Asymmetric Addition of Trimethylsilyl Cyanide to Benzaldehydes Catalyzed by Samarium(III) Chloride and Chiral Phosphorus(V) Reagents

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Chiral phosphorus(V) reagents have been used as resolving agents,[1] auxiliaries[2] or ligands[3] to promote various asymmetric reactions. In general, those P(V)-reagents prepared from *C*2-symmetric diols or diamines do not contain asymmetric phosphorus centers. We speculate that a bis-phosphoramidate reagent, such as **3a**, not only exhibits the advantageous effect of *C*2-symmetry, but also exerts better asymmetric induction for it contains phosphorus stereocenters closer to reactive sites.[4] In this paper, we focus on the combined use of Lewis acid and bis-phosphoramidate reagent in promotion of asymmetric cyanosilylation of benzaldehydes.

Cyanohydrins are important synthons,[5] such as in preparation of α-hydroxy acids and *β*-amino alcohols. Optically active cyanohydrins can be obtained by biological[6] or chemical[7] methods. For example, racemic cyanohydrins can be resolved by lipase-catalyzed acetylation.[5a,6d] A variety of aromatic aldehydes and some aliphatic aldehydes can be converted to optically active cyanohydrins by the catalysis of oxynitrilases.[6a] Catalytic asymmetric addition of HCN or Me_3SiCN onto aldehydes can be achieved by using chiral ligands, such as dipeptides (especially diketopiperazines derived from histidine and phenylalanine),[7f] bisoxazolines,[7j] salens,[7n] Schiff's bases,[7k] sulfoximines,[7m] cinchonine,[7g] and binaphthol,[7q] together with Lewis acids containing Ti(IV) (most frequently used),[7a] Al(III),[7h] B(III),[7c] Y(III),[7p] Sn(II),[7g] or Mg(II)[7j] ions. However, most of reports indicate that the reaction must be conducted at low temperature (e.g. −78 °C) in order to obtain high enantioselectivity.

The bis-phosphoramidate **3a** was prepared in 77% overall yield by treatment of (1*R*,2*S*)-(−)-ephedrine subsequently with $POCl_3$ and ethylenediamine (Scheme 1).[8a] The (2*S*,2′*S*,4*S*,4′*S*,5*R*,5′*R*)-configuration of **3a** was unambiguously determined by NMR and X-ray analyses. A minor diastereomer **3b** exhibiting the (2*R*,2′*R*,4*S*,-4′*S*,5*R*,5′*R*)-configuration was also prepared. By a similar procedure, compound **3c** (the antipode of **3a**) was prepared from (1*S*,2*R*)-(+)-ephedrine. A preliminary survey of the reaction of Me_3SiCN with benzaldehyde in the presence of the chiral ligand **3a** indicated that Lewis acids $SmCl_3$, SmI_3, $LaCl_3$, and $Sc(OTf)_3$ were effective catalysts, whereas $Sm(O\textit{i}\text{-}Pr)_3$ or $Ti(O\textit{i}\text{-}Pr)_4$ were ineffective, in terms of conversion and enantioselectivity. We report herein mainly the $SmCl_3$-catalyzed cyanosilylation of various benzaldehydes.[9] Comparison experiments showed that the $SmCl_3$-catalyzed cyanosilylation was accelerated by addition of the bis-phosphoramidate reagent **3a**. However, use of **3a** alone (as a base) did not promote the cyanosilylation.

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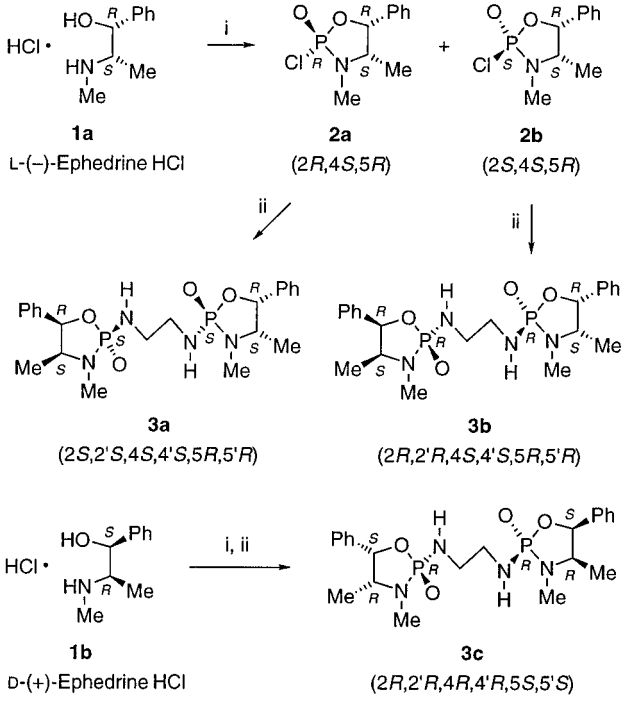
Table 1. Addition Reaction of Benzaldehyde with Trimethylsilyl Cyanide in the Presence of Lewis Acid $SmCl_3$ and Chiral Ligand 3a, Giving the Silyl Ether 4a[a]

entry	$SmCl_3$/equiv	**3a**/equiv	solvent	reaction temp/°C	reaction time/h	product **4a**, ee/%[b]	config[c]
1	0.1	0.1	CH_2Cl_2	25 ± 2	5	65	*R*
2	0.01	0.01	$PhCH_3$	25 ± 2	4.5	72	*R*
3	0.01	0.01	C_6H_{14}	25 ± 2	6	12	*R*
4	0.01	0.01	PhH	25 ± 2	6	51	*R*
5	0.01	0.01	THF	25 ± 2	4.5	8	*R*
6	0.01	0.01	CH_3CN	25 ± 2	4.5	12	*S*
7	0.01	0.01	EtOH	25 ± 2	6	0	
8	0.01	0.01	CH_2Cl_2[d]	25 ± 2	6	42	*R*
9	0.1	0.1	CH_2Cl_2	−15 ± 5	15	75	*R*
10	0.01	0.01	CH_2Cl_2[e]	−15 ± 5	16	67	*R*
12	0.1	0.1[f]	CH_2Cl_2	−15 ± 5	24	63	*R*
11	0.1	0.1[g]	CH_2Cl_2	25 ± 2	4	62	*R*
13	0.01	0.01	$PhCH_3$	−15 ± 5	16	80	*R*
14	0.001	0.003	$PhCH_3$	−15 ± 5	15	84	*R*
15	0.001	0.003[g]	$PhCH_3$	−15 ± 5	15	76	*R*

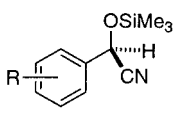
[a] Molar ratio: PhCHO/Me_3SiCN = 1:2. The reaction completed in the indicated time (>97% conversion) according to the ^1H NMR analysis. [b] The ee value was determined by comparison of optical rotation with the reported value[6g] of the cyanohydrin **4b**, $[\alpha]^{20}_D$ +45 ($CHCl_3$, *c* 1). Occasionally, **4b** was converted to the corresponding MTPA ester, of which diastereomeric ratio was determined by the ^{19}F NMR analysis. In entry 13, the silyl ether **4a** was analyzed by HPLC on a Chiralcel OD column. [c] The configuration of major enantiomer. [d] EtOH (0.01 equiv) was added. [e] 2,6-Lutidine (0.05 equiv) was added. [f] The crude ligand **3a**, without recrystallization, was used. [g] The recovered ligand **3a** was reused.

Scheme 1



Reagents and conditions: (i) $POCl_3$, Et_3N, PhH, –10 °C, 6 h; **2a** (85%), **2b** (8%), **2c** (87%). (ii) $H_2NCH_2CH_2NH_2$, Et_3N, THF, 27 °C, 6 h; **3a** (90%), **3b** (93%), **3c** (90%).

A combined use of $SmCl_3$ and bis-phosphoramidate **3a** (with phosphorus stereocenters) showed significant asymmetric induction in the cyanosilylation of benzaldehyde (Table 1). Thus, treatment of PhCHO with Me_3SiCN (1.5−2 equiv), $SmCl_3$ (1 mol %), and ligand **3a** (1 mol %) in toluene (5 mL) at room temperature for 5 h gave a quantitative yield of cyanohydrin silyl ether **4a** with 72% enantiomeric excess (ee). Toluene was the solvent of choice; CH_2Cl_2 and benzene were also suitable, but not hexane, THF, CH_3CN, or EtOH (entries 1−7). The ee value of **4a** was determined by HPLC analysis on a Chiralcel OD column. Furthermore, hydrolysis of **4a** yielded the corresponding dextrorotatory cyanohydrin **4b**.



4a R = H
5a R = *p*-OMe
6a R = *m*-OMe
7a R = *o*-OMe
8a R = *p*-CH_3
9a R = *p*-Ph
10a R = *m*-OPh
11a R = *p*-F
12a R = *p*-CN
13a R = *p*-NO_2

Figure 1. The major enantiomers obtained from the cyanosilylation of benzaldehydes (Tables 1 and 2).

By comparison with the reported optical rotation,[6g] $[\alpha]^{20}_D$ +45 ($CHCl_3$, *c* 1, >99% *R*-isomer), the *R*-configuration for the major enantiomers in **4a** and **4b** was deduced. Cyanohydrin **4b** was also converted to the corresponding MTPA esters **4c**, of which diastereomeric ratio was determined by the ^1H and ^{19}F NMR or HPLC analyses to double check the optical purity of **4a**. The MTPA ester was generally prepared by treatment of a cyanohydrin with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride and Et_3N at room temperature for 1 h. Use of a stronger base, 4-(dimethylamino)pyridine, or prolonged reaction period might cause some degree of racemization.[7d]

The presumed $SmCl_3$−ligand complex was insoluble or sparingly soluble in toluene or CH_2Cl_2 at the outset of cyanosilylation. However, the heterogeneous mixture became homogeneous solution at the end of reaction. After the reaction, the ligand **3a** was easily separated by filtration. The recovered ligand (>80% yield) could be reused in the cyanosilylation with slightly decreased enantioselectivity (compared entries 1 vs 11, and 14 vs 15). Modest enantioselectivity was also procured by using crude ligand **3a** (entry 12). However, the Lewis acid $SmCl_3$ must be kept from moisture, otherwise, the enantioselectivity decreased dramatically. The turnover of this cyanosilylation was very high; thus, up to 84% ee of (*R*)-**4a** was obtained from the reaction at −15 °C (entry 14) using very small amounts of $SmCl_3$ (0.1 mol %) and ligand **3a** (0.3 mol %).

Addition of protic solvent, such as EtOH in entry 8, greatly deteriorated the asymmetric cyanosilylation; however, addition of lutidine only caused a slight change of enantioselectivity (entry 10). Beside solvent effect, the reaction temperature appeared to be another key factor for achieving asymmetric induction. The reaction at −15 °C generally resulted in higher enantioselectivity than

Table 2. Cyanosilylation of Aldehydes Catalyzed by $SmCl_3$ and Ligand 3a[a]

entry	aldehyde	$SmCl_3$/equiv	**3a**/equiv	reaction temp/°C[a]	product	$[\alpha]_D$ ($CHCl_3$)	ee/%	config[b]
1[c]	*p*-$MeOC_6H_4CHO$	0.1	0.1	25 ± 2	**5a**		61[d,e]	*R*
2	*p*-$MeOC_6H_4CHO$	0.002	0.006	−15 ± 5	**5a**	+20.14	90[d,e,f]	*R*
3	*p*-$MeOC_6H_4CHO$	0.001	0.003	−15 ± 5	**5a**	+18.13	81[d,e,f]	*R*
4	*m*-$MeOC_6H_4CHO$	0.002	0.006	−15 ± 5	**6a**	+17.62	83[d,e,f]	*R*
5	*o*-$MeOC_6H_4CHO$	0.002	0.006	−15 ± 5	**7a**	+7.55	80[d,f]	*R*
6[c]	*p*-$CH_3C_6H_4CHO$	0.1	0.11	25 ± 2	**8a**		56[d,e]	*R*
7	*p*-$CH_3C_6H_4CHO$	0.002	0.006	−15 ± 5	**8a**	+18.54	66[d,e,f]	*R*
8	*p*-$CH_3C_6H_4CHO$	0.001	0.01	−15 ± 5	**8a**	+20.29	73[d,e,f]	*R*
9	*p*-PhC_6H_4CHO	0.002	0.006	−15 ± 5	**9a**	+7.35	49[d,f]	*R*
10	*m*-$PhOC_6H_4CHO$	0.002	0.006	−15 ± 5	**10a**	+6.37	45[d,f]	*R*
12	*p*-FC_6H_4CHO	0.002	0.006	−15 ± 5	**11a**	+17.25	77[d,f]	*R*
11[c]	*p*-NCC_6H_4CHO	0.1	0.11	25 ± 2	**12a**		20[d]	*R*
13	*p*-NCC_6H_4CHO	0.002	0.006	−15 ± 5	**12a**	+7.43	35[d,f]	*R*
14	*p*-$O_2NC_6H_4CHO$	0.001	0.003	−15 ± 5	**13a**		12[f]	*R*
15	*p*-$O_2NC_6H_4CHO$	0.002	0.006	−70 ± 5	**13a**	+4.40	29[f]	*R*

[a] The reactions were generally conducted in toluene with a molar ratio of $PhCHO/Me_3SiCN$ = 1:2. [b] The configuration of major enantiomer. [c] The reactions were conducted in CH_2Cl_2. [d] The value was deduced from the optical rotation of the corresponding cyanohydrin. [e] The value was determined by NMR analysis of the corresponding MTPA ester. [f] The value was determined by HPLC analysis of silyl ether on a Chiralcel OD column.

that performed at room temperature. The reaction at lower temperature (such as −40 or −78 °C) was very slow (impractical), though the enantioselectivity might be improved.

As one can expect that (*S*)-**4a** was obtained from the cyanosilylation of benzaldehye by using the antipode **3c** and $SmCl_3$ as the combined catalyst. However, the reaction using ligand **3b** (a diastereomer of **3a**) resulted in a low enantioselectivity.

The asymmetric cyanosilylation of substituted benzaldehydes were also carried out by the catalysis of $SmCl_3$ and **3a** (Table 2). Benzaldehydes bearing electron-donating groups tended to give higher enantioselectivity than those bearing electron-withdrawing groups. The cyanosilylation of 4-methoxybenzaldehyde at −15 °C by using $SmCl_3$ (0.2 mol %) and **3a** (0.6 mol %) yielded the silyl ether **5a** with predominance of (*R*)-enantiomer (90% ee).

The real nature of the active catalyst awaits further investigation. It is not a trivial problem especially in dealing with the $SmCl_3$−ligand complexes of tiny and hygroscopic powder forms. Two preliminary experiments were carried out as follows. First, $SmCl_3$ (0.01 mmol) and **3a** (0.01 mmol) were mixed in CH_2Cl_2 (5 mL). The "clear" solution was taken by filtration through fritted glass (10−16 mm porosity) or by centrifuge. The cyanosilylation of benzaldehyde (1 mmol) was then conducted in this "clear" CH_2Cl_2 solution at room temperature to give the product **4a** with 56% ee (somewhat lower than 65% ee listed in the entry 1 of Table 1). On the other hand, $SmCl_3$ (0.01 mmol) and **3a** (0.01 mmol) were mixed in toluene (5 mL). The "clear" solution and the solid mass were separated. No cyanosilylation was effected in the "clear" toluene solution. On addition of "fresh" toluene to the solid mass, the suspension then functioned as an active catalyst to effect the cyanosilylation with comparable rate and enantioselectivity as shown in the entry 2 of Table 1. At this moment, we cannot conclude whether the solid mass or the minute soluble species is the real catalyst for asymmetric cyanosilylations.

In summary, bis-phosphoramidate reagents **3a** or **3c** bearing phosphorus stereocenters were readily prepared from inexpensive ephedrines, $POCl_3$, and ethylenediamine. Asymmetric cyanotrimethylsilylation of various benzaldehydes was realized by using very small amounts of $SmCl_3$ and the *C*2-symmetric chiral ligand (**3a** or **3c**) at −15 °C or room temperature. Although the enantioselectivity of cyanosilylation products is not extremely high, our method still exhibits several promising features: (i) the cyanosilylation occurs with reasonable enantioselectivity at room temperature, (ii) the bis-phosphoramidate ligand can be used in minute amounts to effect the asymmetric cyanosilylation, and (iii) the ligand is easily separated by simple filtration from the reaction mixture (after trituration with Et_2O) and reused in the cyanosilylation.

Experimental Section

Melting points are uncorrected. Optical rotations were measured on a digital polarimeter with a cuvette of 1 dm length. ^1H NMR spectra were recorded at 200, 300, or 400 MHz; ^{13}C NMR spectra were recorded at 50, 75, or 100 MHz; ^{19}F NMR spectra were recorded at 376 MHz; ^{31}P NMR spectra were recorded at 81, 121, or 162 MHz. Tetramethylsilane (δ = 0 ppm) was used as internal standard in ^1H NMR spectra; phosphoric acid (δ = 0 ppm) or triphenylphosphine (δ = −17.16 ppm) were used as external standards in ^{31}P NMR spectra; trifluorotoluene (δ = −67.73 ppm) was used as external standard in ^{19}F NMR spectra. Mass spectra were recorded at an ionizing voltage of 70 or 20 eV. Merck silica gel 60F sheets were used for analytical thin-layer chromatography. Column chromatography was performed on SiO_2 (70−230 mesh); gradients of EtOAc and *n*-hexane were used as eluents. High-pressure liquid chromatography was carried out on a liquid chromatograph equipped with UV (254 nm) and refractive index detectors. Enantiomeric excess was determined by HPLC using a Chiralcel OD column (0.46 cm ID × 25 cm).

Preparation of Chiral Phosphorus(V) Ligands. A benzene solution (100 mL) of (1*R*,2*S*)-(−)-ephedrine hydrochloric salt (4.1 g, 20 mmol) and Et_3N (10 mL, 72 mmol) was cooled to −10 °C in an ice−salt bath. $POCl_3$ (2.0 mL, 20 mmol) was added dropwise, and the mixture was stirred for 6 h. The resulting precipitates were filtered, and the filtrate was concentrated and subjected to chromatography (silica gel, EtOAc/hexane (1:2)) to give (2*R*,4*S*,5*R*)-2-chloro-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidin-2-one (**2a**, 4.17 g, 85%) and the (2*S*,4*S*,5*R*)-isomer **2b** (0.42 g, 8%).

A THF solution (10 mL) of ethylenediamine (0.7 mL, 11 mmol) and Et_3N (2 mL, 14 mmol) was added dropwise to a THF solution (30 mL) of **2a** (2.6 g, 11 mmol) at room temperature (27 °C). The mixture was stirred for 6 h, and the resulting precipitates were filtered. The filtrate was concentrated to give crude **3a** as solids, which were recrystallized from CH_2Cl_2/EtOAc (1:1) to afford pure product (2.4 g, 90%). (2*S*,2′*S*,4*S*,4′*S*,5*R*,5′*R*)-*N*,*N*′-Bis(3,4-dimethyl-2-oxo-5-phenyl-1,3,2-oxazaphospholan-2-yl)-

ethane-1,2-diamine (**3a**): Solid, mp 199−201 °C; $[\alpha]^{19}_D$ −115.9 ($CHCl_3$, *c* 4); TLC (MeOH/CH_2Cl_2 (1:4)) R_f = 0.41; IR (KBr) 3230, 1453, 1328, 1242 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.69 (6 H, d, J = 6.6 Hz, two CH_3), 2.70 (6 H, d, J = 9.5 Hz, two CH_3), 3.08−3.24 (4 H, m, CH_2), 3.50−3.68 (2 H, m, H-4), 3.66−3.80 (2 H, m, NH, shiftable), 5.64 (2 H, d, J = 6.6 Hz, H-5, H-5′), 7.15−7.38 (10 H, m); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 25.18; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.7, 29.0 (d, J_{P-C} 5.9 Hz), 43.3 (d, J_{P-C} 5.7 Hz), 59.2 (d, J_{P-C} 12.2 Hz), 78.3, 125.6, 127.9, 128.3, 136.4 (d, J_{P-C} 10.4 Hz); FAB-MS *m*/*z* 479.2 (M^+ + 1); HRMS calcd for $[M]^+$ 478.1879, found *m*/*z* 478.1913. Anal. Calcd for $C_{22}H_{32}N_4O_4P_2$: C, 55.23; H, 6.74; N, 11.71. Found: C, 55.23; H, 6.58; N, 11.31.

By a procedure similar to that for **3a**, the minor chloro compound **2b** reacted with ethylenediamine to give **3b** (2*R*,2′*R*,4*S*,4′*S*,5*R*,5′*R*) in 93% yield after recrystallization. Solid, mp 193−195 °C (from CH_2Cl_2/EtOAc (1:1)); $[\alpha]^{28}_D$ −43.01 ($CHCl_3$, *c* 0.6). (1*S*,2*R*)-(+)-Ephedrine hydrochloric acid reacted with $POCl_3$, followed by treatment with ethylenediamine to give **3c** (2*R*,2′*R*,4*R*,4′*R*,5*S*,5′*S*) in 78% total yield. Solid, mp 200−201 °C (from CH_2Cl_2/EtOAc (1:1)); $[\alpha]^{28}_D$ +115.5 ($CHCl_3$, *c* 0.6).

General Procedure for Asymmetric Reaction of Aldehydes and Trimethylsilyl Cyanide. Under an atmosphere of nitrogen, a suspension of $SmCl_3$ (0.5 mg, 0.002 mmol) and ligand **3a** (ground to fine powders, 3.0 mg, 0.006 mmol) in toluene (5 mL) was placed in a flame-dried flask and cooled to −78 °C. Benzaldehyde (freshly distilled, 106 μL, 1.0 mmol) and Me_3SiCN (200−266 μL, 1.5−2.0 mmol) were added sequentially at −78 °C. The heterogeneous mixture was stirred for 24 h while the temperature was kept between −10 and −20 °C in a freezer. The mixture appeared as a homogeneous, transparent solution at this stage. Toluene and excess of Me_3SiCN were removed in vacuo, and the residue was triturated with Et_2O (3 mL). The precipitates were filtered through a pad of anhydrous Na_2SO_4 and rinsed with Et_2O (3 mL). The filtrate was concentrated in vacuo to give a cyanohydrin silyl ether **4a** (201 mg, 99%) enriched in (*R*)-enantiomer. The ratio of enantiomers was determined by HPLC analysis on a Chiralcel OD column (*i*-PrOH/hexane (0.25:100), 2.5 mL/min flow rate). The mixture of precipitates and Na_2SO_4 was taken up with CH_2Cl_2 (3 mL), and the soluble part was concentrated in vacuo to recover the ligand **3a** (80−92%).

General Procedure for Hydrolysis of Silyl Ethers. The cyanohydrin trimethylsilyl ether **4a** (103 mg, 0.5 mmol) was treated with HCl (1 N, 2 mL) in EtOAc (20 mL) at room temperature (27 °C) for 4−6 h. After which, the organic phase was added dropwise into a saturated $NaHCO_3$ solution (30 mL) and stirred for 5−10 min. The organic phase was separated, washed with $NaHCO_3$ (30 mL) and brine, dried (Na_2SO_4), and concentrated in vacuo to give the cyanohydrin **4b** (63 mg, 95%). The enantiomeric excess of **4b** was determined by comparison of optical rotation with the reported value, lit.[6g] $[\alpha]^{20}_D$ +45 ($CHCl_3$, *c* 1).

General Procedure for Preparation of MTPA Esters. A solution of cyanohydrin **4b** (ca. 10 mg) in CH_2Cl_2 (1 mL) was treated with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (ca. 20 mg) and Et_3N (or pyridine, ca. 0.05 mL) at room temperature (27 °C) for 1 h. After which, the mixture was concentrated, and the ratio of resulting MTPA-esters was determined by ^{19}F NMR analysis. Furthermore, the mixture was taken up with EtOAc (10 mL) and H_2O (10 mL). The aqueous phase was separated and extracted with EtOAc (10 mL × 2). The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on a silica gel column by elution with EtOAc/hexane (1:10) to give the MTPA esters of **4b**. The ratio of diastereomers was double checked by ^1H NMR and HPLC analyses. It was noticed that a significant degree of racemization might occur when the reaction was conducted with a stronger base such as 4-(dimethylamino)pyridine.

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Supporting Information Available: Physical and spectral data of compounds **2**−**13b**, ORTEP drawing and crystal data of compound **3a**, and ^1H NMR spectra of **3a** and **3b** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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