

# Catalytic Chiral Leaving Group Strategy for Asymmetric Substitutions at $sp^3$ -Hybridized Carbon Atoms: Kinetic Resolution of $\beta$ -Amino Alcohols by *p*-Methoxybenzylation

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**Abstract:** We developed a catalytic strategy for asymmetric substitution reactions at  $sp^3$ -hybridized carbon atoms using a chiral alkylating agent generated in situ from trichloroacetimidate and a chiral phosphoric acid. The resulting chiral *p*-methoxybenzyl phosphate selectively reacted with  $\beta$ -amino alcohols rather than those without the  $\beta$ -NH functionality. An electronically and sterically tuned chiral phosphoric acid was developed to enable the kinetic resolution of amino alcohols, with good enantioselectivity, through *p*-methoxybenzylation.

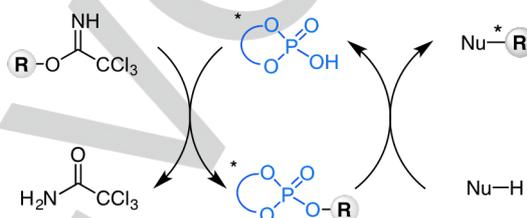
Advances in asymmetric synthesis rely on the development of new catalytic methods that provide an array of versatile enantioselective transformations. Substitution at  $sp^3$ -hybridized carbon atoms is one of the most fundamental transformations in organic synthesis. For this class of reaction, catalytic asymmetric induction is generally achieved by taking advantage of noncovalent interactions such as ion pairing or hydrogen bonding between chiral catalysts and substrates.<sup>[1]</sup> One attractive approach based on covalent interactions involves a chiral leaving group (Figure 1, A).<sup>[2,3]</sup> The chiral source ( $X^*$ ) is directly bonded to the electrophile (R) in the substitution step; therefore, highly enantioselective transformations are achieved. However, this strategy relies on the use of stoichiometric amounts of chiral sources, which is a drawback.

Recently, we developed a chiral phosphoric acid-catalyzed intramolecular  $S_N2'$  reaction in which trichloroacetimidate was used as a leaving group that could be activated by a Brønsted acid through hydrogen-bonding interactions.<sup>[4,5]</sup> During the study, we observed a substitution reaction of an allylic trichloroacetimidate with a chiral phosphoric acid to afford the corresponding organophosphate.<sup>[6]</sup> This finding is the basis of our catalytic chiral leaving group strategy for overcoming the drawback mentioned above (Figure 1, B). An alkylating agent bearing a chiral phosphate as a leaving group can be generated in situ from a chiral phosphoric acid and an appropriate trichloroacetimidate. The generated alkylating agent undergoes asymmetric substitution under the control of the chiral leaving group and enantioselectively gives  $Nu^*-R$  as products, with regeneration of the catalyst.<sup>[7]</sup> Although this strategy for

## A. Conventional strategy - stoichiometric reaction



## B. This work - catalytic reaction

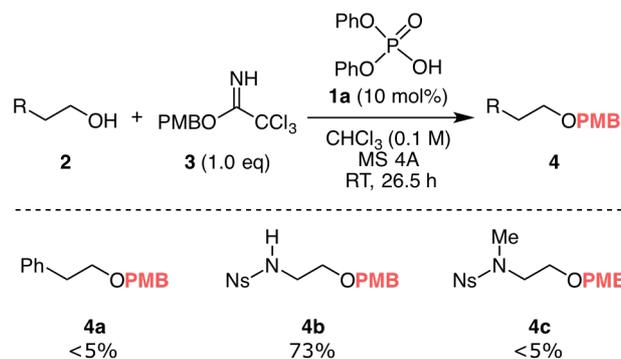


**Figure 1:** Chiral leaving group strategy for asymmetric substitution reactions.

asymmetric transformations, i.e., nucleophilic catalysis, is common for reactions at unsaturated,  $sp^2$ -hybridized carbon atoms, such as acylation<sup>[8]</sup> or allylic substitution,<sup>[9]</sup> the corresponding reaction at saturated,  $sp^3$ -hybridized carbon atoms is unexplored.

Our investigations commenced with the reactivity of the phosphate as a leaving group (Scheme 1). Initially, phenethyl alcohol (**2a**) was treated with 4-methoxybenzyl (PMB)-2,2,2-trichloroacetimidate (**3**) and a catalytic amount of diphenyl phosphate (**1a**) in chloroform at room temperature in the presence of powdered molecular sieves (MS) 4A but was found to be unreactive. To our delight, when *N*-Ns-protected 2-aminoethanol (**2b**) was subjected to the same reaction condition, *p*-methoxybenzylation did proceed to give 73% yield of **4b**. Since *N*-methylated amino alcohol **2c** was completely unreactive, the N-H functionality plays an important role in accelerating the *p*-methoxybenzylation.

**Scheme 1.** Preliminary Study on the Reactivity of PMB Diphenylphosphate<sup>[6]</sup>



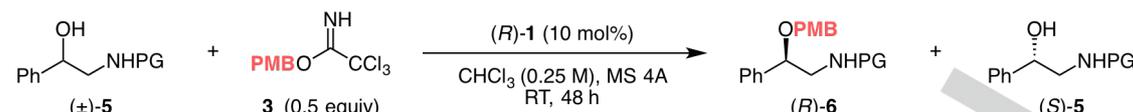
[a] Yields were determined by <sup>1</sup>H NMR analysis using Ph<sub>3</sub>CH as an internal standard. Ns = 2-nitrobenzenesulfonyl

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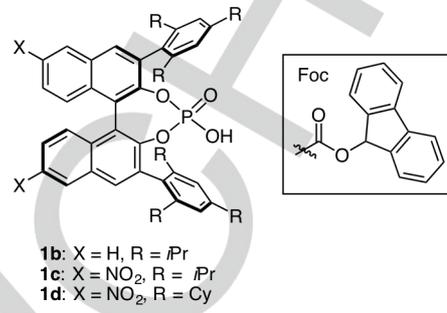
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**Table 1.** Optimization of Reaction Conditions for Kinetic Resolution of **5** via *p*-Methoxybenzylation.<sup>[a]</sup>


entry	<b>1</b>	<b>5</b> (PG)	<b>6</b>	% conv. <sup>b</sup>	<i>s</i>
1	<b>1b</b>	<b>5a</b> (Ns)	<b>6a</b>	0	–
2	<b>1c</b>	<b>5a</b> (Ns)	<b>6a</b>	50	1.2
3	<b>1c</b>	<b>5b</b> (Bz)	<b>6b</b>	42	1.2
4	<b>1c</b>	<b>5c</b> (Fmoc)	<b>6c</b>	48	2.1
5	<b>1c</b>	<b>5d</b> (Cbz)	<b>6d</b>	50	3.4
6	<b>1d</b>	<b>5d</b> (Cbz)	<b>6d</b>	47	4.6
7	<b>1d</b>	<b>5e</b> (Foc)	<b>6e</b>	43	7.7
8 <sup>c</sup>	<b>1d</b>	<b>5e</b> (Foc)	<b>6e</b>	26	8.6

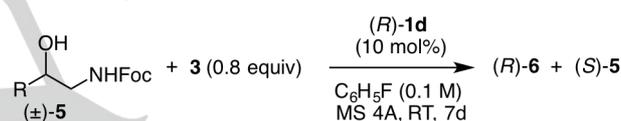


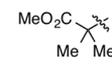
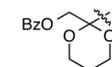
**1b:** X = H, R = *i*Pr  
**1c:** X = NO<sub>2</sub>, R = *i*Pr  
**1d:** X = NO<sub>2</sub>, R = Cy

[a] Reaction conditions: **5** (0.1 mmol), **3** (0.05 mmol), **1** (0.01 mmol), and MS 4A (50 mg) in CHCl<sub>3</sub> (0.4 mL). [b] Calculated from ee values, determined by chiral stationary phase HPLC, of **6** and recovered **5**. [c] Conducted at a concentration of 0.1 M.

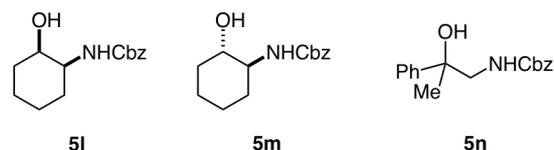
We next turned our attention to whether the chiral organophosphate could provide enantioinduction in the substitution reaction. In light of the initial results, we chose the kinetic resolution of amino alcohols **5** through *p*-methoxybenzylation (Table 1) as a test reaction. The kinetic resolution of racemic secondary alcohols via enantioselective protection is an important process, and many catalytic<sup>[10,11]</sup> and enzymatic methods<sup>[12]</sup> have been developed for this purpose. Despite the widespread use of the *p*-methoxybenzyl (PMB) group in synthetic organic chemistry, there is no report of enantioselective *p*-methoxybenzylation of alcohols,<sup>[13]</sup> as opposed to acylation,<sup>[8,14]</sup> silylation<sup>[15,16]</sup> and acetalization.<sup>[17]</sup> A solution of *N*-(2-nitrobenzenesulfonyl) (Ns) amino alcohol **5a**, PMB trichloroacetimidate (**3**; 0.5 equiv), and (*R*)-binaphthol-derived phosphoric acid **1b**<sup>[18]</sup> (10 mol%) in chloroform was stirred at room temperature in the presence of powdered 4A molecular sieves (4A MS). However, the chiral PMB phosphate derived from **1b** and **3** was so unreactive that PMB ether **6a** was not produced even after 48 h (Table 1, entry 1).<sup>[19]</sup> To overcome this issue, we used our previously reported catalyst **1c**,<sup>[11b]</sup> which bears nitro groups at the 6,6'-positions of the binaphthol backbone and has enhanced leaving group ability. The use of **1c** significantly increased the reactivity, but without enantioinduction (selectivity factor *s* 1.2,<sup>[20]</sup> entry 2). Screening of conventional *N*-protecting groups showed that **5d**, bearing a benzyloxycarbonyl (Cbz) group, gave higher *s* values (entries 2–5). Catalyst **1d**, bearing cyclohexyl (Cy) groups instead of isopropyl groups, improved the selectivity (entry 6). Further investigation of *N*-protecting groups showed that the use of a 9-fluorenyloxycarbonyl (Foc) group increased the *s* value to 7.7 (entry 7). The reaction at a lower concentration (0.1 M) of **5e** resulted in a synthetically useful *s* value of 8.6 (entry 8).

Solvent screening showed that fluorobenzene improved the reaction rate (see SI). The enantiomerically enriched alcohol (*S*)-**5e** was recovered in 29% yield with 96% ee (*s* 8.8; Table 2, entry 1) under these conditions.<sup>[21]</sup> The use of amino alcohol **5f**, bearing an electron-deficient aromatic ring, substantially increased the reaction rate, while preserving the selectivity

**Table 2.** Substrate Scope of Kinetic Resolution.<sup>[a]</sup>

entry	amino alcohol R	<b>5</b>	recovered <b>5</b> %yield <sup>[b]</sup>	er <sup>[c]</sup>	<i>s</i> <sup>[d]</sup>
1	Ph	<b>5e</b>	29	97:3	8.7
2 <sup>[e]</sup>	4-ClC <sub>6</sub> H <sub>4</sub>	<b>5f</b>	32	97:3	8.7
3 <sup>[f]</sup>	Cy	<b>5g</b>	29	95:5	12
4 <sup>[f]</sup>	<i>t</i> -Bu	<b>5h</b>	36	98:2	18
5 <sup>[e]</sup>		<b>5i</b>	42	97:3	20
6 <sup>[f]</sup>		<b>5j</b>	40	>99:1	32
7 <sup>[f]</sup>		<b>5k</b>	34	98:2	14

Unsuccessful substrates (No reaction under the optimal conditions)

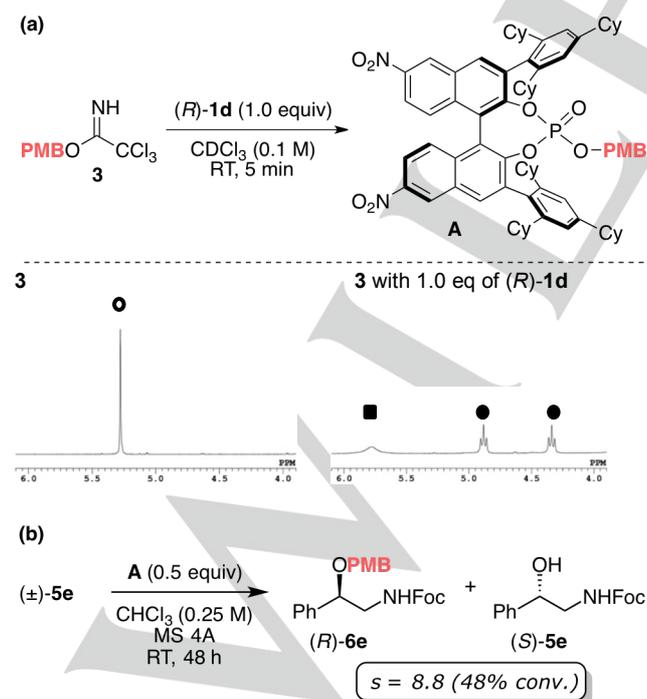


[a] Reactions were carried out on a 0.1 mmol scale. [b] Isolated yields. [c] Determined by chiral stationary phase HPLC. [d] Based on theoretical conversion and er of recovered **5**. [e] Using CHCl<sub>3</sub> as solvent for 4 d. [f] Using 15 mol% of (*R*)-**1d**.

(entry 2). The  $s$  values of kinetic resolutions using amino alcohols with secondary and tertiary alkyl substituents at the stereogenic center were higher than those of reactions using amino alcohols bearing aromatic rings, but the reaction rates were lower (entries 3 and 4). Various functional groups such as nitrile and ester groups were tolerated under the reaction conditions; amino alcohols **5i** and **5j** were resolved with good selectivities (entries 5 and 6). It is worth noting that acetal **5k**, which is potentially sensitive to acids, was inert under these conditions (entry 7). The developed methodology was failed to apply to 2-aminocycloalkanol **5l**, **5m** and tertiary alcohol **5n**, presumably due to the steric hindrance at carbon atoms adjacent to the hydroxyl group or NH functionality.

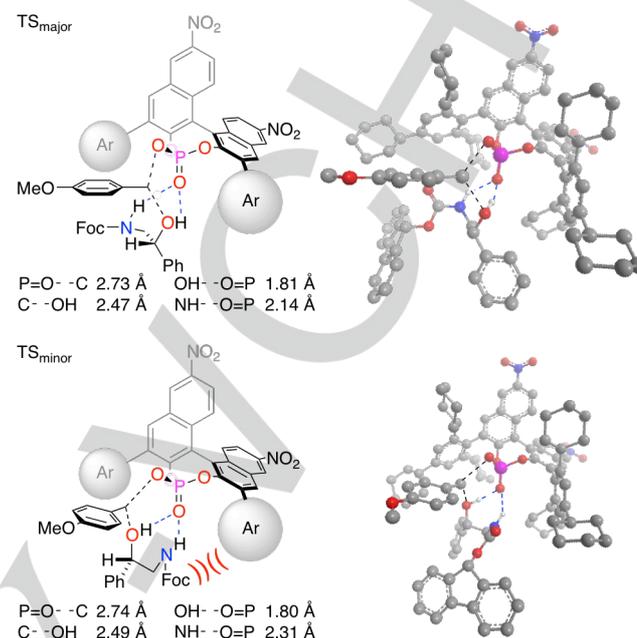
In situ formation of the PMB phosphate was confirmed using  $^1\text{H}$  NMR spectroscopy (Figure 2a). When (*R*)-**1d** (1 equiv) was added to a solution of **3** in  $\text{CDCl}_3$ , the 2H singlet signal from the benzylic proton of **3** at 5.3 ppm (open circle) disappeared within 5 min, and two 1H triplet signals (filled circles) appeared, at 4.9 and 4.3 ppm, with concomitant formation of trichloroacetamide (filled square). This result clearly indicates the formation of PMB phosphate **A**, in which the two benzylic protons are diastereotopic and have spin coupling with each other as well as with the phosphorus atom. We performed a stoichiometric reaction to confirm that **A** is an actual intermediate (Figure 2b). Racemic **5e** was added to a solution of **A**, prepared in situ by mixing **3** (0.5 equiv) and (*R*)-**1d** (0.5 equiv) in the presence of 4A MS. The kinetic resolution proceeded with an  $s$  value comparable to that in the catalytic reaction (Table 1, entry 8). These results verify the reaction pathway shown in Figure 1, B.

The transition state (TS) geometries were calculated at the ONIOM (B3LYP/6-31G\*\*: $\text{HF}/3-21\text{G}$ ) theoretical level (see SI for details).  $\text{TS}_{\text{major}}$  and  $\text{TS}_{\text{minor}}$  that give (*R*)- and (*S*)-**6e**, respectively, are shown in Figure 3. The lengths of the breaking and forming C–O bonds in  $\text{TS}_{\text{major}}$  were 2.73 and 2.47 Å,



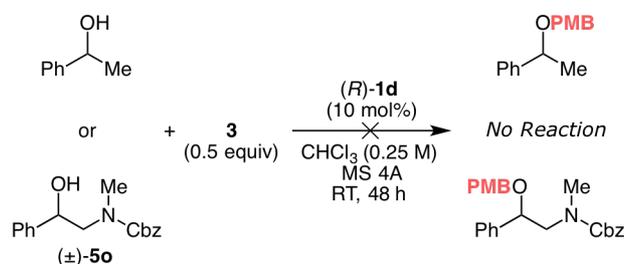
**Figure 2.** Mechanistic studies: (a)  $^1\text{H}$  NMR spectrum of chiral PMB phosphate **A** and (b) kinetic resolution of **5e** with **A**.

respectively, indicating that a loose  $\text{S}_{\text{N}}2$  mechanism is involved. The reactions with 1-phenylethanol and the *N*-methylated analog **5o**, with no adjacent NH functionality failed, thus the two hydrogen bonds,  $\text{OH}\cdots\text{O}=\text{P}$  (1.81 Å) and  $\text{NH}\cdots\text{O}=\text{P}$  (2.14 Å), are probably important in stabilizing the TS (Scheme 2).



**Figure 3.** Chem3D perspective view of transition state structures  $\text{TS}_{\text{major}}$  to give (*R*)-**6e** and  $\text{TS}_{\text{minor}}$  to give (*S*)-**6e** at ONIOM (B3LYP/6-31G\*\*: $\text{HF}/3-21\text{G}$ ) theoretical level.

Analysis of the ONIOM energies sheds light on the mechanism of the observed asymmetric induction. The ONIOM high level layer energy of  $\text{TS}_{\text{major}}$ , which only reflects the energy of the reaction center and the hydrogen bonds (see SI for details) is more stable than that of  $\text{TS}_{\text{minor}}$  by 1.33 kcal/mol. This is probably attributed to the distorted arrangement of the reacting hydroxy, PMB, and phosphate moieties in  $\text{TS}_{\text{minor}}$  caused by steric repulsion between the Foc moiety and one of the cyclohexyl groups. The calculated  $\Delta\Delta\text{G}$  between  $\text{TS}_{\text{major}}$  and  $\text{TS}_{\text{minor}}$  was 1.26 kcal/mol at the M06-2X/6-31G\*\*/CPCM ( $\text{CHCl}_3$ )/ONIOM (B3LYP/6-31G\*\*: $\text{HF}/3-21\text{G}$ ) theoretical level, corresponding to 8.3:1 selectivity at room temperature; this is in good agreement with the experimental results.



**Scheme 2.** Control experiments

In summary, we have developed a novel strategy for catalytic asymmetric substitution reactions using chiral organophosphates generated in situ from phosphoric acids and trichloroacetimidate. This strategy uses a chiral phosphoric acid

as a leaving group, which is its alternative catalytic mode to the conventional hydrogen-bond donor<sup>[22]</sup> or counter anion.<sup>[23]</sup> The first kinetic resolution of amino alcohols through *p*-methoxybenzylation was achieved via this strategy using the novel chiral phosphoric acid **1d**. NMR studies and a stoichiometric reaction verified the catalytic leaving group mechanism, which had previously been proposed based on MS observations<sup>[7a]</sup> and DFT calculations.<sup>[7b]</sup>

## Experimental Section

General Procedure: To a stirred suspension of racemic amino alcohol **5** (0.100 mmol), 4-methoxybenzyl 2,2,2-trichloroacetimidate **3** (22.6 mg, 80.0  $\mu$ mol) and molecular sieves 4A (50 mg) in solvent (1 mL) was added (*R*)-**1d** (10 or 15 mol%), and the resulting mixture was stirred at rt for the indicated time. The reaction was quenched by the addition of MeOH (5 mL), and then the solvent was removed under reduced pressure. After a flash column chromatography on silica gel (hexane/AcOEt 9/1 to 6/4), PMB ether **6** and amino alcohol **5** were obtained. The enantiomeric excess was determined by chiral stationary phase HPLC analysis.

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**Keywords:** asymmetric catalysis • substitution reaction • kinetic resolution • Brønsted acid catalysis •  $\beta$ -amino alcohols

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