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Ir(I)-Catalyzed Enantioselective Secondary sp^3 C–H Bond Activation of 2-(Alkylamino)pyridines with Alkenes

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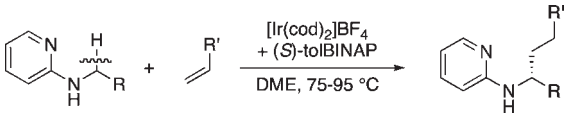
ABSTRACT



A cationic Ir(I)-tolBINAP complex catalyzed an enantioselective C–C bond formation initiated by secondary sp^3 C–H bond cleavage adjacent to a nitrogen atom. The reaction of 2-(alkylamino)pyridines with various alkenes gave chiral amines in good yields with high enantiomeric excesses.

Carbon–hydrogen bonds are ubiquitous in organic compounds, and their direct functionalization is a fascinating transformation in organic synthesis. Thus, synthetic protocols that begin with inactive C–H bond cleavage have attracted much attention from both academia and industry over the past decade, especially with regard to C–C bond formation through transition-metal catalysts.[1] Transformation at sp^2 C–H bonds, such as aromatic and vinylic C–H bonds, has been an important research topic. However, there have been relatively few studies of sp^3 C–H bond activation, due to the greater stability and lower reactivity of sp^3 C–H bonds compared to sp^2 C–H bonds. Recently, the C–C bond-forming coupling of sp^3 C–H bonds with several functional groups, such as alkynes,[2] aryl halides,[3] and boronic acids,[4] has been developed, where the primary sp^3 C–H bond of a methyl group is cleaved with the aid of directing group(s).[5,6] The cleavage of secondary sp^3 C–H bonds is more difficult but more fascinating because the direct generation of a chiral center may be possible. For example, C–H bond activation of the methylene moiety of a nitrogen-containing ring or benzylic position has been reported.[7] However, enantioselective and catalytic C–C bond formation via sp^3 C–H bond

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(1) For selected reviews, see: (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (b) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (c) Dyker, D., Ed. *Handbook of C-H transformations*; Wiley-VCH: Weinheim, Germany, 2005. (d) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (e) Davis, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (f) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (g) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087. (h) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (i) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677.

(2) For selected examples, see: (a) Tokunaga, Y.; Sakakura, T.; Tanaka, M. *J. Mol. Catal.* **1989**, *56*, 305. (b) Sakaguchi, S.; Kubo, T.; Ishii, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2534. (c) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (d) Tsuchikama, K.; Kasagawa, M.; Endo, K.; Shibata, T. *Org. Lett.* **2009**, *11*, 1821.

(3) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570. (c) Chaumontet, M.; Piccardi, R.; Audic, N.; Hitce, J.; Peglion, J.-L.; Baudoin, O. *J. Am. Chem. Soc.* **2008**, *130*, 15157.

(4) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510.

(5) Intramolecular reaction initiated by benzylic sp^3 C-H bond activation without directing group: (a) Dong, C.-G.; Hu, Q.-S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2289. (b) Ren, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3462.

(6) The sp^3 C–H bond borylation without directing group: (a) Ishiyama, T.; Ishida, K.; Takagi, J.; Miyaura, N. *Chem. Lett.* **2001**, *30*, 1082. (b) Shimada, S.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2168. (c) Murphy, J. M.; Lawrence, J. D.; Kawamura, K.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 13684.

(7) Examples of secondary sp^3 C–H bond activation, see: (a) Ishii, Y.; Chatani, N.; Kakiuchi, F.; Murai, S. *Organometallics* **1997**, *16*, 3615. (b) Jun, C.-H.; Hwang, D.-C.; Na, S.-J. *Chem. Commun.* **1998**, 1405. (c) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935. (d) DoBoef, B.; Pastine, S. J.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 6556. (e) Pastine, S.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220.

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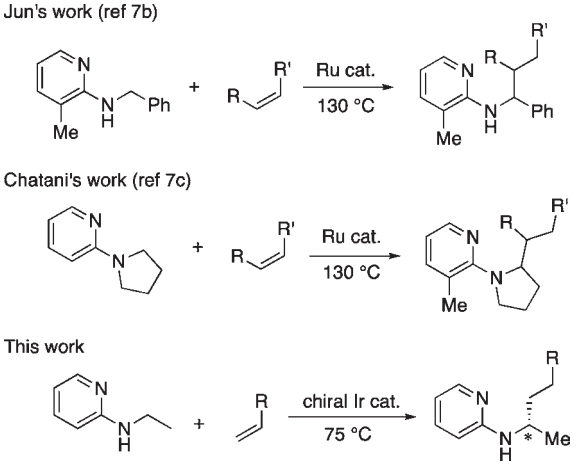
activation is still rare and is limited to a benzylic or allylic position.[8,9]

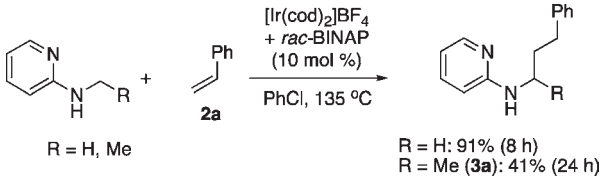
In this communication, we describe an enantioselective secondary sp^3 C−H bond activation of 2-(alkylamino)-pyridine using a chiral cationic Ir(I) catalyst, for which the enantiomeric excess was as high as 90%. Jun reported pioneering work of a Ru-catalyzed reaction of 2-(benzylamino)pyridine with alkenes, which was initiated by secondary sp^3 C−H bond cleavage at the benzylic position (Scheme 1).[7b,10] Murai also reported a Ru-catalyzed reaction of 2-(*N*-pyrrolidinyl)pyridine with alkenes. In contrast, we realized an enantioselective cleavage of secondary sp^3 C−H bond adjacent to nitrogen of 2-(alkylamino)pyridine at relatively lower temperature by using a chiral Ir catalyst.

Scheme 1. Examples of Secondary sp^3 C−H Bond Cleavage Adjacent to Nitrogen of 2-Aminopyridine Derivatives



We previously reported that a cationic Ir-*rac*-BINAP complex catalyzed the sp^3 C−H bond alkenylation of amides with alkynes.[2d] We next focused on the use of cationic Ir complex as an effective catalyst in the activation of the sp^3 C−H bond of 2-(methylamino)pyridine (R = H).[11] The reaction with styrene (2 equiv) proceeded efficiently to give alkylated product in a high NMR yield of 91% under the previous reaction conditions (Scheme 2).[12] We further examined the reaction of 2-(ethylamino)pyridine with styrene (8 equiv): to our delight, secondary sp^3 C−H bond activation proceeded, and the alkylated product **3a** with a chiral center was obtained,[12] albeit in moderate yield even after a longer reaction time. We were then ready to study the enantioselective reaction initiated by secondary sp^3 C−H bond cleavage.

Scheme 2. Reaction of 2-Aminopyridines with Styrene under the Previous Reaction Conditions



When (*S*)-BINAP was used, chiral amine **3a** was obtained with good enantioselectivity (Table 1, entry 1). We further screened the reaction conditions. Initially, several chiral diphosphine ligands were examined (entries 2−5). The enantiomeric excess of **3a** reached 80% with the use of (*S*)-tolBINAP. More bulky xylylBINAP gave a higher yield, but with low *ee*. H_8−BINAP derivatives facilitated the reaction to give **3a** in high yield but with moderate *ee*. Therefore, we decided upon tolBINAP as the best chiral ligand, and next tuned the counteranion of the iridium complex (entries 6−8). However, the results did not exceed those with BF_4. When 1,2-dimethoxyethane (DME) was used as a solvent in place of chlorobenzene, the reaction proceeded efficiently even at 75 °C; the enantioselectivity was improved to ca. 90% and the yield was increased (entry 9). Three equivalent amounts of styrene were sufficient to achieve good yield and high ee at a slightly higher reaction temperature (entry 10).

Subsequently, the scope of alkene was examined for the present enantioselective reaction with 2-(ethylamino)-pyridine using two reaction conditions (methods **A** and **B**) (Table 2). 4-Methoxy- and methyl-substituted styrenes **2b** and **2c** led to the corresponding products **3b** and **3c** in good yields with high enantiomeric excesses (entries 1−4).

(8) For enantioselective sp^3 C−H oxidation/C−C bond formation: (a) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997. (b) Li, Z.; Macleod, P. D.; Li, C.-J. *Tetrahedron: Asymmetry* **2006**, *17*, 590. (c) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882. (d) Benfatti, F.; Capdevila, M. G.; Zoli, L.; Benedetto, E.; Cozzi, P. G. *Chem. Commun.* **2009**, 5919. (e) Guo, C.; Song, J.; Luo, S.-W.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 5558.

(9) For enantioselective hydride transfer/C−C bond formation, see: (a) Murarka, S.; Deb, I.; Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 13226. (b) Kang, Y. K.; Kim, S. M.; Kim, D. Y. *J. Am. Chem. Soc.* **2010**, *132*, 11847. (c) Li, Q.; Yu, Z.-X. *Angew. Chem., Int. Ed.* **2011**, *50*, 2144.

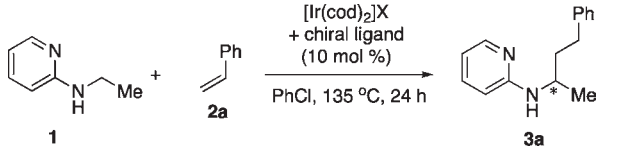
(10) For sp^2 C−H bond activation adjacent to the nitrogen atom of 2-aminopyridine: (a) Chatani, N.; Ishii, Y.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1998**, *63*, 5129. (b) Matsuura, Y.; Tamura, M.; Kochi, T.; Sato, M.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2007**, *129*, 9858. (c) Katagiri, T.; Mukai, T.; Satoh, T.; Hirano, K.; Miura, M. *Chem. Lett.* **2009**, *38*, 118. (d) Gao, K.; Lee., P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *132*, 12249.

(11) From an organometallic aspect, C−H bond cleavage of 2-(dimethylamino)- and 2-(diethylamino)pyridine by using Ir(III)-dihydride complex was reported, where Ir-carbene complexes were obtained: (a) Lee, D.-H.; Chen, J.; Faller, J. W.; Crabtree, R. H. *Chem. Commun.* **2001**, 213. (b) Clot, E.; Chen, J.; Lee, D.-H.; Sung, S. Y.; Appelhans, L. N.; Faller, J. W.; Crabtree, R. H.; Eisenstein, O. *J. Am. Chem. Soc.* **2004**, *126*, 8795.

(12) When the reaction of 2-(dimethylamino)pyridine with styrene was examined under the same reaction conditions, the monoalkylated product was obtained in low yield (10%).

(13) In the last two years, an enantioselective hydroaminoalkylation of amines to substituted alkenes was reported by using chiral Ta and Nb catalysts. Primary sp^3 C−H bond activation of methylaniline derivatives realized moderate to high enantioselectivities. (a) Eisenberger, P.; Ayinla, R. O.; Lauzon, J. M. P.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 8361. (b) Zi, G.; Zhang, F.; Song, H. *Chem. Commun.* **2010**, *46*, 6296. (c) Reznichenko, A. L.; Emge, T. J.; Audorsch, S.; Klauber, E. G.; Hultzsch, K. C.; Schmidt, B. *Organometallics* **2011**, *30*, 921.

Table 1. Optimization of the Reaction Conditions[a]



entry	X	chiral ligand	yield (%)[b]	*ee* (%)
1	BF_4	(*S*)-BINAP	37	70
2	BF_4	(*S*)-tolBINAP	62	80
3	BF_4	(*S*)-xylylBINAP	75	10
4	BF_4	(*S*)-H_8−BINAP	81	56
5	BF_4	(*R*)-DM-H_8−BINAP	84	−37
6	OTf	(*S*)-tolBINAP	48	81
7	PF_6	(*S*)-tolBINAP	24	74
8	BARF	(*S*)-tolBINAP	9	40
9[c]	BF_4	(*S*)-tolBINAP	76	88
10[d]	BF_4	(*S*)-tolBINAP	75	86

[a] Conditions: 2-(ethylamino)pyridine (**1**) (0.1 mmol), styrene (0.8 mmol), PhCl (0.2 mL), unless otherwise noted. [b] Isolated yield. [c] DME was used as a solvent at 75 °C for 48 h. [d] Less amount of styrene (0.3 mmol) was used, and DME was used as a solvent at 85 °C for 72 h.

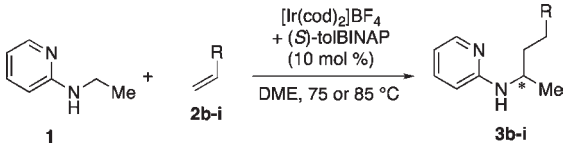
The reaction of styrene **2d** with an electron-withdrawing group, in contrast to electron-donating groups, gave better results with regard to both yield and enantiomeric excess (entries 5 and 6). The steric effect was relatively small for enantioselectivity, and *para*-, *meta*-, and *ortho*-bromo-substituted styrenes gave almost the same results regarding enantiomeric excess (entries 5−10). Other styrene derivatives **2g**, with a more electron-withdrawing fluoro group, and **2h**, with a phenyl group at the *para* position, could be used as substrates (entries 11−14). Allylbenzene (**2i**) could also be used as a coupling partner. Although the yield of the product **3i** was low, the enantioselectivity was acceptable. The yield increased at higher temperature, but the enantiomeric excess decreased (entries 15 and 16).

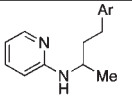
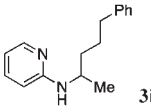
We next subjected a 1,3-diene to the same reaction conditions as above (Scheme 3). The reaction of 1-phenylbuta-1,3-diene (**2j**) proceeded smoothly to give unsaturated amine **3j** only in the *E*-form with high enantioselectivity.

We further submitted 2-(propylamino)pyridine **4** to the reaction with styrene (Scheme 4): it required a longer reaction time, but the corresponding alkylated product **5** was obtained in comparable yield and *ee*.

Chiral amines continue to attract much attention due to their widespread applications in the synthesis of drugs. In most cases, the pharmacological activities of these amines are related to the configuration of the stereogenic center.[14] For example, (*R*)-4-phenylbutan-2-amine is a precursor of the antihypertensive dilevalol.[15] Therefore, we were interested in the potential applications of our products and examined the removal of the pyridyl group: the

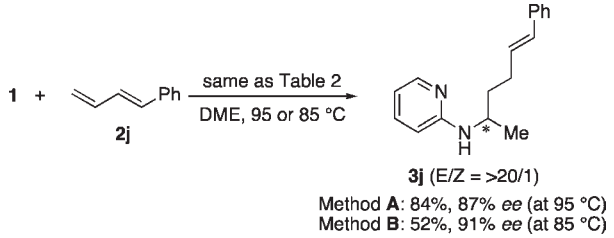
Table 2. Enantioselective Reaction of Various Alkenes[a]



entry	product	method	yield (%)[b]	*ee* (%)
1	 **3b** (Ar = 4-$MeOC_6H_4$)	**A**	76	87
2		**B**	71	85
3	**3c** (Ar = 4-MeC_6H_4)	**A**	77	89
4		**B**	58	89
5	**3d** (Ar = 4-BrC_6H_4)	**A**	89	90
6		**B**	81	87
7	**3e** (Ar = 3-BrC_6H_4)	**A**	83	90
8		**B**	78	87
9	**3f** (Ar = 2-BrC_6H_4)	**A**	76	86
10		**B**	74	84
11	**3g** (Ar = 4-FC_6H_4)	**A**	60	87
12		**B**	68	86
13	**3h** (Ar = 4-PhC_6H_4)	**A**	56	88
14		**B**	67	86
15	 **3i**	**A**	20	70
16[c]		**A**	57	61

[a] Method **A**: 2-(ethylamino)pyridine **1** (0.1 mmol), alkene (0.8 mmol), DME (0.2 mL) at 75 °C for 48 h. Method **B**: 2-(ethylamino)pyridine **1** (0.1 mmol), alkene (0.3 mmol), DME (0.2 mL) at 85 °C for 72 h. [b] Isolated yield. [c] Reaction was examined at 95 °C.

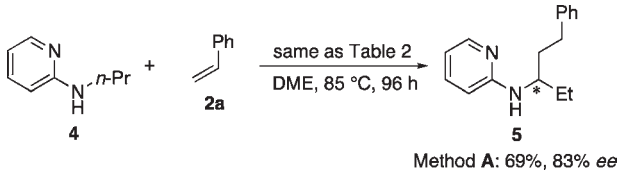
Scheme 3. Ir-Catalyzed Enantioselective Reaction of 1, 3-Diene **2j**



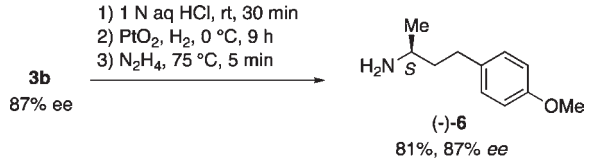
hydrochloride salt of **3b** was treated with PtO_2/H_2[16] and anhydrous hydrazine;[17] this led to formation of the corresponding chiral amine (*S*)-(−)-**6** in 81% yield without a loss of enantiomeric excess (Scheme 5). From this transformation, we could determine that the absolute configuration of **3b** was *S*.

(14) Taylor, K. M.; Snyder, S. H. M. *Science* **1970**, *168*, 1487.
(15) Clifton, J. E.; Collins, I.; Hallett, P.; Hartley, D.; Lunts, L. H. C.; Wicks, P. D. *J. Med. Chem.* **1982**, *25*, 670.
(16) Marciniak, G.; Decolin, D.; Leclerc, G.; Decker, N.; Schwartz, J. *J. Med. Chem.* **1988**, *31*, 2289.
(17) Hase, S. *J. Biochem.* **1992**, *112*, 266.

Scheme 4. Reaction of 2-(Propylamino)pyridine **4**



Scheme 5. Stereospecific Transformation of **3b** into a Chiral Amine



For a preliminary mechanistic study, we used deuterated 2-(ethylamino)pyridine **1-*d*$_2$**: the reaction of **1-*d*$_2$** was examined in the presence of H_2O (10 equiv) and the absence of styrene under the same reaction conditions (Scheme 6). As a result, the recovered substrate had a D content of 55%, and H/D exchange was ascertained. The present result implies that the secondary sp^3 C−H bond was cleaved under the present conditions.

We now assumed that cleavage of secondary sp^3 C−H bond adjacent to a nitrogen atom is an initiation step, and an asymmetric carbon atom is generated.[18] Subsequent alkene insertion to intermediate **A** along with reductive elimination gives a chiral amine as an alkylated product (Scheme 7).[19,20]

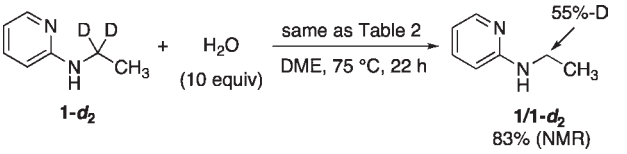
In summary, we have developed a chiral Ir(I)-catalyzed enantioselective C−C bond formation initiated by secondary

(18) By the stoichiometric reaction of 2-(ethylamino)pyridine with the chiral Ir catalyst in NMR tube, a small peak for M−H (−16.04 ppm) was observed in ^{1}H NMR, but the intermediate could not be characterized yet.

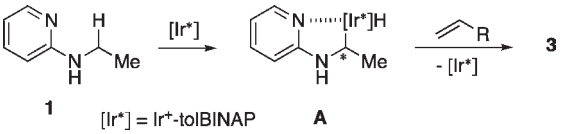
(19) For an example of C−H bond activation including hydroiridation to olefin by using an iridium hydride complex, see: Lin, Y.; Ma, D.; Lu, X. *Tetrahedron Lett*. **1987**, *28*, 3249.

(20) The mechanism including β-hydride elimination, which gives imine, and the subsequent hydrometalation cannot be completely eliminated.

Scheme 6. Reaction of the Deuterated Substrate in the Presence of H_2O



Scheme 7. Possible Mechanism Initiated by Secondary sp^3 C−H Bond Cleavage



sp^3 C−H bond cleavage of 2-(ethylamino)pyridine. Chiral amines were obtained in good yields with high enantiomeric excesses. Asymmetric induction by secondary sp^3 C−H bond activation is a simple and fascinating transformation. To the best of our knowledge, this is the first example of a highly enantioselective C−H bond activation of a methylene group not at an allylic or benzylic position. Further studies on the scope of the substrate and the precise mechanism are in progress in our laboratory.

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