

Ir-catalyzed asymmetric allylic amination using chiral diaminophosphine oxides

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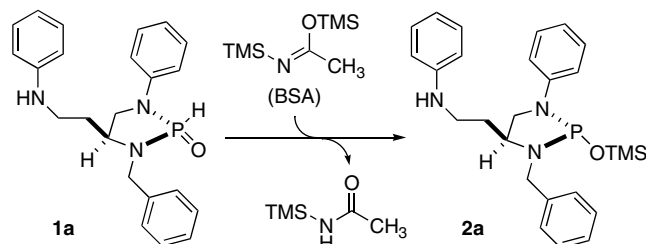
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Abstract—An Ir-catalyzed asymmetric allylic amination using chiral diaminophosphine oxide is described. Asymmetric allylic amination of terminal allylic carbonates proceeded in the presence of 2 mol % of Ir catalyst, 2 mol % of chiral diaminophosphine oxide, 5 mol % of NaPF₆, and BSA, affording the chiral branched allylic amines in up to 95% ee.

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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 catalysts⁵ have been reported. We recently reported Pd-catalyzed asymmetric allylic alkylation⁶ and amination⁷ 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 phosphoramidites 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*)-**1a** (Ir:**1a** = 1:2) were used in CH₂Cl₂ at room temperature (entry 1). In contrast, when 1 mol % of [Ir(cod)Cl]₂ and 2 mol % of (*S,R*)-**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 NaPF₆ (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	<i>x</i>	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.

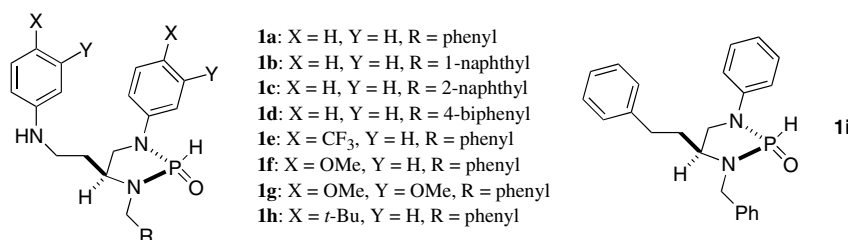
indicated that introduction of substituents onto the aromatic rings attached to the nitrogen atoms tended to improve the enantioselectivity. The best result was obtained using chiral diaminophosphine oxide (*S,R*)-**1h**, which possessed a *t*-Bu substituent on the para-position of the aromatic rings, 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*)-**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.

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*)-**1h**, and 5 mol % of NaPF₆ 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,

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

Entry	(<i>S,R</i>)-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*)-DIAPHOX (2 mol %), NaPF₆ (5 mol %), BSA (3 equiv), benzylamine (3 equiv), CH₂Cl₂ (0.4 M).^b rt: room temperature.^c Isolated yield of **4a**.^d Determined by HPLC analysis.**Figure 1.** Chiral diaminophosphine oxides: (*S,R*)-DIAPHOXs.

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