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Lewis Acid and Hexamethyldisilazane-Promoted Efficient Synthesis of *N*-Alkyl- and *N*-Arylimide Derivatives

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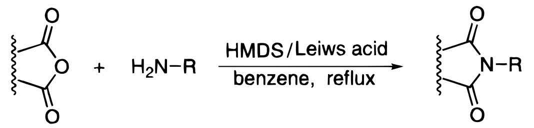
The development of simple and general synthetic routes for widely used organic compounds from readily available reagents is one of the major challenges in organic synthesis. Imide derivatives are among such types of organic compounds with numerous applications in biology[1] and synthetic[2] and polymer[3] chemistry. Despite their wide applicability, available routes for the synthesis of imide derivatives are limited.[4] Among them, the dehydrative condensation of an anhydride and an amine at high temperature[1a] and the cyclization of the amic acid in the presence of acidic reagents are the typical methods of choice.[4i] The direct N-alkylation of maleimide with alcohols under Mitsunobu reaction conditions is an alternative method for the synthesis of imide derivatives in reasonably good yield.[4a] However, each of these routes has its own synthetic problems when applied to a range of derivatives. For instance, synthesis of functionalized maleimide derivatives either by the direct condensation or through the intermediate amic acid cyclization method gives poor yields of the desired maleimide derivatives. Although the amic acid formation proceeds in quantitative yield, the subsequent cyclization results in only low yields of the desired maleimide derivatives together with extensive byproducts due to the incompatibility of the olefin functionality with harsh reaction conditions.[5] Similarly, in the Mitsunobu reaction only a narrow range of imide derivatives can be synthesized because alkanols are used as starting materials. Therefore, synthesis of functionalized imide derivatives is still a challenging endeavor. We describe herein an efficient and mild approach for the synthesis of imide derivatives.

Scheme 1



Taking the lead from the pioneering work of Vorbrüggen[6] on hexamethyldisilazane (HMDS)-mediated reactions as a logical extension, we envisaged that the reaction of an anhydride with an appropriately substituted amine and subsequent *in situ* cyclization of the resulting amic acid in the presence of a Lewis acid and HMDS would give the corresponding imide derivative.[7] In order to substantiate the concept, the *N*-benzylmaleamic acid generated from maleic anhydride and benzylamine in a benzene solution was heated at reflux with equimolar amounts of HMDS and $ZnCl_2$ for 4 h to afford the corresponding maleimide derivative (Scheme 1). This favorable result encouraged us to further improve the efficiency of the reaction to get high yields of imide derivatives in a short reaction time.

In order to optimize the reaction conditions, we briefly investigated the stoichiometric ratio of the reagents and reactants. The amic acid formation was observed almost quantitatively in 1−4 h, stirring in benzene with equimolar amounts of an anhydride and an amine, whereas the molar ratios of HMDS and $ZnCl_2$ showed a significant influence on the reaction time and the yield of imides. Although, theoretically, 1 molar equiv of HMDS seems to be sufficient to complete the reaction, practically the isolated yield of imides was higher using 1.5 molar equiv of HMDS and 1 equiv of $ZnCl_2$. When the reaction was carried out with an excess amount of HMDS (>1.5 equiv) and/or $ZnCl_2$ (>1 equiv), the yield of the imide was reduced drastically and formation of undesired products was observed upon prolonged reflux. In the presence of less than an equimolar quantity of HMDS or $ZnCl_2$, the reaction was not complete even after long refluxing times. The imide formation was not observed even in a trace amount in the absence of either $ZnCl_2$ or HMDS.

Next, cyclization of *N*-benzylsuccinamic acid was examined with various Lewis acids. The results are summarized in Table 1. Among the Lewis acids examined, $ZnBr_2$ gave significantly good results in a short reaction time. $ZnCl_2$ and ZnI_2 also gave good yields of imide, but the reaction was found to be relatively slow with these

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(1) For some recent biological applications, see: (a) Da Settimo, A.; Primofiore, G.; Da Settimo, F.; Simorini, F.; La Motta, C.; Martinelli, A.; Boldrini, E. *Eur. J. Med. Chem.* **1996**, *31*, 49. (b) Langmuir, M. E.; Yang, J.-R.; Moussa, A. M.; Laura, R.; Lecompte, K. A. *Tetrahedron Lett.* **1995**, *36*, 3989. (c) Mayer, A.; Neuenhofer, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1044. (d) Rusiecki, V. K.; Warne, S. A. *Biorg. Med. Chem. Lett.* **1993**, *3*, 707. (e) Wong, S. S. *Chemistry of Protein Conjugation and Cross-linking*; CRC Press: Boca Raton, 1991. (f) Janda, D. K.; Ashley, A. J.; Jones, T. M.; McLeod, D. A.; Schloeder, D. M.; Weinhouse, M. I. *J. Am. Chem. Soc.* **1990**, *112*, 8886. (g) FitzGerald, D.; Idziorek, T.; Batra, J. K.; Willingham, M.; Pastan, I. *Bioconjugate Chem.* **1990**, *1*, 264. (h) Maeda, M.; Kumano, A.; Tirrell, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 7455.

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(3) For recent applications of maleimide derivatives in polymer chemistry, see: (a) Iijima, T.; Suzuki, N.; Fukuda, W.; Tomoi, M. *J. Eur. Polym.* **1995**, *31*, 775. (b) Amou, S.; Nishimura, S.; Takahashi, A.; Hagiwara, T.; Hamana, H.; Narita, T. *J. Polym. Sci. Tech.* **1994**, *51*, 764. (c) Bharel, R.; Choudhary, V.; Varma, I. K. *J. Appl. Polym. Sci.* **1993**, *49*, 31. (d) Dean, B. D. *J. Appl. Polym. Sci.* **1987**, *33*, 2259.

(4) (a) Walker, M. A. *J. Org. Chem.* **1995**, *60*, 5352; *Tetrahedron Lett.* **1994**, *35*, 665. (b) Corrie, J. E. T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2975. (c) Gill, G. B.; James, G. D.; Oates, K. V.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2567. (d) Braish, T. F.; Fox, D. E. *Synlett* **1992**, 979. (e) Dorta, R. L.; Francisco, C. G.; Suarez, E. *Tetrahedron Lett.* **1991**, *35*, 1083. (f) Nielsen, O.; Buchardt, O. *Synthesis* **1991**, 819. (g) Rangnekar, V. M.; Bharmaria, R. P.; Khadse, B. G. *Ind. J. Chem.* **1986**, *25B*, 342. (h) Schwartz, A. L.; Lerner, L. M. *J. Org. Chem.* **1974**, *39*, 21. (i) Mehta, N. B.; Phillips, A. P.; Lui, F. F.; Brooks, R. E. *J. Org. Chem.* **1960**, *25*, 1012.

(5) (a) Garner, P.; Ho, W. B.; Grandhee, S. K.; Youngs, W. J.; Kennedy, V. O. *J. Org. Chem.* **1991**, *56*, 5893. (b) Meyers, A. I.; Lefker, B. A.; Sowin, T. J.; Westrum, L. J. *J. Org. Chem.* **1989**, *54*, 4243.

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(7) Catalytic trimethylsilylation of organic compounds having acidic protons such as alcohols and carboxylic acids by using HMDS and Lewis acids is well known; see: (a) Firouzabadi, H.; Karimi, B. *Synth. Commun.* **1993**, *23*, 1633 and references cited therein. (b) Bruynes, C. A.; Jurriens, T. K. *J. Org. Chem.* **1982**, *47*, 3966.

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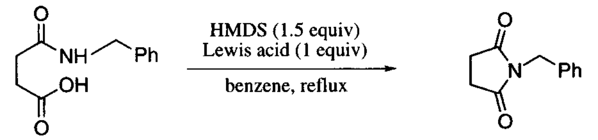
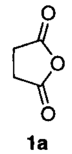
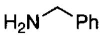
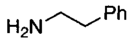
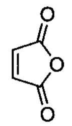
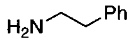
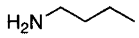
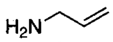
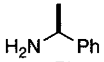
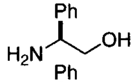
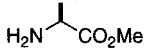
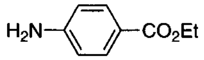
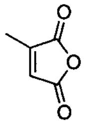
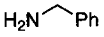
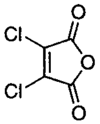
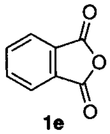
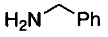
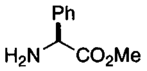
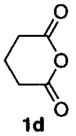
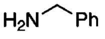
Table 1. Cyclization of *N*-Benzylsuccinamic Acid in the Presence of Various Lewis Acids



entry	Lewis acid	time (h)	yield[a] (%)
1	$ZnCl_2$	2	94
2	$ZnBr_2$	0.5	94
3	ZnI_2	1.5	94
4	$SnCl_4$	5	70
5	$SnCl_2$	2.5	65
6	$AlCl_3$	4	11
7	$MgCl_2$	6	no reaction

[a] Isolated yield.

Table 2. Lewis Acid and HMDS-Promoted Synthesis of Imide Derivatives from Anhydrides and Amines[a]

entry	anhydride	amine	time (h)[b]	imide	yield (%)[c]
1	 **1a**		1	**2a**	91
2			1	**2b**	94
3		H_2N-Ph	1	**2c**	97
4	 **1b**		0.5	**2d**	98
5			0.5	**2e**	95
6			0.5	**2f**	84
7			4[d]	**2g**	73
8			1	**2h**	87
9			6[d,e]	**2i**	84
10			2[e]	**2j**	90
11		H_2N-Ph	1	**2k**	97
12			1[e]	**2l**	93
13	 **1c**		1	**2m**	93
14	 **1d**		1	**2n**	73
15	 **1e**		1	**2o**	94
16			2[e]	**2p**	94
17	 **1d**		2	**2q**	81

[a] Unless specified, a solution of an amine and an anhydride in benzene was stirred at rt for 1 h and subsequently refluxed with 1 equiv of $ZnBr_2$ and 1.5 equiv of HMDS. [b] Refluxing time. [c] Isolated yield. [d] $ZnCl_2$ was used as a Lewis acid. [e] Stirred for 4 h before reflux.

Lewis acids. The yield of the imide was reduced in the presence of strong Lewis acids such as $SnCl_2$ and $AlCl_3$, whereas the imide formation was not observed even in a trace amount with $MgCl_2$. Among various polar and nonpolar solvents examined, the reaction proceeded smoothly in refluxing benzene, giving a high yield of the imide in a short reaction time. Although the amic acid formation in polar solvents such as THF or acetonitrile was found to be better than in nonpolar solvents, the subsequent cyclization step did not afford the concurrent yields of imide derivative.

To show the generality and scope of the Lewis acid and HMDS-promoted imide synthesis, the reaction was examined with various structurally diverse amines and anhydrides. These results are summarized in Table 2. In most cases, the amic acid cyclization proceeded smoothly with 1 molar equiv of $ZnBr_2$ and 1.5 molar equiv of HMDS in refluxing benzene, giving good to excellent yields of the desired succinimide, maleimide, phthalimide, and glutarimide derivatives. Yields of imides derived from maleic anhydride and amines such as allylamine and (−)-phenylglycinol were found to be better with $ZnCl_2$ than with $ZnBr_2$ (Table 2, entries 7 and 9). When chiral amines such as (−)-α-methylbenzylamine, (−)-phenylglycinol, and (+)-phenylglycine methyl ester were used, the corresponding imide derivatives were isolated without racemization under the described reaction conditions (Table 2, entries 8−10 and 16). Surprisingly, no formation of the isoimide was observed in the reaction of citraconic anhydride with benzylamine under our reaction conditions (Table 2, entry 13) in contrast to the recently reported reaction in refluxing acetic acid with sodium acetate affording the isoimide as the major product.[8] Although the mechanistic aspect of the amic acid cyclization cannot be defined clearly, it can be reasonably assumed on the basis of earlier reports[6] that the Lewis acid and HMDS-promoted silylation of an intermediate amic acid to a labile trimethylsilyl ester and subsequent thermal deoxysilylation gives an imide. The formation of thermodynamically stable hexamethyldisiloxane or trimethylsilanol[9] makes this reaction feasible under mild conditions.

In summary, we have demonstrated an economical and practical method for the synthesis of a wide range of imide derivatives by using inexpensive and readily available reagents under mild conditions. In light of its operational simplicity, simple purification procedure, and high efficiency, the procedure is expected to have broad utility, especially in the synthesis of functionalized imide derivatives, for future biological and chemical applications.

Experimental Section

General Methods. (R)-(−)-phenylglycinol was prepared according to previously reported method.[10] All other reactants and reagents were purchased from appropriate commercial

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[9] (a) Grubb, W. T. *J. Am. Chem. Soc.* **1954**, *76*, 3408. (b) Sommer, L. H.; Pietrusza, E. W.; Whitemore, F. C. *J. Am. Chem. Soc.* **1946**, *68*, 2282.

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sources. Succinic, maleic, and phthalic anhydrides were distilled and $ZnCl_2$ sublimed before use. HMDS and all other amines were distilled before use. All solvents were dried and distilled according to standard procedures. All reactions were carried out under an argon atmosphere. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as internal standard. Melting points were determined with a hotstage apparatus and are uncorrected. Enantiomeric purity of chiral imides **2h**, **2j**, and **2p** was determined by HPLC using a 0.46 × 25 cm Daicel Chiralcel OD-H column (flow rate, 0.5 mL/min). For this purpose, the corresponding racemic imides were prepared and coinjected with samples. Enantiomeric purity of **2i** was confirmed by the ^1H NMR of its Mosher ester.

General Procedure for the Synthesis of Imide Derivatives 2a–h and 2j–q. *N*-Benzylsuccinimide (2a). To a stirred solution of succinic anhydride (160 mg, 1.6 mmol) in dry benzene (12 mL) was added dropwise at rt a solution of benzylamine (0.174 mL, 1.6 mmol) in dry benzene (5 mL). During the addition, an exothermic reaction occurred with instantaneous formation of white precipitates. After the addition was complete, the resulting suspension was stirred for an additional 1 h and then $ZnBr_2$ (360 mg, 1.6 mmol) was added in one portion. While the resulting reaction mixture was heated (80 °C), a solution of HMDS (0.506 mL, 2.4 mmol) in dry benzene (5 mL) was added slowly over a period of 30 min, and then the mixture was refluxed for an additional 1 h. The reaction mixture was cooled to room temperature and poured into 0.5 N HCl (30 mL). The aqueous phase was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed successively with 30 mL of saturated $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure to leave the residue, which was purified by flash chromatography (silica gel, 90:10 hexane/EtOAc) to afford **2a** (276 mg, 91%) as a colorless solid: mp 102.5–103.5 °C (hexane, lit.[13] 98.0–99.0 °C); ^1H NMR δ 7.26–7.43 (m, 5H), 4.65 (s, 2H), 2.70 (s, 4H).

***N*-Phenethylsuccinimide (2b):** colorless solid; mp 134.0–135.0 °C (hexane, lit.[12] mp 135.0 °C); ^1H NMR δ 7.16–7.35 (m, 5H), 3.71–3.80 (m, 2H), 2.84–2.93 (m, 2H), 2.65 (s, 4H).

***N*-Phenylsuccinimide (2c):** colorless solid; mp 156.0–157.0 °C (hexane, lit.[13] mp 153.0–154.0 °C); ^1H NMR δ 7.22–7.55 (m, 5H), 2.90 (s, 4H).

***N*-Benzylmaleimide (2d):** colorless solid; mp 69.5–70.5 °C (hexane, lit.[4d] mp 68.5–70.0 °C); ^1H NMR δ 7.26–7.43 (m, 5H), 6.71 (s, 2H), 4.68 (s, 2H).

***N*-Phenethylmaleimide (2e):** colorless solid; mp 111.5–112.5 °C (hexane, lit.[4a] mp 110.0–111.0 °C); ^1H NMR δ 7.16–7.35 (m, 5H), 6.65 (s, 2H), 3.71–3.82 (m, 2H), 2.85–2.96 (m, 2H).

***N*-Butylmaleimide[4i] (2f):** colorless oil; ^1H NMR δ 6.69 (s, 2H), 3.52 (t, J = 7.2 Hz, 2H), 1.49–1.65 (m, 2H), 1.21–1.41 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H).

***N*-Allylmaleimide (2g).** $ZnCl_2$ was used as a Lewis acid: colorless solid; mp 42.5–43.5 °C (hexane, lit.[4d] mp 42.0–44.0 °C); ^1H NMR δ 6.72 (s, 2H), 5.80 (ddt, J = 17.2, 10.0, 5.6 Hz, 1H), 5.12–5.24 (m, 2H), 4.13 (dt, J = 5.6, 1.4 Hz, 2H).

(*S*)-(–)-*N*-α-Methylbenzylmaleimide (2h): colorless oil; $[\alpha]^{22}_D$ –89.3° (c 1.29, $CHCl_3$, lit.[14] $[\alpha]^{25}_D$ –69.25°, neat); ^1H NMR δ 7.20–7.40 (m, 5H), 6.63 (s, 2H), 5.36 (q, J = 7.4 Hz, 1H), 1.83 (d, J = 7.4 Hz, 3H); chiral HPLC >98% ee (t_R 9.40 min, 95:5 hexane/2-propanol).

(*S*)-(+)-*N*-[α-(Methoxycarbonyl)benzyl]maleimide (2j). A solution of maleic anhydride (200 mg, 2.04 mmol) and (*S*)-(+)-phenylglycine methyl ester (0.336 mg, 2.04 mmol) in dry benzene was stirred for 4 h at 50 °C and then refluxed for 2 h to give **2j** (450 mg, 90%) as a colorless solid: mp 88.0 °C (90:10 hexane/EtOAc; lit.[5a] mp 87.0–88.0 °C); $[\alpha]^{22}_D$ +77.2° (c 0.74, $CHCl_3$); IR ($CHCl_3$) 1750, 1720, 1400, 1380 cm^{-1}; ^1H NMR δ 7.48–7.32 (m, 5H), 6.73 (s, 2 H), 5.83 (s, 1 H), 3.79 (s, 3H); ^{13}C NMR δ 169.3, 168.3, 134.2, 134.1, 129.4, 128.5, 128.3, 55.6, 52.9; chiral HPLC >98% ee (t_R 26.52 min, 95:5 hexane/2-propanol). Anal. Calcd for $C_{13}H_{11}O_4N$: C, 63.67; H, 4.52; N, 5.71. Found: C, 64.00; H, 4.46; N, 5.43.

***N*-Phenylmaleimide (2k):** canary yellow solid; mp 89.0–90.0 °C (hexane, lit.[15] mp 89.0–89.8 °C); ^1H NMR δ 7.30–7.55 (m, 5H), 6.86 (s, 2H).

***N*-[*p*-(Ethoxycarbonyl)phenyl]maleimide (2l).** A solution of maleic anhydride (100 mg, 1.02 mmol) and ethyl 4-aminobenzoate (168 mg, 1.02 mmol) in dry benzene was stirred for 4 h at 50 °C and then refluxed for 1 h under similar reaction conditions as described for **2a** to give **2l** (233 mg, 93%) as a colorless solid: mp 114.5–115.5 °C (hexane, lit.[16] mp 112.0 °C); ^1H NMR δ 8.10–8.20 (m, 2H), 7.45–7.55 (m, 2H), 6.89 (s, 2H), 1.40 (t, J = 7.1 Hz, 3H).

***N*-Benzylcitraconimide[4i] (2m):** colorless oil; ^1H NMR δ 7.20–7.40 (m, 5H) 6.33 (q, J = 1.8 Hz, 1H), 4.65 (s, 2H), 2.07 (d, J = 1.8 Hz, 3H).

***N*-Benzyldichloromaleimide (2n):** colorless solid; mp 111.5 °C (hexane, lit.[17] mp 111.5 °C); ^1H NMR δ 7.23–7.42 (m, 5H), 4.74 (s, 2H).

***N*-Benzylphthalimide (2o):** colorless solid; mp 118.5–119.5 °C (hexane, lit.[18] mp 117.0–118.0 °C); ^1H NMR δ 7.65–7.88 (m, 4H), 7.26–7.40 (m, 5H), 4.85 (s, 2H).

(*S*)-(+)-N-[α-(Methoxycarbonyl)benzyl]phthalimide (2p). Under the reaction conditions as described for **2j**, starting from phthalic anhydride (200 mg, 1.35 mmol) and (*S*)-(+)-phenylglycine methyl ester (223 mg, 1.35 mmol), **2p** (374 mg, 94%) was obtained as a colorless solid: mp 116.0–117.0 °C (90:10 hexane/EtOAc); $[\alpha]^{22}_D$ + 7.2 (c 1.4, $CHCl_3$); IR ($CHCl_3$) 1750, 1720, 1390 cm^{-1}; ^1H NMR δ 7.89–7.82 (m, 2H), 7.76–7.69 (m, 2H), 7.59–7.53 (m, 2H) and 7.42–7.32 (m, 3H), 6.02 (s, 1H), 3.82 (s, 3H); ^{13}C NMR δ 168.4, 166.9, 134.3, 134.1, 131.6, 129.6, 128.4, 128.4, 128.0, 123.5, 55.7, 52.9; chiral HPLC >98% ee (t_R 24.49 min, 95:5 hexane/2-propanol). Anal. Calcd for $C_{17}H_{13}O_4N$: C, 69.14; H, 4.43; N, 4.74. Found: C, 69.20; H, 4.38; N, 4.39.

***N*-Benzylglutarimide[18] (2q):** colorless oil; ^1H NMR δ 7.20–7.40 (m, 5H), 4.96 (s, 2H), 2.67 (t, J = 6.5 Hz, 4H), 1.93 (m, 2H).

(*R*)-(+)-*N*-(1-Phenyl-2-hydroxyethyl)maleimide (2i). To a solution of maleic anhydride (286 mg, 2.91 mmol) in dry THF (15 mL) was added a solution of (*R*)-(–)-phenylglycinol (400 mg, 2.91 mmol) in THF (4 mL). The resulting reaction mixture was stirred for 4 h, and then hexane (10 mL) was added. Precipitated maleamic acid was separated by decanting the solvent and washed with dry ether. To a suspension of the amic acid in dry benzene (25 mL) was added $ZnCl_2$ (397 mg, 2.91 mmol), and the mixture was heated to 80 °C. A solution of HMDS (1.1 mL, 5.25 mmol) in dry benzene (5 mL) was added in three equal portions over 30 min. The reaction mixture was refluxed for an additional 6 h and concentrated under reduced pressure to leave the residual solid, which was dissolved in THF (5 mL) containing 0.1 N HCl (9:1). The solution was stirred for 15 min and evaporated to dryness. The residue was partitioned between EtOAc and saturated $NaHCO_3$ solution, and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic solvents were washed with saturated brine, dried over Na_2SO_4, filtered, and concentrated to give a thick liquid, which was purified by flash chromatography (silica gel, 70:30 hexane/EtOAc–hexane) to furnish **2i** (532 mg, 84%) as a colorless solid: mp 48.0–49.0 °C (80:20 hexane/EtOAc); $[\alpha]^{22}_D$ +47.8° (c 0.5, $CHCl_3$); IR ($CHCl_3$) 3450 (br), 1710, 1405, 1370 cm^{-1}; ^1H NMR δ 7.31–7.38 (m, 5H), 6.71 (s, 2H), 5.26 (dd, J = 5.1, 9.1 Hz, 1H), 4.51 (dd, J = 9.2, 11.6 Hz, 1H), 4.08 (dd, J = 5.1, 11.6 Hz, 1H), 2.30 (br, 1H, OH); ^{13}C NMR δ 171.4, 136.6, 134.1, 128.7, 128.2, 127.8, 127.7, 62.0, 57.3. Anal. Calcd for $C_{12}H_{11}O_3N$: C, 66.35; H, 5.10; N, 6.44. Found: C, 65.89; H, 5.19; N, 6.16. The Mosher ester[19] of **2i**: >98% ee; ^1H NMR δ 7.33–7.45 (m, 5H), 6.58 (s, 2H), 5.48 (dd, J = 5.2, 10.7 Hz, 1H), 5.31 (t, J = 10.8 Hz, 1H), 4.82 (dd, J = 5.3, 10.8 Hz, 1H), 3.46 (m, 3H).

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