Novel Sequential Process from *N*-Methoxyamides and Vinyl Grignard Reagents: New Synthesis of *β*-Aminoketones

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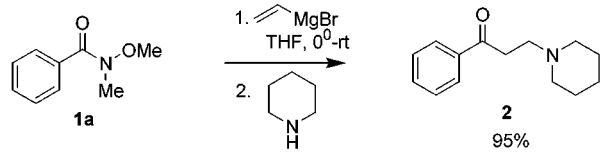
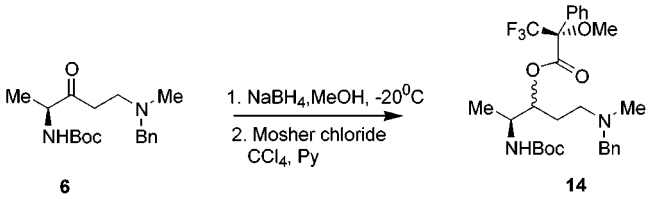
β-Aminoketones and corresponding *γ*-amino alcohols are useful synthetic intermediates. They have been used in the synthesis of natural products[1] and are structural fragments of a number of pharmaceutically important compounds and drugs most prominent of which are Prozac[2] and Lipitor.[3] Classical methods for the synthesis of *β*-aminoketones include Mannich reaction[4] of methyl ketones with amine and paraformaldehyde, the utilization of *β*-haloalkyl ketones in alkylation reactions, and vinyl ketones in 1,4-conjugate addition reactions with amines.[5]

Our attempt to prepare vinylphenyl ketone from corresponding Weinreb amide and vinylmagnesium bromide resulted in desired product along with *β*-(*N*-methoxy-*N*-methyl)aminoethylphenyl ketone. However, the first report on such side-reaction was published by Wuts and co-workers[6] who found that the desired enone from the reaction of Weinreb amide of leucine derivative with vinylmagnesium bromide was contaminated with *β*-aminoketone. This side-reaction was so prevalent that authors abandoned that particular approach to their target molecule. Similar observation has been made by Wickberg and co-workers[7] who characterized unstable *β*-aminoketone intermediates in their synthesis of 1,4-diketones from Weinreb amides and methylcyclopropenyllithium. Utilizing these observations we described in our preliminary communication[8] a direct synthesis of *β*-aminoketones from amides. In that procedure the amino function in the starting amide would become amino function in the *β*-aminoketone. However, reactivity of amides was variable with Weinreb amides providing the highest yield and shortest reaction time. Now we are able to report that Weinreb amides can serve as common starting materials for the efficient synthesis of a variety of *β*-aminoketones. In this expansion of the scope of our original procedure, Weinreb amides undergo sequential transformation consisting of nucleophilic substitution with different vinyl-Grignard reagents followed by Michael type reactions with a number of amines.

Scheme 1



Scheme 2



The sequence is outlined in Scheme 1 for the representative example of *N*-methyl-*N*-methoxybenzamide **1a**.

The net result of the process is "insertion of ethylene" into amide. Table 1 illustrates many applications of the reported methodology. Its versatility is demonstrated by changing a nature of all three components of the sequential process, i.e., starting amide, vinyl nucleophile and N-nucleophile. Thus, aromatic amides **1a** and **1c** and aliphatic amides **1b** and **1d** can be successfully employed as starting substrates. No significant racemization was observed when the optically active derivative of alanine **1b** used as a starting material (entry 5). The Mosher ester **14** prepared from **6** (Scheme 2) was compared with a similar Mosher ester synthesized from racemic aminoketone *rac*-**6** which in turn was obtained from racemic amide *rac*-**1b**. ^{1}H NMR spectrum of Mosher ester from chiral series contained two singlets for N-Me group and two doublets for C-Me group with a ratio ∼2.5:1 indicating a presence of two major diastereomers. One additional singlet and doublet with less than 5% intensity were also present. Racemic series provided Mosher ester as a mixture of four diastereomers with a ratio ∼1:2.5:1:2.5, as four peak sets were found for N-Me and C-Me groups. Comparison of two ^{1}H NMR spectra revealed that minor racemization may have occurred and it accounts for <5%.

On the reagent side, in addition to unsubstituted vinylmagnesium bromide (entries 1−5, 9−11), 1- and 2-substituted vinyl reagents (entries 6−8, 12) also effectively participate in the reaction. For example, the α-methyl-*β*-aminoketones **7**, **8**, **13**, and the *β*-methyl-*β*-aminoketone are available by this approach. Reduction of the last product by $NaBH_4$ to the stable *β*-amino alcohol **9** was used to prevent *β*-elimination of the ketone during chromatography on silica gel. The reaction of optically active **1b** with isopropenylmagnesium bromide and morpholine provided the ketone **13** as a ∼2:1 mixture of diastereomers differing in the configuration of the newly created chiral center.

The third component of the sequential procedure, the N-nucleophile, also can be varied as exemplified with amines (entries 1−9, 12) and hydrazines (entries 10, 11).

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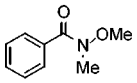
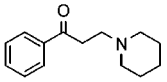
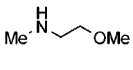
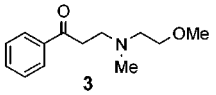
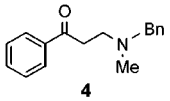
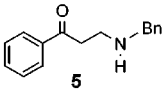
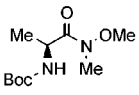
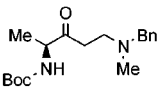
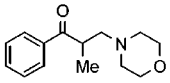
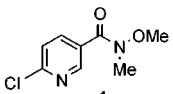
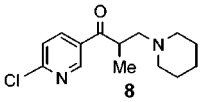
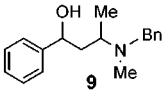
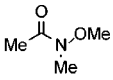
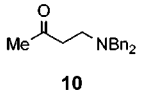
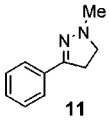
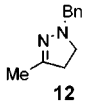
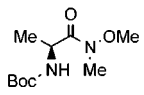
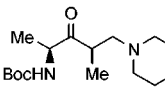
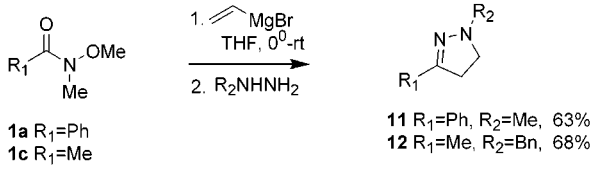
Table 1. One-Pot Synthesis of β-Aminoketones and Pyrazolines from Weinreb Amides

Entry	Weinreb Amide	Grignard Reagent	N-Nucleophile	Product[a]	Isolated Yield (%)
1.	 **1a**			 **2**	95
2.	**1a**			 **3**	91
3.	**1a**		BnNHMe	 **4**	89
4.	**1a**		$BnNH_2$	 **5**	51
5.	 **1b**		BnNHMe	 **6**	78[b]
6.	**1a**			 **7**	93[c]
7.	 **1c**			 **8**	70[c]
8.	**1a**		BnNHMe	 **9**	56[d]
9.	 **1d**		Bn_2NH	 **10**	60
10.	**1a**		H_2NNHMe	 **11**	63
11.	**1d**		H_2NNHBn	 **12**	68
12.	 **1b**		BnNHMe	 **13** (~2:1 by ^{1}H NMR)	90[b,c]

[a] 1.1 equiv of Grignard reagent and 1.5 equiv of amine were used in standard procedure unless stated otherwise. [b] 2.5 equiv of the Grignard reagent was used. [c] 2.5 equiv of amine was used. [d] Yield is based on two steps including reduction of ketone to **9** by $NaBH_4$ in MeOH at 0 °C.

In the latter case pyrazoline products **11** and **12** are obtained[9] as a result of three consecutive transformations: nucleophilic substitution, 1,4-conjugate addition, and intramolecular cyclization leading to a hydrazone formation (Scheme 3). Thus, synthesis of pyrazolines is achieved by creating three new bonds in a single step. With regard to amines, secondary ones are better reagents than primary amines (entry 4) since 1,4-conjugate addition products with primary amines undergo further additions giving rise to side products.

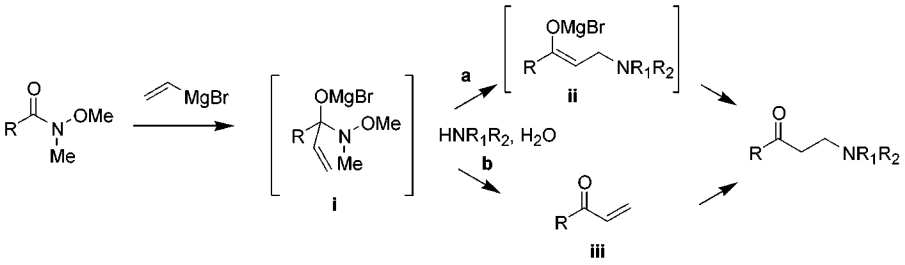
Scheme 3



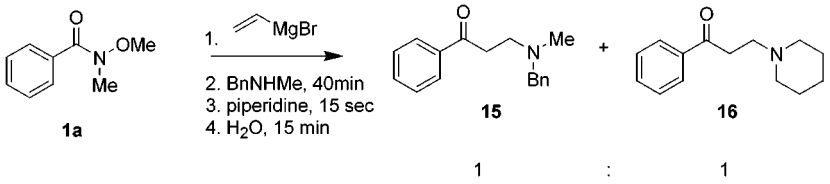
The mechanism of the reported transformation (Scheme 4) may involve the conversion of tetrahedral intermediate

(9) For common methods for the synthesis of pyrazolines, see: Jarboe, C. H. In *Heterocyclic Compounds: Pyrazoles, Pyrazolines, Pyrazolidines, Imidazoles and Condensed Rings*; Wiley: R. H., Ed; J. Wiley & Sons: NewYork, 1967; pp 177−206.

Scheme 4



Scheme 5



i[10] to the final β-aminoketone through possible pathways a or b. Consequently, intermediates **ii** and **iii** can be envisioned.

The crossover experiment (Scheme 5) ruled out irreversible formation of **ii**. Indeed, the hypothetical enolate **ii** formed from tetrahedral intermediate **i** and *N*-benzylmethylamine could not be affected by the second amine, piperidine, and could only hydrolyze to β-benzylmethylaminoketone. Because both aminoketones **15** and **16** were found in the reaction mixture (LC-MS and ^{1}H NMR), it is most likely that our sequential reaction proceeds through the pathway b where vinyl ketone **iii** that forms from **i** after addition of water undergoes Michael type reaction with amine.

All N-nucleophiles in the last step must compete with *N*-methyl-*N*-methoxyamine (or corresponding magnesium amide) that forms along with **iii** in the process of decomposition of tetrahedral intermediate **i**. It is interesting to note that generally no product arising from addition of *N*-methyl-*N*-methoxyamine to the ketone **iii** was observed. The only exception was the reaction between amide **1b**, vinylmagnesium bromide, and dibenzylamine (entry 9) when 9% of *N*-methyl-*N*-methoxyamine analogue of the major product **10** was also isolated.

In summary, we have discovered a new mild and efficient sequential transformation[11] for the facile and rapid preparation of β-aminoketones or their derivatives,[12] e.g., pyrazolines, utilizing readily available and stable Weinreb amides[13] as common starting materials. The reaction proceeds in good to excellent yields for a variety of amides, vinyl Grignard reagents and N-nucleophiles. Application of the methodology in medicinal chemistry for parallel and solid-phase syntheses[14] can also be anticipated.

Experimental Section

General Methods. All reactions were carried out under an atmosphere of dry nitrogen. Commercially available anhydrous tetrahydrofuran was used without prior distillation. NMR spectra were obtained in $CDCl_3$ at 300 or 400 MHz for ^{1}H and 75 or 100 MHz for ^{13}C.

General Procedure for the Synthesis of 2−13. To a solution of starting amide (2.0 mmol) in dry THF (20 mL) at 0 °C was added a 1 M solution of vinylmagnesium bromide (2.2 mmol) in THF within 1 min. After 10 min the mixture was allowed to attain ambient temperature and was stirred for 1 h. This mixture was treated with amine (3.0 mmol) followed by water (3 mL). The mixture was stirred for 20 min, diluted with ethyl acetate, and washed twice with water. The organic layer was separated, concentrated, and chromatographed on SiO_2 (EtOAc−hexane) to afford β-aminoketones or pyrazolines.

3-Piperidinopropiophenone 2. ^{1}H NMR δ 7.91 (m, 2H), 7.58−7.42 (m, 3H), 3.21 (t, J = 8.5 Hz, 2H), 2.82 (t, J = 8.5 Hz, 2H), 2.49 (m, 4H), 1.60 (m, 4H), 1.43 (m, 2H); ^{13}C NMR 198.8, 136.7, 132.7, 128.2, 127.7, 54.3, 53.6, 36.1, 25.7, 24.0; MS *m*/*z* 218 (M + H). Anal. Calcd for $C_{14}H_{19}NO\cdot0.5H_2O$: C 74.30; H 8.91; N 6.19. Found: C 74.06; H 8.52; N 5.85.

3-(*N*-Methyl-*N*-methoxyethylamino)propiophenone 3. ^{1}H NMR δ 7.98 (m, 2H), 7.55 (m, 1H), 7.48 (m, 2H), 3.51 (t, J = 6.0 Hz, 2H), 3.37 (s, 3H), 3.22 (t, J = 8.5 Hz, 2H), 2.92 (t, J = 8.5 Hz, 2H), 2.67 (t, J = 6.0 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR 199.0, 136.6, 132.8, 128.3, 127.7, 70.1, 58.5, 56.5, 52.4, 42.3, 36.1; MS *m*/*z* 222 (M + H); HRMS calcd for $C_{13}H_{19}NO_2$ 222.1494 (M + H), found 222.1496.

3-(*N*-Methyl-*N*-benzylamino)propiophenone 4. ^{1}H NMR δ 7.92 (m, 2H), 7.52 (m, 1H), 7.43 (m, 2H), 7.30−7.20 (m, 5H), 3. 54 (s, 2H), 3.18 (t, J = 8.0 Hz, 2H), 2.89 (t, J = 8.0 Hz, 2H), 2.24 (s, 3H); ^{13}C NMR 199.3, 138.7, 136.8, 132.9, 128.8, 128.5, 128.1, 127.9, 126.9, 62.3, 52.4, 42.1, 36.8; MS *m*/*z* 254 (M + H). Anal Calcd for $C_{17}H_{19}NO\cdot0.03H_2O$: (253.88) C 80.43; H 7.57; N 5.52. Found: C 80.04; H 7.47; N 5.32.

3-Benzylaminopropiophenone 5. ^{1}H NMR δ 7.92 (m, 2H), 5.55 (m, 1H), 7.45 (m, 2H), 7.39−7.20 (m, 5H), 3.83 (s, 2H), 3.23 (t, J = 8.0 Hz, 2H), 3.05 (t, J = 8.0 Hz, 2H), 1.90 (broad s, 1H); MS *m*/*z* 240 (M + H).

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(11) For a discussion of sequential transformations in organic chemistry, see: (a) Hall, N. *Science* **1994**, *266*, 32. (b) Tietze, L. F.; Modi, A. *Med. Res. Rev*. **2000**, *20*, 304. (c) Tietze, L. F. *Chem Rev*. **1996**, *96*, 115. (d) Bunce, R. A. *Tetrahedron* **1995**, *48*, 13103. (e) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 131. (f) Posner, G. H. *Chem. Rev*. **1986**, *86*, 831.

(12) The advantage of this one-pot procedure over two-step alternative can be shown by comparison of our synthesis of **4** (89% yield) with Ely Lilly's two-step Mannich−Michael approach to **4** (64−70% yield and use of 10 equiv of amine). Pedregal Tercero, C. ES2101650, 1997; *Chem Abstr*. **1998**, *128*, 114779c.

(13) (a) Raghuram, T.; Vijaysaradhi, S.; Singh, I.; Singh, J. *Synth. Commun*. **1999**, *29*, 3215. (b) Aidhen, I. S.; Ahuja, J. R. *Tetrahedron Lett*. **1992**, *33*, 5431. (c) Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett*. **1997**, *38*, 2685. (d) Handa, S.; Gibson, C. L. *Tetrahedron Asymmetry* **1996**, *7*, 1281.

(14) For solid-phase Weinreb amides, see: (a) Salvino, J. M.; Mervic, M.; Mason, H. J.; Kiesow, T.; Teager, D.; Airey, J.; Labaudiniere, R. *J. Org. Chem*. **1999**, *64*, 1823. (b) Fehrentz, J.-A.; Paris, M.; Heitz, A.; Velek, J.; Winternitz, F.; Martinez, J. *J. Org. Chem*. **1997**, *62*, 6792. (c) Dinh, T. Q.; Armstrong, R. W. *Tetrahedron Lett*. **1996**, *37*, 1161.

(*R*)-2-(*N*-*tert*-Butoxycarbonyl)amino-5-(*N*-methyl-*N*-benzylamino)-3-pentanone 6. $[\alpha]_D$ +6.2° (*c* 1.90; CH_2Cl_2); ^{1}H NMR δ 7.28 (m, 5H), 5.46 (broad s, 1H), 4.31 (m, 1H), 3.50 (s, 2H), 2.71 (m, 4H), 2.19 (s, 3H), 1.44 (s, 9H), 1.31 (d, J = 6.0 Hz, 3H); ^{13}C NMR 208.5, 138.4, 128.7, 128.0, 125.879.3, 62.1, 55.0, 51.8, 41.7, 37.0, 28.1, 17.3; MS *m*/*z* 321 (M + H); HRMS calcd for $C_{18}H_{28}N_2O_3$ 321.2178 (M + H), found 321.2178.

2-Methyl-3-morpholinopropiophenone 7. ^{1}H NMR δ 7.95 (m, 2H), 7.54 (m, 1H), 7.46 (m, 2H), 3.73 (m, 1H), 3.59 (m, 4H), 2.86 (dd, J = 8.0 and 13.5 Hz, 1H), 2.45−2.38 (m, 5H), 1.20 (d, J = 8.5 Hz, 3H); ^{13}C NMR 203.8, 137.0, 132.9, 128.4, 128.1, 66.9, 62.0, 53.9, 38.3, 16.1; MS *m*/*z* 234 (M + H). Anal. Calcd for $C_{14}H_{19}NO_2$: (233.31) C 72.07; H 8.21; N 6.00. Found: C 71.84; H 8.01; N 5.92.

3-Piperidino-2-methyl-1-[3-(6-chloropyridyl)]-1-propanone 8. ^{1}H NMR δ 8.96 (d, J = 2.5 Hz, 1H), 8.20 (dd, J = 2.5 and 9.0 Hz, 1H), 7.43 (d, J = 9.0 Hz, 1H), 3.67 (m, 1H), 2.80 (dd, J = 9.0 and 13.0 Hz, 1H), 2.48−2.28 (m, 5H), 1.50−1.30 (m, 6H), 1.18 (d, J = 9.0 Hz, 3H); ^{13}C NMR 202.0, 154.9, 149.8, 138.0, 131.1, 124.0, 62.6, 54.8, 39.3, 25.8, 24.0, 15.6; MS *m*/*z* 267 (M + H). Anal. Calcd for $C_{14}H_{19}N_2ClO$: (266.77) C 63.03, H 7.18, 10.50. Found: C 62.78, H 7.03, N 10.41.

3-(*N*-Methyl-*N*-benzylamino)-3-methyl-1-phenylpropanol 9. To a solution of benzamide **1** (1. 09 g, 6.6 mmol) in dry THF (60 mL) at 0 °C was added a 0.5 M solution of 1-propenylmagnesium bromide (15 mL, 7.3 mmol) in THF within 1 min. After 10 min, the mixture was allowed to attain ambient temperature and was stirred for 1 h. This mixture was treated with *N*-benzylmethylamine (1.60 g, 13.2 mmol) followed by water (8 mL). The mixture was stirred for 20 min, diluted with ethyl acetate, and washed twice with water. Organic layer was separated, concentrated, and dissolved in MeOH (50 mL). To this solution was added $NaBH_4$ (0.50 g, 13.2 mmol) at 0 °C and resulting mixture stirred at ambient temperature for 2 h. The mixture was quenched with water, concentrated under vacuo, and diluted with ethyl acetate. After washing with 1 N HCl and water, the organic layer was separated, concentrated, and chromatographed on SiO_2 (EtOAc−hexane) to afford **9** (1.00 g, 56%). ^{1}H NMR δ 7.60 (broad s, 1H), 7.41−7.20 (m, 5H), 4.86 (dd, J = 1.5 and 10.5 Hz, 1H), 3.75 (d, J = 12.0 Hz, 1H), 3.58 (d, J = 12.0 Hz, 1H), 3.27 (m, 1H), 2.22 (s, 3H), 1.86 (ddd, J = 10.5, 14.5 and 21.0 Hz, 1H), 1.50 (ddd, J = 1.5, 4.5 and 14.5 Hz, 1H), 1.02 (d, J = 7.5 Hz, 3H); ^{13}C NMR 145.1, 138.1, 129.0, 128.5, 128.1, 127.3, 126.8, 125.4, 75.6, 58.9, 58.6, 41.7, 34.9, 11.9; MS *m*/*z* (M + H) 270. Anal. Calcd for $C_{18}H_{23}NO\cdot0.1H_2O$: (171.13) C 79.72, H 8.62, 5.16. Found: C 79.45, H 8.23, N 4.80.

4-Dibenzylamino-2-butanone 10. ^{1}H NMR δ 7.30−7.13 (m, 10H), 3.53 (broad s, 4H), 2.78 (t, J = 8.0 Hz, 2H), 2.59 (t, J = 8.0 Hz, 2H), 1.98 (s, 3H); ^{13}C NMR 207.8, 139.1, 128.7, 128.1, 126.8, 58.2, 48.4, 41.8, 29.4; MS *m*/*z* 268 (M + H); HRMS calcd for $C_{18}H_{21}NO$ 268.1701 (M + H), found 268.1704.

1-Methyl-3-phenyl-4,5-dihydropyrazole 11. ^{1}H NMR δ 7.61 (m, 2H), 7.35−7.23 (m, 3H), 3.13 (t, J = 8.3 Hz, 2H), 2.94 (t, J = 8.3 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR 151.5, 132.8, 128.3, 128.2, 125.6, 56.0, 43.3, 33.2; MS *m*/*z* 161 (M + H). Anal. Calcd for $C_{10}H_{12}N_2$: (160.22) C 74.97; H 7.55; N 17.48. Found: C 75.17; H 7.65; N 17.21.

1-Benzyl-3-methyl-4,5-dihydropyrazole 12. ^{1}H NMR δ 7.39−7.20 (m, 5H), 4.10 (s, 2H), 2.88 (t, J = 10.0 Hz, 2H), 2.50 (t, J = 10.0 Hz, 2H), 1.94 (s, 3H); ^{13}C NMR 152.4, 137.6, 128.6, 128.0, 126.8, 61.0, 53.7, 36.7, 15.9; MS *m*/*z* 175 (M + H). Anal. Calcd for $C_{11}H_{14}N_2$: (174.24) C 75.82, H 8.10, N 16.08. Found: C 75.56, H 8.19, N 15.96.

(*R*)-2-(*N*-*tert*-Butoxycarbonylamino)-5-morpholino-4-methyl-3-pentanone 13. ^{1}H NMR δ 4.40 (m, 1H), 3.67 (m, 4H), 3.18−2.96 (m, 1H), 2.75−2.20 (m, 6H), 1.46 and 1.44 (2s, 9H), 1.31 (m, 3H), 1.08 and 1.04 (2D, J = 7 Hz, 3H); MS *m*/*z* 301 (M + H); HRMS calcd for $C_{15}H_{28}N_2O_4$ 301.2127 (M + H), found 301.2140.

***N*-Methyl-*N*-methoxy-2-[(*tert*-butoxycarbonyl)amino]-propanamide (*rac*-1b)** was synthesized according to the procedure[6] described for the synthesis of Boc-leucine Weinreb amide. Boc-DL-alanine (1.9 g, 10.0 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride salt (1.2 g, 12.3 mmol), and triethylamine (2.8 mL, 20.1 mmol) were mixed in dry CH_2Cl_2 (30 mL), and DEPC (diethyl phosphorocyanidate) (3.0 mL, 19.8 mmol) was then added, causing a slight exothermic reaction. The reaction mixture was stirred at ambient temperature overnight and then was poured into water and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was removed in vacuo, affording the crude product as a greasy yellow solid. Purification by flash chromatography (EtOAc−hexanes, 2:3) afforded the desired product as a white solid, 2.11 g (96%). ^{1}H NMR δ 5.25 (broad d, 1H), 4.69 (m, 1H), 3.77 (s, 3H), 3.20 (s, 3H), 1.44 (s, 9H), 1.31 (d, J = 7 Hz). MS *m*/*z* 233 (M + H).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for **2**−**13** and ^{1}H NMR spectra for Mosher esters **14** from chiral and racemic series. This material is available free of charge via the Internet at http://pubs.acs.org.

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