

Asymmetric Catalysis

Use of a Catalytic Chiral Leaving Group for Asymmetric Substitutions at sp³-Hybridized Carbon Atoms: Kinetic Resolution of β-Amino Alcohols by *p*-Methoxybenzylation

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Abstract: A catalytic strategy was developed for asymmetric substitution reactions at sp^3 -hybridized carbon atoms by using a chiral alkylating agent generated in situ from trichloroacetimidate and a chiral phosphoric acid. The resulting chiral pmethoxybenzyl phosphate selectively reacts with β -amino alcohols rather than those without a β -NH functionality. The use of an electronically and sterically tuned chiral phosphoric acid enables the kinetic resolution of amino alcohols through p-methoxybenzylation with good enantioselectivity.

Advances in asymmetric synthesis rely on the development of new catalytic methods that provide an array of versatile enantioselective transformations. Substitution at sp³-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.^[1] One attractive approach based on covalent interactions involves a chiral leaving group (Figure 1 A).^[2,3] The chiral source (X*) is directly bonded to the electrophile (R) in the substitution step, which allows highly enantioselective transformations to be 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 $S_N 2'$ reaction in which trichloroacetimidate was used as a leaving group that could be activated by a Brønsted acid through hydrogen-bonding interactions.^[4,5] During the study, we observed a substitution reaction of an allylic trichloroacetimidate with a chiral phosphoric acid to afford the corresponding organophosphate.^[6] This finding is the basis of our strategy for overcoming the drawback mentioned above, that is, the use of a catalytic chiral leaving group (Figure 1B). An alkylating agent bearing a chiral

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Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201607208. A. Conventional strategy - stoichiometric reaction

 $R - X^* + Nu \longrightarrow R - Nu + X^*$

B. This work - catalytic reaction



Figure 1. Use of a chiral leaving group for asymmetric substitution reactions.

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 the product, with regeneration of the catalyst.^[7] Although this strategy for asymmetric transformations (nucleophilic catalysis) is common for reactions at unsaturated sp²-hybridized carbon atoms, such as acylation^[8] or allylic substitution,^[9] the corresponding reaction at saturated sp³-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 PMB-2,2,2-trichloroacetimidate (**3**) and a catalytic amount of diphenyl phosphate (**1a**) in chloroform at room temperature in the presence of powdered 4A molecular sieves (MS) but was found to be unreactive. To our delight, when N-Ns-protected 2-aminoethanol **2b** was subjected to the same reaction conditions, *p*-methoxybenzy-lation proceeded to give **4b** in 73 % yield. Since N-methylated amino alcohol **2c** was completely unreactive, the N–H functionality plays an important role in accelerating the *p*-methoxybenzylation.

We next turned our attention to whether the chiral organophohsphate 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 through enantiose-lective protection is an important process, and many cata-

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Scheme 1. A preliminary study on the reactivity of PMB diphenylphosphate.^[a] [a] Yields were determined by ¹H NMR analysis using Ph₃CH as an internal standard. PMB = 4-methoxybenzyl. MS = molecular sieves, Ns=2-nitrobenzenesulfonyl.

lytic^[10,11] and enzymatic methods^[12] have been developed for this purpose. Despite the widespread use of the PMB group in synthetic organic chemistry, there is no report of enantioselective *p*-methoxybenzylation of alcohols,^[13] in contrast to acylation,^[8,14] silylation,^[15,16] and acetalization.^[17] A solution of Ns amino alcohol 5a, PMB trichloroacetimidate (3; 0.5 equiv), and (R)-binaphthol-derived phosphoric acid 1b^[18] (10 mol%) in chloroform was stirred at room temperature in the presence of powdered 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).^[19] To overcome this, we used our previously reported catalyst 1c,^[11b] 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;^[20] Table 1, entry 2). Screening of conventional N-protecting groups showed that 5d, which bears a benzyloxycarbonyl (Cbz) group, gave higher s values (Table 1, entries 2-5). Catalyst 1d, which bears 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 (Table 1, entry 7). The reaction at a lower concentration (0.1M) of 5e resulted in a synthetically useful s value of 8.6 (Table 1, entry 8).

Solvent screening showed that fluorobenzene improves the reaction rate (see the Supporting Information). The enantiomerically enriched alcohol (S)-5e was recovered in 29% yield with 96% ee (s = 8.8; Table 2, entry 1) under these conditions.^[21] The use of amino alcohol 5 f, which bears an electron-deficient aromatic ring, substantially increased the reaction rate while preserving the selectivity (Table 2, entry 2). The s values for kinetic resolutions using amino

Table 2: Substrate scope of the kinetic resolution.[a]

(R´ (±	OH NHFoc + 3)-5	(0.8 equiv)	(<i>R</i>)-1d (10 mol%) C ₆ H ₅ F (0.1 M MS 4A, RT,	→ (<i>R</i>)- 6 + 1) 7d	(S)- 5			
Entry	Amino alcoh R	ol 5	Recov % yield ^[b]	vered 5 e.r. ^[c]	s ^[d]			
1 2 ^[e]	Ph 4-ClC ₂ H,	5 e 5 f	29 32	97:3 97:3	8.7 8.7			
_ 3 ^[f] ⊿ ^[f]	Cy	5 g 5 h	29 36	95:5 98·2	12			
5 ^[e]	NC X	51	42	97:3	20			
6 ^[f]	MeO ₂ C , 'tr Me Me	5 j	40	>99:1	32			
7 ^[f]	BzO	5 k	34	98:2	14			
Unsuccessful substrates (No reaction under the optimal conditions)								

VHCD2



[a] Reactions were carried out on a 0.1 mmol scale. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] Based on theoretical conversion and the e.r. of recovered 5. [e] Using CHCl₃ as a solvent for 4 d. [f] Using 15 mol% of (R)-1d.

Table 1: Optimization of reaction conditions for the kinetic resolution of 5 through *p*-methoxybenzylation.^[a]

	Ph	H NHPG + (±)- 5	MH PMBO CCI ₃ 3 (0.5 equiv)	(<i>R</i>)- 1 (1 CHCl ₃ (0.2 RT,	10 mol%) 5 M), MS 4A , 48 h	Ph NHPG + (R)-6	OH Ph (S)- 5
Entry	1	5 (PG)	6	% conv. ^[b]	S		
1	1 b	5a (Ns)	6a	0	_	R V R	
2	1c	5 a (Ns)	6a	50	1.2	X	
3	1c	5b (Bz)	6 b	42	1.2) R	Foc
4	1c	5c (Fmoc)	6c	48	2.1		
5	1c	5 d (Cbz)	6 d	50	3.4		
6	٦d	5d (Cbz)	6 d	47	4.6	R	322 O (1)
7	٦d	5e (Foc)	6e	43	7.7	X	
8 ^[c]	1 d	5 e (Foc)	6e	26	8.6	R	R
						1b: X = H, R = <i>i</i> Pr 1c: X = NO ₂ , R = <i>i</i> Pr 1d: X = NO ₂ , R = Cy	

[a] Reaction conditions: 5 (0.1 mmol), 3 (0.05 mmol), 1 (0.01 mmol), and MS 4A (50 mg) in CHCl₃ (0.4 mL). PG = protecting group. [b] Calculated from ee values, determined by HPLC on a chiral stationary phase, of 6 and recovered 5. [c] Conducted at a concentration of 0.1 M.

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alcohols with secondary and tertiary alkyl substituents at the stereogenic center were higher than those for reactions using amino alcohols bearing aromatic rings, but the reaction rates were lower (Table 2, entries 3 and 4). Various functional groups, for example, nitrile and ester groups, were tolerated under the reaction conditions; amino alcohols **5i** and **5j** were resolved with good selectivities (Table 2, 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 method could not be applied to 2-aminocycloal-kanols **5l**, **5m**, or tertiary alcohol **5n**, presumably due to steric hindrance at the carbon atoms adjacent to a hydroxyl group or NH functionality.

In situ formation of the PMB phosphate was confirmed using ¹H NMR spectroscopy (Figure 2a). When (R)-1d (1 equiv) was added to a solution of 3 in CDCl₃, the 2H



Figure 2. Mechanistic studies: a) ¹H NMR spectrum of chiral PMB phosphate **A** and b) kinetic resolution of **5** e with **A**.

singlet signal from the benzylic proton of **3** at 5.3 ppm (open circle) disappeared within 5 min, and two 1H triplet signals (solid circles) appeared at 4.9 and 4.3 ppm, with concomitant formation of trichloroacetamide (solid square). This result clearly indicates the formation of PMB phosphate **A**, in which the two benzylic protons are diastereotopic and show 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**, which was prepared in situ by mixing **3** (0.5 equiv) and (*R*)-1**d** (0.5 equiv) in the presence of 4A MS. The kinetic resolution proceeded with an *s* value comparable to that for the catalytic reaction (Table 1, entry 8). These results verify the reaction pathway shown in Figure 1B.

The transition state (TS) geometries were calculated at the ONIOM (B3LYP/6-31G**:HF/3-21G) level of theory (see



Figure 3. Chem3D perspective view of transition state structures TS_{major} (which gives (*R*)-**6e**) and TS_{minor} (which gives (*S*)-**6e**) at the ONIOM (B3LYP/6-31G**:HF/3-21G) level of theory.

the Supporting Information for details). TS_{major} and TS_{minor} , which give (*R*)- and (*S*)-**6e**, respectively, are shown in Figure 3. The lengths of the breaking and forming C–O bonds in TS_{major} were 2.73 and 2.47 Å, respectively, thus indicating that a loose S_N2 mechanism is involved. Reactions with 1-phenylethanol and the N-methylated analogue **5o**, which has no adjacent NH functionality, failed. The two hydrogen bonds, OH···O=P (1.81 Å) and NH···O=P (2.14 Å) are thus probably important in stabilizing the TS (Scheme 2).

Analysis of the ONIOM energies sheds light on the mechanism of the observed asymmetric induction. The ONIOM high-layer energy of TS_{major} , which only reflects the energy of the reaction center and the hydrogen bonds (see the Supporting Information for details), is more stable than that of TS_{minor} by 1.33 kcalmol⁻¹. This can probably be attributed to the distorted arrangement of the reacting hydroxy, PMB, and phosphate moieties in TS_{minor} , which is caused by steric repulsion between the Foc moiety and one of the cyclohexyl groups. The calculated $\Delta\Delta G$ between TS_{major} and TS_{minor} was 1.26 kcalmol⁻¹ at the M06-2X/6-31G**/CPCM (CHCl₃)// ONIOM (B3LYP/6-31G**:HF/3-21G) level of theory, which corresponds to 8.3:1 selectivity at room temperature. This is in good agreement with the experimental results.



Scheme 2. Control experiments.

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

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 μ mol), and 4A molecular sieves (50 mg) in solvent (1 mL), (*R*)-**1d** (10 or 15 mol%) was added 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 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 HPLC analysis with a chiral stationary phase.

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 $(1-ee')]/\ln[(1-C)(1 + ee')] = \ln[1-C(1 + ee)]/\ln[1-C(1-ee)]$ and C = ee'/(ee'' + ee), where *C* is conversion, and *ee* and *ee''* are the enantiomeric excesses of the product and the recovered starting material, respectively: a) H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249; b) see Ref. [10a].

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Asymmetric Catalysis

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Use of a Catalytic Chiral Leaving Group for Asymmetric Substitutions at sp³-Hybridized Carbon Atoms: Kinetic Resolution of β -Amino Alcohols by *p*-Methoxybenzylation



By your leave: A strategy for asymmetric substitutions based on the use of a catalytic chiral leaving group was demonstrated with a chiral phosphate generated in situ from trichloroacetimidate and a chiral phosphoric acid. An electronically and sterically tuned chiral phosphoric acid was developed to enable the kinetic resolution of amino alcohols through *p*methoxybenzylation with good enantioselectivity.

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