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Ir-catalyzed asymmetric allylic alkylation using chiral diaminophosphine oxides: DIAPHOXs. Formal enantioselective synthesis of (−)-paroxetine

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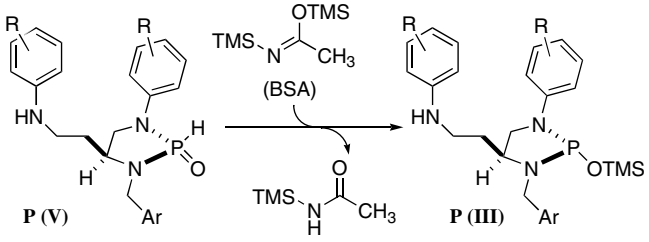
Abstract—An Ir-catalyzed asymmetric allylic alkylation using chiral diaminophosphine oxide is described. Asymmetric allylic alkylation of terminal allylic carbonates proceeded using 5 mol % of Ir catalyst, 5 mol % of DIAPHOX **1i**, 10 mol % of $NaPF_6$, 10 mol % of LiOAc, and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), affording the corresponding branched products in excellent yield and in up to 95% ee. The developed catalytic asymmetric reaction was successfully applied to a formal enantioselective synthesis of (−)-paroxetine.

Transition-metal catalyzed asymmetric allylic alkylation is one of the most powerful methods for introducing chirality on the allylic carbon. Various types of asymmetric allylic alkylations have been reported.[1] Pd-catalyzed asymmetric allylic alkylation normally favors nucleophilic addition to the less substituted allylic terminus, although ligands can influence this selectivity.[2] In contrast, asymmetric allylic alkylation using W-,[3] Mo-,[4] Ir-,[5] and Rh-catalysts[6] favors attack at the more substituted terminus, providing chiral branched products regioselectively.[7] We recently reported that aspartic acid-derived P-chirogenic diaminophosphine oxides (DIAPHOXs) are useful chiral preligands in several Pd-catalyzed asymmetric allylic substitutions.[8,9] In these reactions, chiral diaminophosphine oxides are activated in situ by *N*,*O*-bis(trimethylsilyl)acetamide (BSA)-induced tautomerization, affording trivalent diamidophosphite species, which function as the actual ligands (Scheme 1). The present chiral ligand system was also applicable to Ir-catalyzed asymmetric allylic amination of terminal allylic carbonates to give branched allylic amines, which was dramatically accelerated by the addition of $NaPF_6$.[10] The success of the asymmetric allylic amination led us to examine asymmetric allylic alkylation using the Ir–DIAPHOX–$NaPF_6$ catalyst system.[11,12] We report herein an Ir-catalyzed asymmetric allylic alkylation using DIAPHOXs. The developed catalytic asymmetric reaction was successfully applied to the formal enantioselective synthesis of (−)-paroxetine.



Scheme 1. BSA-induced tautomerization of DIAPHOXs.

We first examined asymmetric allylic alkylation of cinnamyl carbonate **2a** with dimethyl malonate using (S,R_P)-**1a** (Table 1 and Fig. 1). Although no reaction occurred when 2.5 mol % of chloro(1,5-cyclooctadiene)iridium(I) dimer ($[Ir(cod)Cl]_2$) and 5 mol % of (S,R_P)-**1a** (Ir/**1a** = 1/1) were used, the same reaction proceeded in the presence of 10 mol % of $NaPF_6$, affording branched product (*S*)-**3a** with high regioselectivity (29% yield, **3a**/**3a**′ = 97/3, 75% ee) (entry 1).[13] The addition of LiCl remarkably increases both reactivity and enantioselectivity in the Ir-catalyzed asymmetric allylic alkylation.[5b,c,g] Thus, we investigated the effect of

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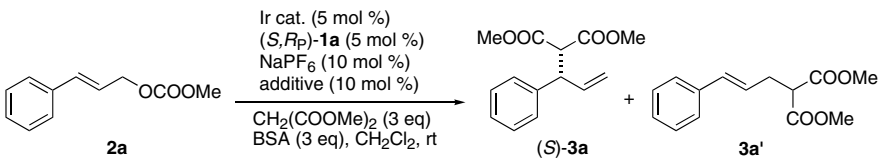
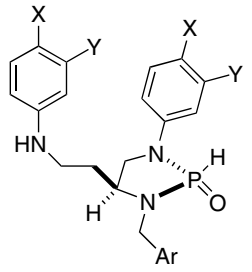
Table 1. Optimization of the reaction conditions



2a (S)-3a 3a'

Entry	Additive	Conc. (M)	Time (h)	Yield[a] (%)	Ratio[b] (**3a**/**3a**′)	ee[c] (% ee)
1	—	0.4	24	29	97/3	75
2	LiCl	0.4	24	95	97/3	72
3	LiOAc	0.4	24	71	95/5	90
4	NaOAc	0.4	24	39	93/7	73
5	KOAc	0.4	24	36	95/5	80
6	CsOAc	0.4	24	38	97/3	85
7	$Mg(OAc)_2{\cdot}4H_2O$	0.4	24	77	99/1	80
8	$Zn(OAc)_2$	0.4	24	93	98/2	60
9	$In(OAc)_3$	0.4	24	92	98/2	60
10	Bu_4NOAc	0.4	24	42	99/1	60
11	LiOAc	0.5	24	73	96/4	88
12	LiOAc	0.25	24	90	95/5	88

[a] Isolated yield of **3a**+**3a**′.
[b] Determined by ^{1}H NMR analysis of the crude sample.
[c] Determined by HPLC analysis.



1a: X = H, Y = H, Ar = phenyl
1b: X = OMe, Y = H, Ar = phenyl
1c: X = OMe, Y = OMe, Ar = phenyl
1d: X = *t*-Bu, Y = H, Ar = phenyl
1e: X = CF_3, Y = H, Ar = phenyl
1f: X = H, Y = H, Ar = 1-naphthyl
1g: X = H, Y = H, Ar = 2-naphthyl
1h: X = H, Y = H, Ar = 4-biphenyl
1i: X = H, Y = H, Ar = 3-biphenyl

Figure 1. (S,R_P)-DIAPHOXs.

additives in detail. Although reactivity was significantly improved when LiCl was used as the additive, there was a slight decrease in the enantioselectivity (entry 2). Both reactivity and enantioselectivity, on the other hand, were affected by the addition of acetate salts (entries 3–10). The best enantioselectivity (90% ee) was obtained when LiOAc was used as the additive (entry 3). Further optimization with regard to the reaction concentration resulted in the formation of branched product (*S*)-**3a** in good yield (90% yield, **3a**/**3a**′ = 95/5) with 88% ee. The increased reactivity under the diluted reaction condition is likely related to the solubility of LiOAc in CH_2Cl_2 (entries 3, 11, and 12). We next attempted to improve the regioselectivity and enantioselectivity by tuning the structure of DIAPHOX (Table 2). Studies of the effect of substituents on the aromatic rings revealed that DIAPHOX **1i**, which possesses a 3-biphenyl group at the benzylic moiety, was best for asymmetric induction (90% ee), giving the branched product (*S*)-**3a** in good yield with excellent regioselectivity (93% yield, **3a**/**3a**′ = 99/1) (entry 9).

Having developed efficient conditions,[14] we examined the scope and limitations of different substrates (Table 3). Using 5 mol % of Ir catalyst, 5 mol % of (S,R_P)-**1i**, 10 mol % of $NaPF_6$, and 10 mol % of LiOAc, asymmetric allylic alkylation of various terminal allylic carbonates were performed using dimethyl malonate as the nucleophile. Terminal allylic carbonates with an electron-donating group, as well as an electron-withdrawing group, on the aromatic ring are tolerated in this reaction, giving the corresponding branched products in good yield with high regio- and enantioselectivity (entries 1–8). In addition, terminal allylic carbonates with a naphthyl substituent (entries 9 and 10) or a heteroaromatic substituent (entry 11) were also applicable to this reaction, affording the corresponding product with good enantioselectivity. On the other hand, asymmetric allylic alkylation of **2l**, a substrate with an alkyl substituent, gave the linear product predominantly (branched/linear = 39/61) and the enantiomeric excess of the branched product was moderate (entry 12).

Thus, the present catalytic asymmetric reaction had broad generality for γ-aryl substituted-terminal allylic

Table 2. Ir-catalyzed asymmetric allylic substitution of **2a** with dimethyl malonate using **1a**–**i**[a]

Entry	DIAPHOX	Time (h)	Yield[b] (%)	Ratio[c] (**3a**/**3a**′)	ee[d] (% ee)
1	**1a**	24	90	95/5	88
2	**1b**	24	94	98/2	88
3	**1c**	24	98	96/4	85
4	**1d**	24	78	90/10	45
5	**1e**	24	17	97/3	85
6	**1f**	24	54	95/5	57
7	**1g**	24	69	96/4	74
8	**1h**	24	92	97/3	82
9	**1i**	24	92	99/1	90

[a] Conditions: Ir cat. (5 mol %), (S,R_P)-DIAPHOX (5 mol %), $NaPF_6$ (10 mol %), LiOAc (10 mol %), dimethyl malonate (3 equiv), BSA (3 equiv), CH_2Cl_2 (0.25 M).
[b] Isolated yield of **3a**+**3a**′.
[c] Determined by ^{1}H NMR analysis of the crude sample.
[d] Determined by HPLC analysis.