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Ir-catalyzed asymmetric allylic amination using chiral diaminophosphine oxides

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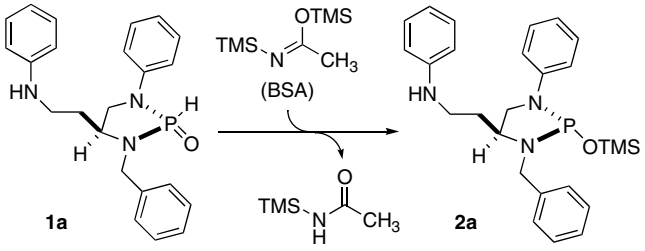
Abstract—An Ir-catalyzed asymmetric allylic amination using chiral diaminophosphine oxide is described. Asymmetric allylic amination of terminal allylic carbonates proceeded in the presence of 2 mol % of Ir catalyst, 2 mol % of chiral diaminophosphine oxide, 5 mol % of $NaPF_6$, and BSA, affording the chiral branched allylic amines in up to 95% ee.

Considerable effort has been directed toward the catalytic asymmetric synthesis of α-chiral amines, due to the ubiquity of the chiral amine unit in biologically active compounds. Among the various approaches reported to date,[1] a transition metal-catalyzed asymmetric allylic amination reaction is one of the most powerful methods for the synthesis of chiral allylic amines.[2] Several reactions of this type using Pd,[3] Ir,[4] or other transition metal catalysts[5] have been reported. We recently reported Pd-catalyzed asymmetric allylic alkylation[6] and amination[7] using aspartic acid-derived P-chirogenic diaminophosphine oxides: DIAPHOXs.[8,9] Detailed mechanistic studies on this catalyst system[6b] revealed that chiral diaminophosphine oxide **1a** is activated by *N*,*O*-bis(trimethylsilyl)acetamide (BSA)-induced tautomerization to afford trivalent phosphorus compound **2a**, which functions as the actual ligand (Scheme 1). Phosphites and phosphoroamidites are effective ligands in Ir-catalyzed allylic substitution reactions of terminal allylic electrophiles to give branched products.[10,11] The diamidophosphite structure of **2a** led us to hypothesize that the present ligand system could be extended to Ir-catalyzed asymmetric allylic substitution reactions. We describe herein an Ir-catalyzed asymmetric allylic amination using chiral diaminophosphine oxides.



Scheme 1. BSA-induced tautomerization of **1a** to **2a**.

We first examined asymmetric allylic amination of cinnamyl carbonate **3a** with benzylamine (Table 1). No reaction occurred when 1 mol % of chloro(1,5-cyclooctadiene)iridium(I) dimer ($[Ir(cod)Cl]_2$) and 4 mol % of (S,R_P)-**1a** (Ir:**1a** = 1:2) were used in CH_2Cl_2 at room temperature (entry 1). In contrast, when 1 mol % of $[Ir(cod)Cl]_2$ and 2 mol % of (S,R_P)-**1a** (Ir:**1a** = 1:1) were used, branched product **4a** was obtained in 63% ee, even though the yield was only 10% (entry 2). In this reaction, the formation of linear products **4a′** was not observed in ^1H NMR analysis of the crude sample. Encouraged by this result, we investigated the effect of various additives. Both the reactivity and enantioselectivity were dramatically affected by the counter anion of sodium salts (entries 2–5), and the best reactivity was obtained when hexafluorophosphate salt was used. Although there was a slight decrease in the enantiomeric excess (59% ee), branched product **4a** was obtained in 99% yield using 5 mol % of $NaPF_6$ (entry 7).[12] We next attempted to improve the enantioselectivity by tuning the structure of the chiral diaminophosphine oxide (Table 2 and Fig. 1). Detailed investigations into the ligand structure

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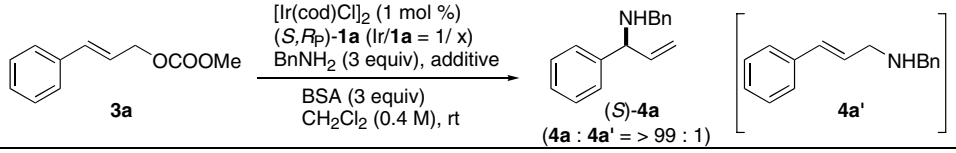
Table 1. The effect of additive



Entry	x	Additive (mol %)	Time (h)	Yield[a] (%)	ee[b] (% ee)
1	2	—	22	No reaction	—
2	1	—	22	10	63
3	1	NaI (10)	22	16	60
4	1	$NaBF_4$ (10)	22	70	66
5	1	NaBARF (10)[c]	7	93	21
6	1	$NaPF_6$ (10)	7	86	58
7	1	$NaPF_6$ (5)	7	99	59
8	1	$NaPF_6$ (2)	12	95	58

[a] Isolated yield of **4a**.
[b] Determined by HPLC analysis.
[c] BARF: tetrakis(3,5-bis-trifluoromethyl-phenyl)borate.

indicated that introduction of substituents onto the aromatic rings attached to the nitrogen atoms tended to improve the enantioselectivity. The best result was obtained using chiral diaminophosphine oxide (S,R_P)-**1h**, which possessed a *t*-Bu substituent on the para-position of the aromatic rings, and the enantiomeric excess of **4a** increased to 92% ee when the reaction was performed at −20 °C (entry 11). On the other hand, when the reaction was performed using (S,R_P)-**1i**, a diaminophosphine oxide without a nitrogen atom on the side-arm, there was no significant change in the enantioselectivity compared with that obtained using **1a** (entry 9). This result indicates that this series of diaminophosphine oxides coordinates to the Ir metal in a monodentate manner through the phosphorus atom.

Table 2. Optimization of the structure of (S,R_P)-DIAPHOX using asymmetric allylic amination of **3a** with benzylamine[a]

Entry	(S,R_P)-DIAPHOX	Temp[b] (°C)	Time (h)	Yield[c] (%)	ee[d] (% ee)
1	**1a**	rt	7	99	59
2	**1b**	rt	19	71	45
3	**1c**	rt	19	26	47
4	**1d**	rt	19	55	65
5	**1e**	rt	19	10	73
6	**1f**	rt	19	51	60
7	**1g**	rt	19	25	68
8	**1h**	rt	19	93	86
9	**1i**	rt	19	99	58
10	**1h**	4	24	98	91
11	**1h**	−20	48	96	92

[a] Reaction conditions: $[Ir(cod)Cl]_2$ (1 mol %), (S,R_P)-DIAPHOX (2 mol %), $NaPF_6$ (5 mol %), BSA (3 equiv), benzylamine (3 equiv), CH_2Cl_2 (0.4 M).
[b] rt: room temperature.
[c] Isolated yield of **4a**.
[d] Determined by HPLC analysis.

Having developed efficient conditions,[13] we examined the scope and limitation of different substrates (Table 3). When 2 mol % of Ir catalyst, 2 mol % of (S,R_P)-**1h**, and 5 mol % of $NaPF_6$ were used, asymmetric allylic amination of **3a** with primary amines and an α-branched primary amine proceeded at −20 °C to provide the corresponding branched allylic amines in good yield and in high enantioselectivity (entries 1–3). In contrast, there was a decreased enantioselectivity when morpholine was used as a nucleophile. When 2 mol % of the catalyst was used, asymmetric allylic amination **3a** proceeded at room temperature to give the corresponding product with 65% ee (entry 4).[14] Asymmetric allylic amination of various terminal allylic carbonates was also examined using benzylamine as the nucleophile. Aromatic substituents with electron-donating and electron-withdrawing functionalities were tolerant to this reaction, giving the products with good to high enantioselectivities (entries 5–12). Terminal allylic carbonates with a naphthyl substituent (entries 13 and 14) or a heteroaromatic substituent (entry 15) were also applicable to this reaction, affording the corresponding product with good enantioselectivity. In addition, asymmetric allylic amination of **5**, a substrate with an alkyl substituent, was examined using 2 mol % of the catalyst, giving the corresponding product **6** in 74% yield with 68% ee,

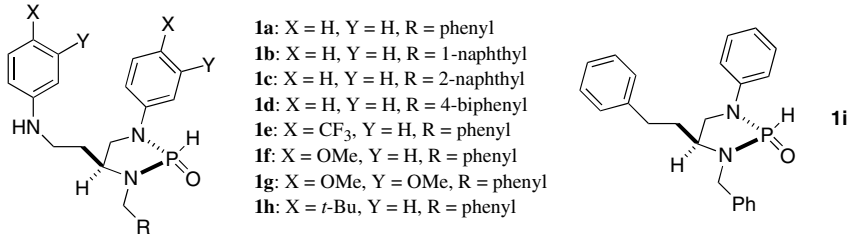
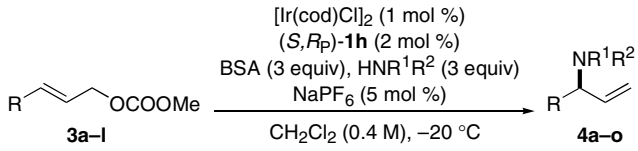


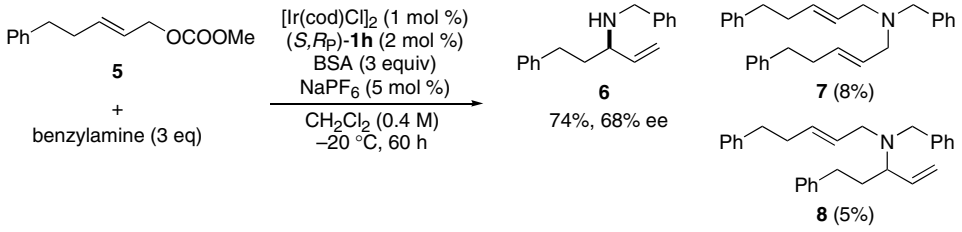
Figure 1. Chiral diaminophosphine oxides: (S,R_P)-DIAPHOXs.

Table 3. The substrate scope



Entry	Substrate	Amine	Product	Time (h)	Yield[a] (%)	Ratio[b] (branched/linear)	ee[c] (% ee)
1	**3a**: R = phenyl	Benzylamine	**4a**	48	96	>99/1	92 (*S*)
2	**3a**: R = phenyl	Frufurylamine	**4b**	48	95	>99/1	94
3	**3a**: R = phenyl	Isopropylamine	**4c**	60	98	>99/1	92
4[d]	**3a**: R = phenyl	Morpholine	**4d**	24	96	>99/1	65
5	**3b**: R = 4-methoxyphenyl	Benzylamine	**4e**	24	99	>99/1	91
6	**3c**: R = 4-fluorophenyl	Benzylamine	**4f**	36	99	>99/1	92
7	**3d**: R = 4-chlorophenyl	Benzylamine	**4g**	48	99	>99/1	94
8	**3e**: R = 4-(trifluoromethyl)-phenyl	Benzylamine	**4h**	96	90	>99/1	94
9[e]	**3f**: R = 3-methoxyphenyl	Benzylamine	**4i**	60	97	>99/1	88
10	**3g**: R = 3-fluorophenyl	Benzylamine	**4j**	48	92	>99/1	95
11	**3h**: R = 2-methoxyphenyl	Benzylamine	**4k**	48	97	>99/1	93
12	**3i**: R = 2-fluorophenyl	Benzylamine	**4l**	36	99	>99/1	88
13[e]	**3j**: R = 1-naphthyl	Benzylamine	**4m**	60	98	>99/1	87
14[e]	**3k**: R = 2-naphthyl	Benzylamine	**4n**	60	97	>99/1	87
15	**3l**: R = 2-furanyl	Benzylamine	**4o**	36	94	>99/1	88

[a] Isolated yield of the branched product.
[b] Determined by ^{1}H NMR analysis of the crude sample.
[c] Determined by HPLC analysis.
[d] Reaction was performed at room temperature.
[e] Reactions were performed at −5 °C.



Scheme 2. Asymmetric allylic amination of **5**.

accompanied by 8% of linear–linear product **7** and 5% of branched–linear product **8** (Scheme 2).

In conclusion, we achieved the Ir-catalyzed asymmetric allylic amination using chiral diaminophosphine oxides, which was dramatically accelerated by the addition of $NaPF_6$. Using the Ir–DIAPHOX–$NaPF_6$ catalyst system, the reactions proceeded with excellent branched/linear selectivity, affording the corresponding branched allylic amines in up to 95% ee. Studies of application to other nucleophiles, as well as mechanistic investigations into the catalyst system are in progress.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.003.

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12. Although the role of hexafluorophosphate anion is unknown, we speculate that, at the present stage, a cationic iridium complex might be formed by the anion exchange between hexafluorophosphate ion and a coordinated species around the Ir metal, resulting in the increased reactivity. Investigation of the mechanism is ongoing.
13. *General procedure for the Ir-catalyzed asymmetric allylic amination (Table 3, entry 1)*: To a stirred mixture of $[Ir(cod)Cl]_2$ (1.43 mg, 0.00213 mmol), (S,R_P)-**1h** (2.15 mg, 0.00426 mmol), $NaPF_6$ (1.79 mg, 0.0107 mmol), and **3a** (41.0 mg, 0.213 mmol) in CH_2Cl_2 at room temperature was added BSA (152 μL, 0.639 mmol), and the solution was stirred for 5 min at the same temperature. After the reaction mixture was cooled down to −20 °C, benzylamine (70 μL, 0.639 mmol) was added and the resulting mixture was stirred for 48 h. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate: 20/1) to give (S)-**4a** as yellow oil (46.6 mg, 96%, 92% ee). The enantiomeric excess was determined by HPLC analysis (DAICEL CHIRALCEL OD-H, 2-propanol/hexane/diethylamine 0.25/99.74/0.01, flow rate 0.5 mL/min, t_R 15.1 min [(R)-isomer] and 17.4 min [(S)-isomer], detection at 254 nm).
14. There was no improvement in the enantioselectivity when the reaction was performed at a lower temperature.