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Utility of the Iridium Complex of the Pybox Ligand in Regio- and Enantioselective Allylic Substitution

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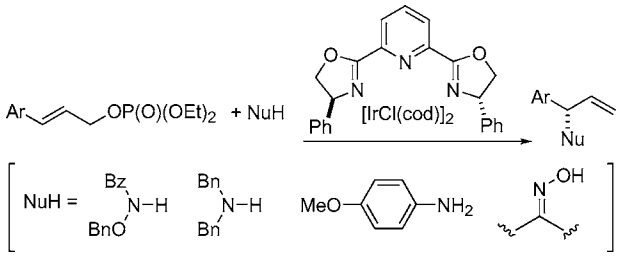
ABSTRACT



The viability of the iridium complex of pybox as chiral catalyst in allylic substitutions and the enantioselective synthesis of branched products was studied. Among several chiral ligands evaluated, the iridium complex of pybox having a phenyl group catalyzed the reaction with high activity to form the branched amines with good enantioselectivities when hydroxylamine, amine, and aniline were employed as a nucleophile. The allylic substitution with oximes proceeded smoothly to give the branched oxime ethers with good enantioselectivities.

Chiral catalysts for allylic substitution have received considerable attention.[1] Traditionally, ligands with phosphorus as donor atoms have been employed. In recent years, a variety of nitrogen ligands have proven to be highly useful as well.[1]

The box and pybox ligands are efficient nitrogen ligands in numerous asymmetric reactions.[2] The palladium complex of the bidentate box ligand has been shown to induce high stereoselectivity in the allylic substitution.[1−3] In contrast, the utility of the C_2-symmetric pybox ligand in transition-metal-catalyzed allylic substitution is largely unexplored, [4] although the pybox ligand has the advantage of increased rigidity when it behaves as a tridentate.[2,5] We now report the results of experiments to prove the utility of the pybox ligand in allylic substitution. As shown below, the iridium complex of pybox with a phenyl group catalyzed the reaction with high activity to form the branched products with good enantioselectivities.[6]

The viability of the pybox ligand in iridium-catalyzed allylic amination is the first focus of our efforts (Scheme 1). Takeuchi first reported that a high degree of regiocontrol in allylic amination and alkylation was achieved by using

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(6) Recently, the iridium-idane-pybox catalyst was used in a reductive aldol reaction. See: Zhao, C.-X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829.

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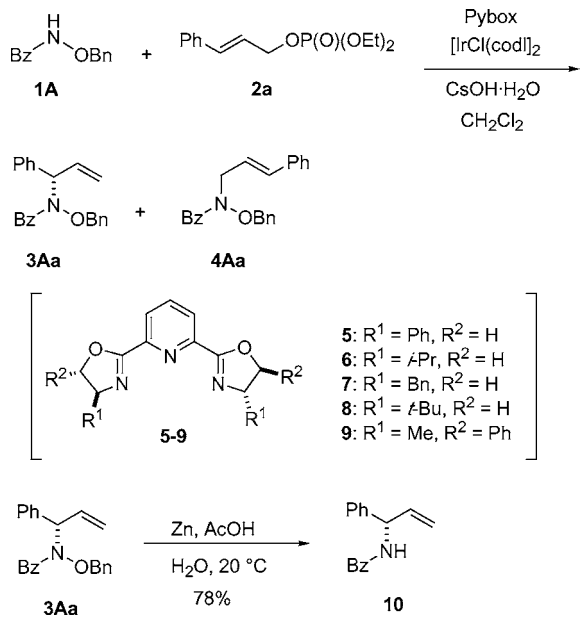
Scheme 1. Iridium−Pybox-Catalyzed Allylic Substitution with Hydroxylamine **1A**



an iridium catalyst.[7] Therefore, the control of regio- and enantioselectivities has been a subject of current interest.[8−10] We recently reported that both nitrogen and oxygen atoms on hydroxylamines having an N-electron-withdrawing substituent acted as reactive nucleophiles.[11]

On the basis of these results, we first investigated the enantioselective iridium-catalyzed allylic amination with hydroxylamine **1A** under basic conditions. As a linear achiral electrophile, the phosphate **2a** was employed to prove the efficiency of chiral ligands.[10] Table 1 outlines the optimization of the pybox ligands **5**−**9**. To a suspension of hydroxylamine **1A** and $CsOH·H_2O$ in CH_2Cl_2 was added a solution of phosphate **2a**, $[IrCl(cod)]_2$, and chiral ligand in CH_2Cl_2.

Table 1. Reaction of Phosphate **2a** with Hydroxylamine **1A** by Using $CsOH·H_2O$[a]

entry	ligand	T (°C)	time (h)	% yield[b] (ratio[c])	% ee
1	**5**	20	1	94 (76:24)	79
2	**5**	−20	8	89 (86:14)	92
3	**5**	−40	17	86 (90:10)	92
4	**6**	−20	50	27 (74:26)	33
5	**7**	−20	50	17 (51:49)	43
6	**8**	−20	50	nr	
7	**9**	−20	50	56 (85:15)	−79

[a] $[IrCl(cod)]_2$ (4 mol %) was employed, and reactions were carried out in CH_2Cl_2 in the presence of $CsOH·H_2O$. [b] Combined yields of **3Aa** and **4Aa**. [c] Ratio for **3Aa**:**4Aa**.

Among several evaluated ligands (entries 1−7), the iridium complex of pybox **5** having a phenyl group catalyzed the reaction with high activity to form the branched amine **3Aa** with 79% ee after being stirred at 20 °C for 1 h (entry 1). Although other aryl pybox ligands having 4-fluorophenyl, 4-methoxyphenyl, and 3,4,5-trimethoxyphenyl groups were also evaluated, the iridium−pybox **5** complex has shown the best reactivity. The degree of regio- and enantioselectivities was shown to be dependent on the reaction temperature; thus changing the temperature from 20 to −40 °C led to an increase in regioselectivity to 90:10 and enantioselectivity to 92% ee (entry 3). The absolute configuration of **3Aa** was determined to be *S* by the zinc-mediated reduction of the N−O bond of **3Aa** to convert *N*-((*S*)-1-phenylallyl)benzamide **10**.[12] In regard to the solvent effect, the replacement of CH_2Cl_2 with toluene or THF led to a decrease in the regio- and enantioselectivities. Additionally, other achiral allylic reagents were also tested under the optimized reaction conditions. However, no reaction occurred when cinnamyl methyl carbonate or cinnamyl acetate was employed; thus, the linear phosphate such as cinnamyl phosphate **2a** was a reactive electrophile for the iridium−pybox-catalyzed reaction.

The base influenced the regio- and enantioselectivities of the reaction of phosphate **2a** with hydroxylamine **1A** (Table 2). Good regio- and enantioselectivities were obtained when a weak base such as $CsOH·H_2O$, Cs_2CO_3, or $Ba(OH)_2·H_2O$ was employed (entries 4−6). In the presence of $Ba(OH)_2·H_2O$, the reaction proceeded smoothly at −40 °C to give a

Table 2. Effect of Base on Reaction of Phosphate **2a** with Hydroxylamine **1A**[a]

entry	base	T (°C)	time (h)	% yield[b] (ratio[c])	% ee
1	Et_2Zn	20	1	88 (64:36)	31
2	K_2CO_3	20	3	91 (94:6)	39
3	Cs_2CO_3	20	1	66 (87:13)	66
4	$Ba(OH)_2·H_2O$	20	1	92 (63:37)	70
5	$Ba(OH)_2·H_2O$	−20	1	92 (76:24)	90
6	$Ba(OH)_2·H_2O$	−40	10	91 (81:19)	92

[a] $[IrCl(cod)]_2$ (4 mol %) was employed, and reactions were carried out by using ligand **5** in CH_2Cl_2. [b] Combined yields of **3Aa** and **4Aa**. [c] Ratio for **3Aa**:**4Aa**.

(7) (a) Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* **2001**, *123*, 9525. (b) Takeuchi R.; Kashio, M. *J. Am. Chem. Soc.* **1998**, *120*, 8647. For a review, see: (c) Takeuchi, R. *Synlett* **2002**, 1954.

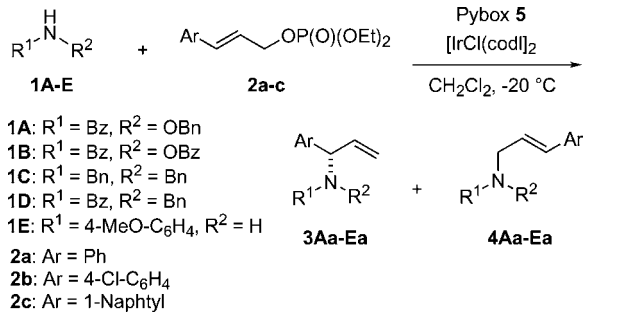
(8) For some examples, see: (a) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1681. (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4546. (c) Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761. (d) Trost, B. M.; Tsui, H.-C.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 3534. (e) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471.

(9) For some related examples, see: (a) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2426. (b) Alexakis, A.: Polet, D. *Org. Lett.* **2004**, *6*, 3529. (c) Shu, C.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4794. (d) Shu, C.; Leitner, A.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4797. (e) Lipowsky, G.; Helmchen G. *Chem. Commun.* **2004**, 116. (f) Fisher, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1629. (g) López, F.; Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 3426. (h) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164. (i) Fuji, K.; Kinoshita, N.; Tanaka K.; Kawabata, T. *Chem. Commun.* **1999**, 2289. (j) Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741.

good yield of the branched oxime ether **3Aa** with 92% ee (entry 6).

To study the viability of the iridium−pybox **5** complex in allylic amination, we next investigated the reaction of phosphates **2a**−**c** with amines **1A**−**E** (Scheme 2). All

Scheme 2. Iridium−Pybox-Catalyzed Allylic Amination



reactions were carried out in CH_2Cl_2 at −20 °C in the presence of $CsOH·H_2O$. The reaction of phosphate **2b** having an electron-withdrawing substituent on the aromatic ring proceeded slowly to give the product **3Ab** with 87% ee (Table 3, entry 1). Excellent regio- and enantioselectivities

Table 3. Allylic Amination of Phosphates **2a**−**c** with Amine **1A**−**E** in the Presence of $CsOH·H_2O$[a]

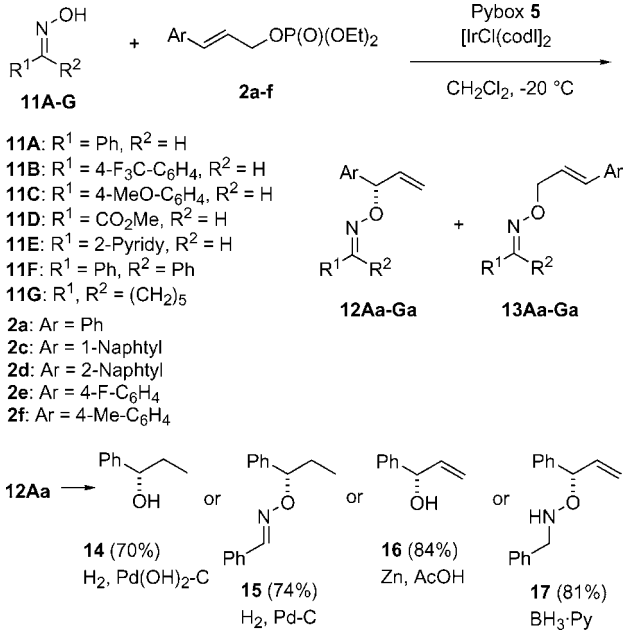
entry	amine	phospate	time (h)	% yield[b] (ratio[c])	% ee
1	**1A**	**2b**	20	75 (70:30)	87
2	**1A**	**2c**	30	95 (>95:5)	96
3	**1B**	**2a**	12	73 (73:27)	87
4	**1C**	**2a**	1	91 (71:29)	95
5	**1D**	**2a**	20	nr	
6	**1E**	**2a**	3	86 (90:10)	88

[a] $[IrCl(cod)]_2$ (4 mol %) was employed, and reactions were carried out by using ligand **5** in CH_2Cl_2 at −20 °C in the presence of $CsOH·H_2O$. [b] Combined yields of **3Aa-Ea** and **4Aa-Ea**. [c] Ratio for **3Aa-Ea**:**4Aa-Ea**.

were observed in the reaction of phosphate **2c** having a bulky 1-naphthyl group with **1A** (entry 2). The hydroxylamine **1B**, having two N-electron-withdrawing substituents, worked well in the presence of $CsOH·H_2O$ (entry 3). The reaction of **2a** with basic dibenzylamine **1C** proceeded smoothly to give the product **3Ca** with 95% ee (entry 4). In contrast, the reaction with benzylamine **1D** having a N-electron-withdrawing substituent did not take place (entry 5). Additionally, the iridium−pybox complex was effective for the reaction of **2a** with less reactive aniline derivative **1E** to give the product with good enantioselectivity (entry 6). In contrast to hydroxylamines **1A** and **1B** having N-electron-withdrawing substituents, the reactions with basic amines **1C** and **1E** also proceeded without base.

We next investigated the utility of the iridium−pybox **5** complex in enantioselective allylic substitution with oxygen nucleophiles. The oxygen nucleophile of choice was oxime, since it has shown an excellent reactivity in our recent work on allylic substitution (Scheme 3).[13]

Scheme 3. Iridium−Pybox-Catalyzed Allylic Substitution with Oximes **11A**−**11G**



The base also influenced the selectivity of the reaction of phosphate **2a** with oxime **11A** (Table 4). The good regio- and enantioselectivities were obtained when $Ba(OH)_2·H_2O$ was employed at −20 °C to gave the oxime ether **12Aa** with 95% ee and 90:10 ratio (entry 6).

Several phosphates **2c**−**f** having bulky 1-naphthyl or 2-naphthyl substituents and having an electron-withdrawing

Table 4. Effect of Base on Reaction of Phosphate **2a** with Oxime **11A**[a]

entry	base	time (h)	% yield[b] (ratio[c])	% ee
1[d]	*n*-BuLi	3	40 (66:34)	80
2[d]	K_2CO_3	3	64 (89:11)	73
3[d]	CsOAc	3	18 (98:2)	40
4[d]	Cs_2CO_3	2	80 (86:14)	80
5[d]	$Ba(OH)_2·H_2O$	1	81 (88:12)	81
6[e]	$Ba(OH)_2·H_2O$	20	87 (90:10)	95
7[e]	$CsOH·H_2O$	20	52 (89:11)	85

[a] $[IrCl(cod)]_2$ (4 mol %) was employed, and reactions were carried out by using ligand **5** in CH_2Cl_2. [b] Combined yields of **12Aa** and **13Aa**. [c] Ratio for **12Aa**:**13Aa**. [d] Reactions were carried out at 20 °C. [e] Reactions were carried out at −20 °C.

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Table 5. Reaction of Phosphates **2a**−**f** with Oximes **11A**−**G** in the Presence of $Ba(OH)_2 \cdot H_2O$[a]

entry	oxime	phosphate	time (h)	% yield[b] (ratio[c])	% ee
1[f]	**11A**	**2c**	35	83 (94:6)	90
2[e]	**11A**	**2d**	30	81 (83:17)	89
3[f]	**11A**	**2e**	40	89 (69:31)	90
4[d]	**11A**	**2f**	20	84 (83:17)	90
5[d]	**11B**	**2a**	20	91 (90:10)	92
6[e]	**11C**	**2a**	30	85 (88:12)	93
7[d]	**11D**	**2a**	10	94 (94:6)	89
8[d]	**11E**	**2a**	20	81 (82:18)	76
9[f]	**11F**	**2a**	40	64 (89:11)	94
10[d]	**11G**	**2a**	20	52 (83:17)	73

[a] Reactions were carried out by using ligand **5** in CH_2Cl_2 at −20 °C. [b] Combined yields of **12Aa-Ga** and **13Aa-Ga**. [c] Ratio for **12Aa-Ga**:**13Aa-Ga**. [d] $[IrCl(cod)]_2$ (4 mol %) was employed. [e] $[IrCl(cod)]_2$ (6 mol %) was employed. [f] $[IrCl(cod)]_2$ (8 mol %) was employed.

substituent on the aromatic ring worked well (Table V, entries 1−3). Next, several oximes **11B**−**G** were employed (entries 5−10). The stability of conjugate base of oximes would be important for the nucleophilic property of an oxygen atom of oximes. The reaction of aldoximes **11B** and **11D** containing an electron-withdrawing substituent proceeded smoothly as a result of the extra stabilization of conjugate base of oximes by an electron-withdrawing substituent (entries 5 and 7). The aldoxime **11C** containing an electron-donating substituent also produced an excellent yield of product by using 6 mol % of $[IrCl(cod)]_2$, after being stirred for 30 h (entry 6). The aldoxime **11E** containing a basic 2-pyridinyl group, a bulky ketoxime **11F**, and aliphatic ketoxime **11G** also worked well under similar reaction conditions, allowing facile incorporation of structural variety (entries 8−10).

The oxime ether **12Aa** could be converted into **14**−**17** via the selective reduction of C═C, C═N, or N−O bond of **12Aa**. The absolute configuration of **12Aa** was determined to be *S* by comparison of **14** with authentic spectral data.[14] These oxime ethers are an attractive substrate for the addition of carbon radicals and organometallic nucleophiles.[15]

In conclusion, we have demonstrated that the iridium complex of the pybox ligand acts as an effective chiral catalyst in allylic substitution. The allylic substitution of phosphates with amines and oximes gave the branched amines and oxime ethers with good enantioselectivities.

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Supporting Information Available: Experimental procedure and characterization data and ^1H and ^{13}C NMR spectra of all obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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