Endo, K.; Shibata, T. *Adv. Synth. Catal.* **2009**, *351*, 2850. (c) Tsuchikama, K.; Kasagawa, M.; Endo, K.; Shibata, T. *Org. Lett.* **2009**, *11*, 1821. (d) Tsuchikama, K.; Kasagawa, M.; Endo, K.; Shibata, T. *Synlett* **2010**, 97. (e) Shibata, T.; Hashimoto, Y.; Otsuka, M.; Tsuchikama, K.; Endo, K. *Synlett* **2011**, 2075. (f) Shibata, T.; Hirashima, H.; Kasagawa, M.; Tsuchikama, K.; Endo, K. *Synlett* **2011**, 2171.

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(14) Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586.

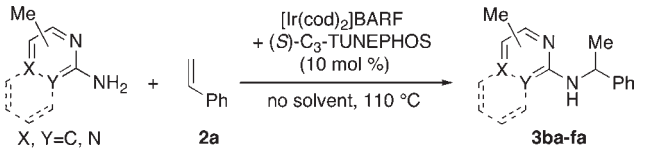
(15) When $[Rh(cod)_2]$BARF was used in place of $[Ir(cod)_2]$BARF, no hydroaminated adduct was detected.

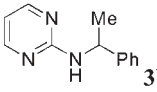
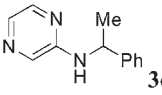
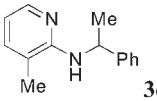
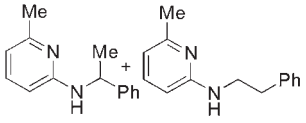
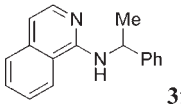
(16) In the presence of three equivalent amounts of styrene, the ee was slightly improved, but the yield was low (35%, 73% ee).

proceeded without any solvent in high yield with perfect regioselectivity and good enantioselectivity (entry 13). A long reaction time was required but a low catalyst loading of 2 mol % was achieved (entry 15). We used the conditions employed in entry 13 for further investigation.

Subsequently, the scope of heteroaromatic amines was examined for the present transformation using styrene (**2a**) as a standard alkene (Table 2). 2-Aminopyrimidine (**1b**) led to the corresponding product **3ba** with good yield, albeit with low enantiomeric excess (entry 1). 2-Aminopyrazine (**1c**) remained unconsumed, and amine **3ca** was obtained in moderate yield and enantiomeric excess (entry 2). Methyl-substituted 2-aminopyridines **1d** and **1e** reacted with styrene to give products in high yield, but with low enantioselectivity (entries 3 and 4). The coordination of the nitrogen of the pyridine ring to Ir would be crucial for the control of regioselectivity, and anti-Markovnikov adduct **4ea** was ascertained as a minor product in the reaction of **1e** (entry 4). 1-Aminoisoquinoline (**1f**) was a favorable substrate, and the highest *ee* was achieved along with perfect regioselectivity (entry 5).

Table 2. Reaction of Heteroaromatic Amines with Styrene[a]

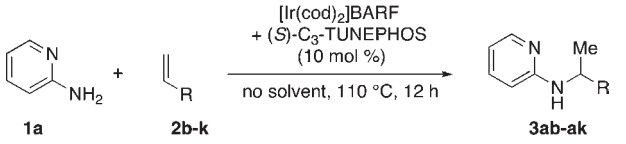


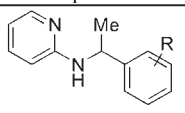
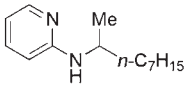
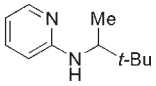
entry	product	time (h)	yield[b] (%)	*ee* (%)
1	 **3ba**	48	81	44
2[c]	 **3ca**	43	42	65
3	 **3da**	24	84	26
4	 **3ea** + **4ea**	24	91 (6.6:1)[d]	38
5	 **3fa**	24	58	83

[a] Conditions: heteroaromatic amine **1** (0.1 mmol), styrene (**2a**) (0.8 mmol), unless otherwise noted. [b] Isolated yield. [c] PhCl (0.2 mL) was used as a solvent. [d] The ratio was determined by ^{1}H NMR.

We next investigated the scope of alkenes in the reaction of 2-aminopyridine (**1a**) as a standard amine (Table 3). 4-Methoxy- and 4-methyl-substituted styrenes **2b** and **2c** led to the corresponding products **3ab** and **3ac** in high yields with good enantiomeric excesses (entries 1 and 2). In the reaction of styrene derivatives **2d**–**f** with an electron-withdrawing group, in contrast to electron-donating groups, the enantioselectivity was slightly decreased (entries 3–5). The steric effect played an important role in this reaction, and *ortho*-bromo-substituted styrene gave the product **3ah** in low yield with moderate enantiomeric excess (entry 7). Aliphatic alkenes, 1-nonene (**2i**) and 3,3-dimethylbut-1-ene (**2j**), could be also used as a coupling partner, and Markovnikov adducts **3ai** and **3aj** were exclusively obtained, although the *ee* was low (entries 8,9). It is noteworthy that, in all the entries, including bulky alkenes such as **2j**, perfect regioselectivity was achieved, and the branched amines were the only products.

Table 3. Reaction of Various Alkenes with 2-Aminopyridine[a]



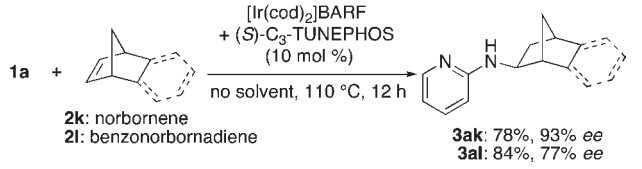
entry	product	yield (%)[b]	*ee* (%)
1	 **3ab** (R = 4-OMe)	87	74
2	**3ac** (R = 4-Me)	85	73
3	**3ad** (R = 4-F)	83	71
4	**3ae** (R = 4-Cl)	81	68
5	**3af** (R = 4-Br)	84	66
6	**3ag** (R = 3-Br)	86	67
7	**3ah** (R = 2-Br)	20	43
8	 **3ai**	60	11
9[c]	 **3aj**	79	7

[a] Conditions: 2-aminopyridine (**1a**) (0.1 mmol), alkene **2** (0.8 mmol), unless otherwise noted. [b] Isolated yield. [c] 3,3-Dimethylbut-1-ene (1.6 mmol) was subjected in PhCl (0.2 mL) at 135 °C for 24 h.

Norbornene derivatives were good substrates, giving bicyclic amines **3ak** and **3al** in high yield (Scheme 2). In particular, the enantioselectivity exceeded 90% in the reaction of norbornene.

For a preliminary mechanistic study, the reaction of aniline with styrene was examined under the same reaction conditions. But only a trace amount of the hydroaminated product was detected. A tentative mechanism for Ir-catalyzed hydroamination of alkenes with heteroaromatic

Scheme 2. Enantioselective Reaction of Norbornene Derivatives

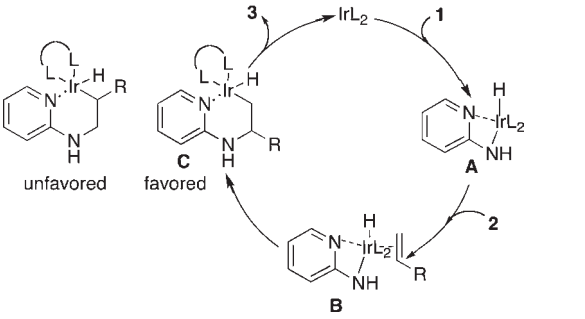


amines was shown in Scheme 3. Pyridine-directed N−H bond activation of 2-aminopyridine is an initial step to afford intermediate **A**.[17] An alkene inserts into the Ir−N bond to give the more favored intermediate **C**, which is derived into Markovnikov hydroaminated products **3**.

In summary, we described a protocol for the chiral cationic Ir(I)-catalyzed intermolecular regio- and enantioselective hydroamination of styrene derivatives with heteroaromatic amines, which afforded various chiral branched amines exclusively. Further studies on substrate scope and the precise mechanism are in progress in our laboratory.

(17) By the stoichiometric reaction of 2-aminopyridine (**1a**) with the chiral Ir catalyst in an NMR tube, a small peak for M−H (−12.5 ppm) was observed in the ^{1}H NMR, but the intermediate could not be fully characterized yet.

Scheme 3. Tentative Mechanism for Regioselective Intermolecular Hydroamination



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Supporting Information Available. The experimental procedure and physical property of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.