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An Asymmetric Ammonia Synthon for Michael Additions[1]

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The highly diastereoselective 1,4-addition of lithiated chiral amine 1 to α,β-unsaturated esters, followed by hydrogenolysis of the benzylic-type C–N bonds of the 1,4-adducts, provides an asymmetric ammonia synthon for Michael additions. Under optimized conditions, lithiated 1 adds to α,β-unsaturated *tert*-butyl esters in dimethoxyethane at –63 °C in high yield with very high diastereoselectivity. Small, large, functionalized, and chiral β-ester substituents are amenable, with (*S*)-1 consistently adding to (*E*)-3 from the top as drawn in Table II. Hydrogenolysis liberates the β-amino esters with typically 95–99% ee.

The direct control of stereochemistry at nitrogen-bearing stereocenters is not nearly as well developed as the control of stereochemistry at oxygen-bearing centers. Our approach to the stereoselective formation of carbon–nitrogen bonds involves the diastereoselective 1,4-addition of a chiral lithium amide to an α,β-unsaturated ester followed by cleavage of the chiral auxiliary on nitrogen providing an asymmetric ammonia synthon (eq 1).[2,3] For this process, the structure of the lithium amide must both promote diastereoselectivity and allow auxiliary cleavage. In this paper, we report the 1,4-addition of the lithium amide of 3,5-dihydro-4*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepine (1) to a variety of esters with high diastereoselectivity and the hydrogenolysis of the benzylic-type C–N bonds of the resulting adducts yielding β-amino esters with high enantiomeric and diastereomeric excesses. These materials are important as peptide components[4,5] and β-lactam precursors.[6]

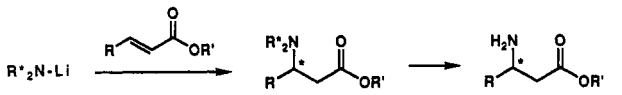
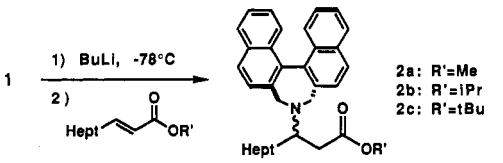


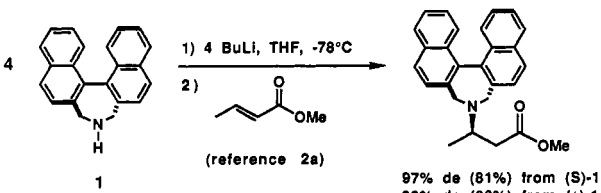
Table I. Optimization with Respect to Solvent, Ester Substituent, and Stoichiometry



entry	R′	solvent	equiv R_2NLi	diastereomer ratio (yield, %)
1	Me	THF	4.0[a]	20:1 (44)
2	Me	THF	1.0[a]	20:1 (25)
3	Me	THF/HMPA (4:1)	1.0[a]	3:1 (18)
4	Me	THF/20 equiv TMEDA	4.0[a]	12:1 (28)
5	Me	toluene	1.0[a]	3:1 (6)
6	Me	THF/4 equiv 12-crown-4[c]	4.0[a]	44:1 (60)
7	Me	THF/4 equiv 12-crown-4[d]	4.0[a]	24:1 (42)
8	iPr	THF/8 equiv 12-crown-4[c]	4.0[b]	17:1 (65)
9	tBu	THF/4 equiv 12-crown-4[c]	4.0[b]	37:1 (88)
10	tBu	THF/1 equiv 12-crown-4[c]	1.0[b]	16:1 (43)
11	tBu	DME[e]	1.5[b]	53:1 (80)
12	tBu	DME[e]	1.1[b]	66:1 (70)
13	tBu	DME[e]	1.0[b]	62:1 (66)
14	iPr	DME[e]	1.5[b]	30:1 (63)
15	Me	DME[e]	2.0[a]	22:1 (32)

[a] Reaction with (±)-1. [b] Reaction with (*S*)-1. [c] BuLi added to 1 plus 12-crown-4. [d] 12-Crown-4 added to 1 plus BuLi. [e] Reaction at –63 °C.

Our previously reported conditions for the diastereoselective addition of lithiated 1 to methyl crotonate (eq 2)[2a,7] worked poorly with methyl decenoate (Table I, entry 1).



1,2-Addition and/or γ-deprotonation appeared to lower

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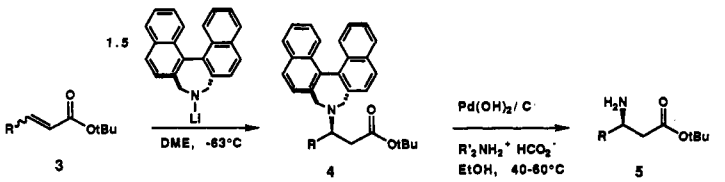
0022-3263/92/1957-2114$03.00/0

Table II. Substrate Variation under Optimized Conditions



compd	R	diastereomer ratio (yield, %)	$R'_2NH_2^+$	% ee (yield, %) config
a	(*E*)-Me	66:1 (83)	morpholinium	>95 (68)[a] R
b	(*E*)-Hept	53:1 (80)	morpholinium	96 (80)[b]
c	(*Z*)-Hept	1:8 (39)		
d	(*E*)-iBu	69:1 (74)	morpholinium	97 (80)[b]
e	(*E*)-iPr	34:1 (69)	NH_4^+	>99 (57)[b,c] *S*
f	(*E*)-tBu(Me)$_2$SiO	43:1 (86)	NH_4^+	>99 (81)[c] *R*
g	(*E*)-tBu(Me)$_2$SiO	150:1 3*R* (66)[d]	NH_4^+	147:1[e] (78) 3*R*, 4*R*
h		9.4:1 (49)	NH_4^+	8:1[e,f] (66) 3*S*, 4*R*

[a] Isolated as the Mosher amide. [b] Isolated as the 1-naphthamide. [c] 100% de **4e** and **4f** hydrogenolyzed. [d] Reaction with (*R*)-**1**. [e] Diastereomer ratio. [f] **4h** as an 8:1 mixture of diastereomers hydrogenolyzed.

the yield of the desired 1,4-adduct. In order to improve the regio- and stereoselectivity, the reaction solvent, ester alkoxy group, and stoichiometry were varied (Table I). Decreasing the lithium amide to ester ratio lowered the yield, as observed previously in THF (entry 2).[2a] The polar additives HMPA[8,9] and TMEDA lowered the selectivity (entries 3 and 4). The less polar solvent toluene also gave poor results (entry 5). In contrast, 1 equiv of 12-crown-4 (per lithium) in THF improved the yield and selectivity of the 1,4-addition. This effect was only observed when the 12-crown-4 was added to the amine before the butyllithium (entry 6); addition of 12-crown-4 to the preformed lithium amide had little effect (entry 7). For each of these additions to methyl decenoate, the same diastereomer of **2a** predominated (entries 1–7).

Increasing the size of the ester alkoxy group from methyl to isopropyl to *tert*-butyl improved the yield of 1,4-addition (entries 6, 8, and 9). Decreasing the number of equivalents of lithium amide still lowered the yield (entry 10). Changing the solvent from stoichiometric 12-crown-4 in bulk THF to bulk DME gave superior results. In DME, the addition to *tert*-butyl decenoate proceeded with high yield and high selectivity, even with 1.5–1.1 equiv of lithium amide (entries 11 and 12). The size of the ester substituent still had to be maintained, however (entries 14 and 15).

The optimum system, *tert*-butyl esters in DME with 1.5 equiv of lithiated **1**, was explored with other substrates (Table II). The size of the β-substituent was quite variable for (*E*)-esters. High diastereoselectivities and yields were observed with R = methyl (**3a**), heptyl (**3b**), isobutyl (**3d**), and isopropyl (**3e**). The one (*Z*)-ester examined, **3c**, gave reversed face selectivity. Compatibility with heteroatoms was confirmed with the siloxy substrates **3f** and **3g**. These substrates required longer reaction times, but still showed good selectivities. Ester **3g** is significant in that it is hindered, oxygenated, and *chiral*. Maintaining the ester configuration but switching the lithium amide configuration allowed testing for reagent-controlled diastereoselection.[10] Opposite enantiomers of lithiated **1** preferentially approached opposite faces of **3g**, establishing that the face selectivity of the reagent overrides the face selectivity of the substrate.

Various conditions were explored for the hydrogenolysis of the benzylic-type C–N bonds of Michael adducts **4a–h**. Palladium hydroxide on carbon (Pearlman's catalyst)[11] in ethanol at 45 °C with morpholineum formate or ammonium formate[12] as the hydrogen donor gave the best results (Table II). Moist commercial catalyst (Aldrich) had to be dried before use (60 °C (1 mmHg), 3 h). Other palladium catalysts gave partial reduction of the naphthalene rings. No reaction occurred under 1 atm of hydrogen. Ammonium formate worked the best for substrates prone to β-elimination, e.g., **4e**. The catalyst was always treated with the hydrogen donor before adding the substrate in order to avoid epimerization of **4** and/or racemization of **5**. When **4f** was treated with Pearlman's catalyst before the addition of the reducing agent, nearly racemic **5f** was obtained.[13] Epimerization was completely avoided under the optimized conditions: hydrogenolysis of diastereomercially pure Michael adducts **4e** and **4f** gave enantiomerically pure β-amino esters **5e** and **5f** within the limits of detection by HPLC. In each case, the high diastereomeric excess of Michael adducts **4** translated to high enantiomeric excess (or in the case of **4g** and **4h**, diastereomeric excess) of β-amino esters **5**.

In five correlated examples representing small, large, oxygenated, and chiral β-ester substituents (**4a**, **4e**, **4f**, **4g**, and **4h**, see Experimental Section), a given enantiomer of the chiral lithium amide consistently approaches the same face of (*E*)-olefins: lithiated (*S*)-**1** approaches (*E*)-**3** from the top as drawn in Table II. Consistent (although not correlated) diastereofacial preference is even maintained throughout the various conditions listed in Table I. The reversed diastereoselectivity in additions to (*E*)- and (*Z*)-*tert*-butyl 2-decenoate (**3b** and **3c**, Table II) is consistent with a cyclic (closed) transition state whereby the chiral auxiliary determines the facial approach and opposite placements of R and H give opposite diastereomers of **4** (eq 3).[7] In an open transition state where the meshing

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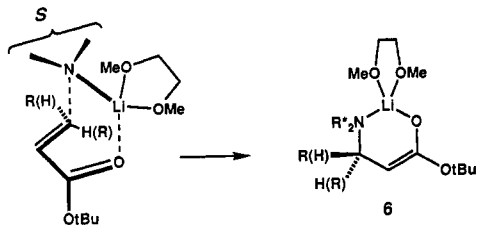

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of the amine's stereochemistry with that of the newly forming stereocenter determines the relative energies of the diastereomeric transition states, the same diastereomer would likely predominate from (*E*)- and (*Z*)-alkenes.[14] The aggregation state of the lithium amide is not known, although equal diastereoselectivities in additions employing racemic and resolved **1** are consistent with the addition of a monomer in that mixed configuration aggregates are available to the racemate which are not available to the enantiomerically pure species.[2a,15] The importance of timing in the addition of 12-crown-4 to the reaction mixture (Table I entries 6 and 7) establishes that different active forms of the lithium amide are possible in this solvent system and that they do not rapidly equilibrate.

Under optimized conditions in DME, lithiated **1** adds stereoselectively to a variety of substrates providing an asymmetric ammonia synthon for Michael additions. Diastereoselective reactions of the intermediate enolates **6** will be reported shortly.

Experimental Section

General. All reactions were conducted under argon. Tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled from sodium/benzophenone, triethylamine was distilled from CaH_2, and ethanol was distilled from sodium and diethyl phthalate. Other solvents and the α,β-unsaturated ester substrates were dried over molecular sieves. Butyllithium was titrated with 1,3-diphenylacetone *p*-tosylhydrazone.[16] Amine **1** was synthesized and resolved according to ref 2a. The α,β-unsaturated ester substrates were prepared by standard techniques.[17] Palladium hydroxide on carbon (Pearlman's catalyst, 20% palladium, Aldrich) was dried at 60 °C at 1 mmHg for 3 h before use. HPLC was performed on a 25-cm (10-mm i.d.) Regis Pirkle Type 1-A column or an ISCO 25-cm (4.6-mm i.d.) silica column as indicated and detected at 280 nm. Elemental analyses were performed by the Microanalytical Laboratory at the University of California, Berkeley.

(*E*)-*tert*-Butyl 2-Decenoate (3b) and (*Z*)-*tert*-Butyl 2-Decenoate (3c).[18] A solution of 2.5 mL (16.0 mmol) of octanal and 6.63 g (18.0 mmol) of *tert*-butyl (triphenylphosphoranylidene)acetate[19] in 15 mL of toluene was heated at reflux for 2 h. The reaction mixture was cooled, filtered through silica gel, and concentrated. Flash chromatography (2% ether in petroleum ether) yielded 2.44 g (68%) of **3b** (R_f 0.14) and 277.4 mg (8%) of **3c** (R_f 0.22). **3b**: IR (film) 2940, 2905, 2840, 1700, 1650, 1460, 1360, 1280, 1090 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.85 (dt, J = 15.6, 7.0 Hz, 1 H), 5.72 (dt, J = 15.3, 5.7 Hz, 1 H), 2.09–2.17 (m, 2 H), 1.45 (s, 9 H), 1.34–1.41 (m, 2 H), 1.24 (br s, 8 H), 0.85 (t, J = 6.5 Hz, 3 H); ^{13}C NMR (53.6 MHz, $CDCl_3$) δ 166.1, 148.1, 122.8, 79.8, 32.0, 31.7, 29.1, 29.0, 28.12, 28.08, 22.6, 14.0. **3c**: ^1H NMR (250 MHz, $CDCl_3$) δ 6.07 (dt, J = 11.6, 7.4 Hz, 1 H), 5.63 (dt, J = 11.6, 1.7 Hz, 1 H), 2.58 (ddt, J = 1.7, 7.5, 6.9 Hz, 2 H), 1.46 (s, 9 H), 1.14–1.48 (m, 10 H), 0.85 (t, J = 6.5 Hz, 3 H); ^{13}C NMR (53.6 MHz, $CDCl_3$) δ 165.9, 148.9, 121.3, 79.8, 31.8, 29.2, 29.1, 28.8, 28.2, 22.6, 14.1.

(*E*)-*tert*-Butyl 5-(*tert*-Butyldimethylsiloxy)-2-pentenoate (3f). To an excess of 1,3-propanediol (50.0 mL, 690 mmol) in 150 mL of THF was added 5.00 g (33.3 mmol) of *tert*-butyldimethylsilyl chloride and 10.0 mL (71.7 mmol) of triethylamine. The reaction mixture was stirred for 1 h, concentrated, and partitioned between ether and water. The ether layer was dried over $MgSO_4$, concentrated, diluted with petroleum ether, filtered through silica gel, and concentrated to 5.35 g (85%) of 3-(*tert*-butyldimethylsiloxy)-1-propanol which was used without further purification: IR (film) 3377 (br), 2953, 2872, 1481, 1393, 1368, 1261, 1099, 1011, 960, 843, 785, 740 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.80 (t, J = 5.6 Hz, 2 H), 3.77 (t, J = 5.6 Hz, 2 H), 2.60 (br s, 1 H), 1.75 (tt, J = 5.59, 5.64 Hz, 2 H), 0.87 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (53.6 MHz, $CDCl_3$) δ 61.7, 60.9, 34.2, 25.4, -3.9, -5.8.

To 3.86 mL (44.2 mmol) of oxalyl chloride in 225 mL of CH_2Cl_2 at -78 °C was added 3.41 mL (47.8 mmol) of dimethyl sulfoxide. After 10 min, a solution of 5.35 g (27.5 mmol) of 3-(*tert*-butyldimethylsiloxy)-1-propanol in 56 mL of CH_2Cl_2 at -78 °C was added via cannula. After 15 min, 14.5 mL (104 mmol) of triethylamine was added. After 5 min, 20.1 g (53.4 mmol) of *tert*-butyl (triphenylphosphoranylidene)acetate[19] in 100 mL of CH_2Cl_2 at -78 °C was added, and the reaction mixture was warmed to 0 °C and then to room temperature.[20] Concentration and Kugelrohr distillation (60 °C (1.0 mmHg)) gave 6.25 g of clear oil which was flash chromatgraphed (10% ether in hexanes) yielding 3.71 g (46%) of **3f**: IR (film) 2940, 2915, 2840, 1705, 1650, 1468, 1390, 1360, 1145, 990, 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.79 (dt, J = 15.7, 7.1 Hz, 1 H), 5.72 (dt, J = 15.7 1.5 Hz, 1 H), 3.65 (t, J = 6.5 Hz, 2 H), 2.32 (ddt, J = 1.4, 7.1, 6.5 Hz, 2 H), 1.41 (s, 9 H), 0.83 (s, 9 H), 0.01 (s, 6 H); ^{13}C NMR (53.6 MHz, $CDCl_3$) δ 165.6, 144.3, 124.6, 79.8, 61.5, 35.4, 28.0, 25.8, 18.2, -5.4. Anal. Calcd for $C_{15}H_{30}SiO_3$: C, 62.89; H, 10.55. Found: C, 62.95; H, 10.52.

(*R*)-(*E*)-*tert*-Butyl 5-(*tert*-Butyldimethylsiloxy)-4-methyl-2-pentenoate (3g). To a solution of 5.00 mL (45.3 mmol) of (*S*)-methyl 3-hydroxy-2-methylpropanoate and 9.48 mL (68.0 mmol) of triethylamine in 200 mL of CH_2Cl_2 was added 7.17 g (47.6 mmol) of *tert*-butyldimethylsilyl chloride. The reaction mixture was stirred at room temperature for 24 h, washed with water, dried over $MgSO_4$, concentrated, and flash chromatographed (10% ether in hexanes) yielding 10.3 g (98%) of (*S*)-methyl 2-methyl-3-(*tert*-butyldimethylsiloxy)propanoate as an oil: ^1H NMR (200 MHz, $CDCl_3$) δ 3.73 (dd, J = 6.9, 9.7 Hz, 1 H), 3.63 (s, 3 H), 3.61 (dd, J = 6.0, 9.7 Hz, 1 H), 2.60 (m, 1 H), 1.09 (d, J = 7.0 Hz, 3 H), 0.83 (s, 9 H), -0.01 (s, 6 H); ^{13}C NMR (53.6 MHz, $CDCl_3$) δ 175.3, 65.2, 51.4, 42.4, 25.7, 18.1, 13.4, -5.6.

To 4.08 g (17.3 mmol) of (*S*)-methyl 2-methyl-3-(*tert*-butyldimethylsiloxy)propanoate dissolved in 100 mL of THF at 0 °C was added 22.8 mL (22.8 mmol) of BH_3·THF (1.00 M in THF). The reaction mixture was allowed to slowly warm to room temperature overnight, cooled to 0 °C, and slowly treated with a solution of triethylamine in methanol until bubbling ceased. Most of the THF was removed by rotary evaporation, water was added, and the mixture was extracted with ether. The combined ether extracts were washed with brine and dried over $MgSO_4$. Flash chromatography (40% ether in petroleum ether) yielded 3.55 g (98%) of (*R*)-3-(*tert*-butyldimethylsiloxy)-2-methyl-1-propanol: $[\alpha]_D$ -2.30° (*c* 12.63, ethanol); IR (film) 3396 (v br) 2908, 2283, 1472, 1395, 1359, 1258, 1091, 1044, 942, 913, 835, 775 cm^{-1}; ^1H

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NMR (200 MHz, $CDCl_3$) δ 3.44–3.67 (m, 4 H), 3.06 (br s, 1 H), 1.75–1.89 (m, 1 H), 0.83 (s, 9 H), 0.78 (d, J = 6.9 Hz, 3 H), 0.00 (s, 6 H); ^{13}C NMR (53.6 MHz, $CDCl_3$) δ 68.1, 67.5, 37.1, 25.7, 18.1, 13.0, −5.6, −5.7.

To 2.23 mL (25.6 mmol) of oxalyl chloride in 136 mL of CH_2Cl_2 at −78 °C was added 2.07 mL (28.9 mmol) of dimethyl sulfoxide. After 10 min, a solution of 3.55 g (17.0 mmol) of (*R*)-3-(*tert*-butyldimethylsiloxy)-2-methyl-1-propanol in 34 mL of CH_2Cl_2 at −78 °C was added via cannula. After 15 min, 8.77 mL (62.9 mmol) of triethylamine was added. After 10 min, 12.2 g (32.3 mmol) of *tert*-butyl (triphenylphosphoranylidene)acetate[19] in 80 mL of cold CH_2Cl_2 was added. The reaction mixture was allowed to warm to 0 °C and then room temperature.[20] Concentration and Kugelrohr distillation (100 °C (1.3 mmHg)) gave 3.08 g of oil which was flash chromatographed (3% ether in petroleum ether) yielding 2.70 g (53%) of **3g**: $[\alpha]_D$ 20.6° (*c* 1.02, ethanol); IR (film) 2953, 2939, 2904, 2855, 1719, 1663, 1481, 1389, 1369, 1292, 1257, 1144, 1102, 983, 836, 779 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.79 (dd, J = 7.2, 15.8 Hz, 1 H), 5.70 (dd, J = 1.3, 15.8 Hz, 1 H), 3.52 (dd, J = 6.5, 9.7 Hz, 1 H), 3.46 (dd, J = 6.4, 9.7 Hz, 1 H), 2.38–2.50 (m, 1 H), 1.45 (s, 9 H), 1.01 (d, J = 6.8 Hz, 3 H), 0.86 (s, 9 H), 0.01, (s, 6 H); ^{13}C NMR (53.6 MHz, $CDCl_3$) δ 165.9, 149.9, 122.6, 79.6, 66.9, 38.9, 28.1, 25.8, 18.2, 15.5, −5.4. Anal. Calcd for $C_{16}H_{32}SiO_3$: C, 63.95; H, 10.73. Found: C, 64.33; H, 10.95.

Adduct 2a. To a solution of 187.2 mg (0.634 mmol) of (±)-**1** in 12 mL of THF at −78 °C was added 0.29 mL (0.63 mmol) of BuLi (2.22 M in hexanes). The solution was stirred for 5 min at −78 °C before adding a solution of 29.2 mg (0.158 mmol) of (*E*)-methyl 2-decenoate in 2.5 mL of THF at −78 °C via cannula. The reaction mixture was stirred at −78 °C for 30 min before quenching with a solution of 33.9 mg (0.634 mmol) of NH_4Cl in 8 mL of water. Most of the THF was removed by rotary evaporation, and the remaining mixture was extracted four times with ether. The combined ether extracts were washed with brine and dried over Na_2SO_4. Flash chromatography (20% ether in hexanes) yielded 33.0 mg (44%) of **2a** as a 20:1 mixture of diastereomers: IR (film) 3048, 2930, 2282, 1736, 1625, 1596, 1463, 1360, 1205, 814, 756 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 7.71–7.75 (m, 4 H), 7.58–7.60 (m, 2 H), 7.42–7.43 (m, 2 H), 7.15–7.22 (m, 2 H), 6.96–7.00 (m, 2 H), 3.57 (d, J = 12.3 Hz, 2 H), 3.50 (d, J = 12.2 Hz, 2 H), 3.45–3.53 (m, 1 H), 3.40 (s, 3 H), 2.49 (dd, J = 14.4, 5.9 Hz, 1 H), 2.21 (dd, J = 14.4, 7.9 Hz, 1 H), 1.25–1.41 (m, 12 H), 0.89–0.92 (m, 3 H); ^{13}C NMR (125.76 Hz, C_6D_6) δ 173.3, 135.8, 135.6, 134.0, 132.5, 129.4, 129.1, 128.9, 128.4, 126.6, 126.1, 62.7, 52.5, 51.5, 38.2, 33.9, 32.7, 30.4, 30.2, 27.6, 23.6, 14.8. Anal. Calcd for $C_{33}H_{37}NO_2$: C, 82.63; H, 7.77; N, 2.92. Found: C, 82.80; H, 7.84; N, 2.76.

For reference, a mixture of the diastereomers of **2a** was prepared by heating 409.5 mg (1.386 mmol) of (±)-**1** and 0.766 mg (0.866 mmol) of (*E*)-methyl 2-decenoate in 9 mL of methanol at reflux overnight. Flash chromatography yielded 90.4 mg (22%) of **2a** as a 1:1 mixture of diastereomers. ^1H NMR (200 MHz, C_6D_6) corresponding to the minor diastereomer from above: δ 7.70–7.76 (m, 4 H), 7.57–7.61 (m, 2 H), 7.37–7.45 (m, 2 H), 7.16–7.23 (m, 2 H), 6.94–7.02 (m, 2 H), 3.55 (d, J = 12.5 Hz, 2 H), 3.48 (d, J = 12.3 Hz, 2 H), 3.40–3.48 (m, 1 H), 3.36 (s, 3 H), 2.42 (dd, J = 14.3, 5.7 Hz, 1 H), 2.31 (dd, J = 14.3, 8.2 Hz, 1 H), 1.25–1.55 (m, 12 H), 0.87–0.95 (m, 3 H). ^{13}C NMR (125.76 Hz, C_6D_6) of the 1:1 mixture of diastereomers: δ 173.3, 173.1, 135.7, 135.6, 134.0, 132.45, 132.40, 129.4, 129.1, 128.9, 128.8, 128.4, 126.6, 126.1, 63.2, 62.7, 52.9, 52.5, 51.55, 51.51, 39.0, 38.2, 33.9, 33.7, 32.73, 32.70, 30.4, 30.2, 27.8, 27.6, 23.6, 23.5, 14.8.

The lithium amide addition was repeated under various conditions as described in Table I. For reactions in the presence of a cosolvent, the cosolvent was added to the cold solution of **1**, except for entry 7, where the 12-crown-4 was added to the cold solution of lithiated **1**. Diastereomer ratios were determined by ^1H NMR integration of the diastereotopic methoxy singlets at 3.36 and 3.40 ppm.

Adduct 2b. A solution of 51.2 mg (0.173 mmol) of (±)-**1** and 56 μL (0.35 mmol) of 12-crown-4 in 3.4 mL of THF was cooled to −78 °C and treated with 77 μL (0.173 mmol) of BuLi (2.22 M in hexanes). The reaction mixture was warmed in a −20 °C bath for 15 min and then cooled back to −78 °C. After 15 min, a solution of 9.6 mg (43 μmol) of (*E*)-isopropyl 2-decenoate in 0.80 mL of THF at −78 °C was added via cannula. The reaction was quenched after 30 min with a solution of 9.3 mg (0.173 mmol) of NH_4Cl in 4 mL of water. Most of the THF was removed by rotary evaporation, and the remaining mixture was extracted four times with ether. The combined ether extracts were washed with brine and dried over Na_2SO_4. Flash chromatography (10% ether in hexanes) yielded 14.5 mg (65%) of **2b** as a 17:1 mixture of diastereomers (determined by HPLC: Pirkle column, 2% DME in hexanes, 2.0 mL/min, retention times 24.2 and 25.6 min, second peak predominant): IR (film) 2960, 2840, 1725, 1505, 1180, 1170, 905 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 7.70–7.76 (m, 4 H), 7.57–7.61 (m, 2 H), 7.43–7.47 (m, 2 H), 7.16–7.24 (m, 2 H), 6.94–7.02 (m, 2 H), 5.10 (sept, J = 6.2 Hz, 1 H), 3.62 (d, J = 12.2 Hz, 2 H), 3.53 (d, J = 12.2 Hz, 2 H), 3.42–3.53 (m, 1 H), 2.49 (dd, J = 6.5, 14.1 Hz, 1 H), 2.26 (dd, J = 7.7, 14.1 Hz, 1 H), 1.26–1.52 (m, 12 H), 1.11 (d, J = 6.2 Hz, 3 H), 1.05 (d, J = 6.2 Hz, 3 H), 0.88–0.95 (m, 3 H); ^{13}C NMR (53.6 MHz, C_6D_6) δ 171.9, 135.2, 135.1, 133.5, 131.9, 129.1, 128.8, 128.4, 127.8, 126.1, 125.6, 67.2, 62.9, 52.4, 39.1, 33.2, 32.2, 30.0, 29.7, 27.4, 23.1, 22.0, 21.9, 14.4. Anal. Calcd for $C_{35}H_{41}NO_2$: C, 82.80; H, 8.14; N, 2.76. Found: C, 82.55; H, 8.23; N, 2.69.

An analogous reaction where the lithium amide solution was not warmed above −78 °C gave a 52% yield of **2b** as a 10:1 mixture of diastereomers.

For reference, a mixture of the diastereomers of **2b** was prepared by heating 306.2 mg (1.037 mmol) of (±)-**1**, 2.247 g (10.58 mmol) of (*E*)-isopropyl 2-decenoate, and a drop of triethylamine at 140 °C for 24 h. Excess (*E*)-isopropyl 2-decenoate was removed under vacuum, and flash chromatography (20% ether in hexanes) yielded 85.5 mg (16%) of **2b** as a 1:1 mixture of diastereomers. ^1H NMR (250 MHz, C_6D_6) corresponding to the minor diastereomer from above: δ 7.70–7.76 (m, 4 H), 7.57–7.60 (m, 2 H), 7.40–7.46 (m, 2 H), 7.16–7.23 (m, 2 H), 6.95–7.01 (m, 2 H), 5.03–5.10 (m, 1 H), 3.59 (d, J = 12.3 Hz, 2 H), 3.50 (d, 12.2 Hz, 2 H), 3.43–3.49 (m, 1 H), 2.44 (dd, J = 6.1, 14.0 Hz, 1 H), 2.30 (dd, J = 8.1, 14.0 Hz, 1 H), 1.25–1.56 (m, 12 H), 1.04 (d, J = 6.5 Hz, 3 H), 1.01 (d, J = 6.5 Hz, 3 H), 0.90–0.95 (m, 3 H). ^{13}C NMR (53.6 MHz, C_6D_6) of the 1:1 mixture of diastereomers: δ 171.9, 171.8, 135.2, 135.1, 133.5, 131.9, 128.93, 128.89, 128.8, 128.3, 128.2, 127.8, 126.1, 125.6, 67.2, 62.9, 62.5, 52.4, 52.1, 39.1, 38.4, 33.4, 33.1, 32.3, 30.0, 29.8, 27.4, 27.2, 23.1, 21.94, 21.89, 14.4.

Adduct 4a. To a solution of 197.9 mg (0.670 mmol) of (*S*)-**1** in 8 mL of DME at −63 °C was added 0.300 mL (0.670 mmol) of BuLi (2.21 M in hexanes). After 5 min, a solution of 63.5 mg (0.447 mmol) of **3a** in 8 mL of DME at −63 °C was added via cannula. The reaction mixture was stirred at −63 °C for 30 min before quenching with a solution of 35.8 mg (0.670 mmol) of NH_4Cl in 15 mL of water. Most of the DME was removed by rotary evaporation, and the remaining mixture was extracted four times with ether. The combined ether extracts were washed with brine and dried over Na_2SO_4. Flash chromatography (50% ether in hexanes) yielded 162.9 mg (83%) of **4a** as a 66:1 mixture of diastereomers (determined by HPLC: Pirkle column, 5% 2-propanol in hexanes, 0.600 mL/min, retention times 42.60 and 44.61 min, second peak predominant): IR (film) 3051, 2975, 2937, 2865, 1727, 1506, 1463, 1367, 1300, 1156, 820, 757 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 7.70–7.75 (m, 4 H), 7.57–7.61 (m, 2 H), 7.36–7.40 (m, 2 H), 7.19–7.28 (m, 2 H), 6.94–7.02 (m, 2 H), 3.59 (d, J = 12.3 Hz, 2 H), 3.44 (d, J = 12.2 Hz, 2 H), 3.35–3.54 (m, 1 H), 2.51 (dd, J = 6.7, 14.0 Hz, 1 H), 2.21 (dd, J = 8.0, 14.0 Hz, 1 H), 1.40 (s, 9 H), 1.01 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (53.6 MHz, C_6D_6) δ 171.3, 135.3, 135.1, 133.5, 131.9, 128.7, 128.3, 126.1, 125.6, 79.5, 57.4, 52.2, 42.5, 28.2, 17.5. Anal. Calcd for $C_{30}H_{31}NO_2$: C, 82.35; H, 7.14; N, 3.20. Found: C, 82.70; H, 7.17; N, 3.14.

For reference, a mixture of the diastereomers of **4a** was prepared by heating 93.7 mg (0.317 mmol) of (±)-**1** and 3.22 g (22.7 mmol) of **3a** at 140 °C overnight. Excess **3a** was removed under vacuum, and flash chromatography (50% ether in hexanes) yielded 72.7 mg (52%) of **4a** as a 1:1 mixture of diastereomers. ^1H NMR (250 MHz, C_6D_6) corresponding to the minor diastereomer from above: δ 7.71–7.74 (m, 4 H), 7.57–7.63 (m, 2 H), 7.36–7.43 (m, 2 H), 7.16–7.23 (m, 2 H), 6.94–7.02 (m, 2 H), 3.56 (d, J = 12.2 Hz, 2 H), 3.43 (d, J = 12.1 Hz, 2 H), 3.35–3.49 M, 1 H), 2.47 (dd, J = 6.6, 14.0 Hz, 1 H), 2.19 (dd, J = 7.8, 14.0 Hz, 1 H), 1.40 (s, 9 H), 0.97 (d, J = 6.9 Hz, 3 H). ^{13}C NMR (53.6 MHz, C_6D_6) of the 1:1 mixture of diastereomers: δ 171.34, 171.27, 135.27, 135.25, 135.21, 135.1, 133.50, 133.47, 131.9, 128.8, 128.7, 128.3, 126.1, 125.6, 79.5, 57.8, 57.4, 52.2, 52.1, 42.5, 42.1, 28.2, 18.0, 17.5.

Stereochemistry was correlated by reduction of the lithium amide adduct to the corresponding amino alcohol. To a solution of 86.2 mg (0.197 mmol) of **4a** (58:1 mixture of diastereomers) in 20 mL of THF at 0 °C was added 15.7 mg (0.415 mmol) of $LiAlH_4$. The solution was allowed to warm to room temperature over 12 h and then treated with 9 mL of wet ether followed by 5 g of Celite. Filtration and flash chromatography (3% triethylamine and 20% ethanol in hexanes) yielded 36.0 mg (50%) of the amino alcohol: ^1H NMR (250 MHz, $CDCl_3$) δ 7.81–7.84 (m, 4 H), 7.48–7.51 (m, 2 H), 7.28–7.37 (m, 4 H), 7.09–7.16 (m, 2 H), 5.25 (br s, 1 H), 3.70–3.85 (m, 2 H), 3.75 (d, J = 12.5 Hz, 2 H), 3.38 (d, J = 12.5 Hz, 2 H), 2.96–3.04 (m, 1 H), 1.81–1.89 (m, 1 H), 1.41–1.49 (m, 1 H), 0.97 (d, J = 6.6 Hz, 3 H). Integration of the diastereotopic methyl resonances at 0.97 and 0.86 ppm indicated a >50:1 ratio of diastereomers and 3*R* stereochemistry.[21]

Adduct 4b. To a solution of 105.5 mg (0.357 mmol) of (*S*)-1 in 4 mL of DME at −63 °C was added 0.17 mL (0.36 mmol) of BuLi (2.11 M in hexanes). After 5 min, a solution of 53.9 mg (0.238 mmol) of **3b** in 4.5 mL of DME at −63 °C was added via cannula. The reaction mixture was stirred at −63 °C for 30 min before quenching with a solution of 19.1 mg (0.357 mmol) of NH_4Cl in 10 mL of water. Most of the DME was removed by rotary evaporation, and the remaining mixture was extracted four times with ether. The combined ether extracts were washed with brine and dried over Na_2SO_4. Flash chromatography (10% ether in hexanes) yielded 99.1 mg (80%) of **4b** as a 53:1 mixture of diastereomers (determined by HPLC: Pirkle column, 2% DME in hexanes, 2.0 mL/min, retention times 18.5 and 19.9 min, second peak predominant): IR (film) 3030, 2960, 2915, 2850, 1750, 1500, 1360, 1310, 1120 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 7.71–7.77 (m, 4 H), 7.57–7.60 (m, 2 H), 7.44–7.47 (m, 2 H), 7.15–7.22 (m, 2 H), 6.94–7.00 (m, 2 H), 3.63 (d, J = 12.2 Hz, 2 H), 3.53 (d, J = 12.2 Hz, 2 H), 3.43–3.48 (m, 1 H), 2.23 (dd, J = 7.8, 14.1 Hz, 1 H), 2.45 (dd, J = 6.4, 14.0 Hz, 1 H), 1.42 (s, 9 H), 1.25–1.52 (m, 12 H), 0.90 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (53.6 MHz, C_6D_6) δ 171.8, 135.24, 135.19, 133.5, 131.9, 128.8, 128.7, 128.3, 127.8, 126.1, 125.6, 79.5, 62.9, 52.5, 40.1, 33.0, 32.2, 30.0, 29.7, 28.2, 27.4, 23.1, 14.4. Anal. Calcd for $C_{36}H_{43}NO_2$: C, 82.88; H, 8.31; N, 2.68. Found: C, 83.26; H, 8.20; N, 2.64.

Adduct 4c. To a solution of 163.3 mg (0.554 mmol) of (*S*)-1 in 6.5 mL of DME at −63 °C was added 0.249 mL (0.554 mmol) of BuLi (2.23 M in hexanes). After 5 min, a solution of 83.9 mg (0.371 mmol) of **3c** in 7 mL of DME at −63 °C was added via cannula. The reaction mixture was stirred at −63 °C for 30 min before quenching with a solution of 29.6 mg (0.554 mmol) of NH_4Cl in 12 mL of water. Most of the DME was removed by rotary evaporation, and the remaining mixture was extracted four times with ether. The combined ether extracts were washed with brine and dried over Na_2SO_4. Flash chromatography (10% ether in hexanes) yielded 35.5 mg (39%) of **4c** as an 8:1 mixture of diastereomers (determined by HPLC was described for **4b**, first peak predominant): ^1H NMR (250 MHz, C_6D_6) δ 7.70–7.74 (m, 4 H), 7.58–7.61 (m, 2 H), 7.41–7.44 (m, 2 H), 7.19–7.22 (m, 2 H), 6.95–7.01 (m, 2 H), 3.60 (d, J = 12.2 Hz, 2 H), 3.50 (d, J = 12.2 Hz, 2 H), 3.40–3.56 (m, 1 H), 2.41 (dd, J = 6.1, 14.0 Hz, 1 H), 2.27 (dd, J = 8.0, 14.0 Hz, 1 H), 1.29–1.55 (m, 12 H), 1.37 (s, 9 H), 0.92 (t, J = 6.5 Hz, 3 H); ^{13}C NMR (53.6 MHz, C_6D_6) δ 171.8, 135.2, 133.5, 131.9, 128.9, 128.3, 127.2, 127.1, 126.1, 125.6, 79.5, 62.6, 52.1, 39.4, 33.4, 32.3, 30.0, 29.8, 28.2, 27.2, 23.1, 14.4.

Adduct 4d. To a solution of 97.4 mg (0.330 mmol) of (*S*)-1 in 5 mL of DME at −78 °C was added 0.145 mL (0.331 mmol) of BuLi (2.28 M in hexanes). After 5 min, 40.5 mg (0.220 mmol) of **3d** in 2.5 mL of DME at −63 °C was added via cannula. The reaction mixture was stirred at −63 °C for 30 min before quenching with a solution of 17.6 mg (0.330 mmol) of NH_4Cl in 10 mL of water. Most of the DME was removed by rotary evaporation, and the remaining mixture was extracted four times with ether. The combined ether extracts were washed with brine and dried over Na_2SO_4. Flash chromatography (10% ether in hexanes) yielded 77.8 mg (74%) of **4d** as a 69:1 mixture of diastereomers (determined by HPLC: Pirkle column, 5% DME in hexanes, 1.00 mL/min, retention times 25.72 and 26.92 min, second peak predominant): IR (film) 2965, 2357, 1730, 1378, 1258, 1110 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 7.70–7.76 (m, 4 H), 7.57–7.61 (m, 2 H), 7.41–7.46 (m, 2 H), 7.19–7.23 (m, 2 H), 6.94–7.02 (m, 2 H), 3.59 (d, J = 12.2 Hz, 2 H), 3.51 (d, J = 12.1 Hz, 2 H), 3.45–3.62 (m, 1 H), 2.44 (dd, J = 5.7, 14.0 Hz, 1 H), 2.13 (dd, J = 8.2, 14.0 Hz, 1 H), 1.67–1.80 (m, 1 H), 1.41 (s, 9 H), 1.16–1.54 (m, 2 H), 0.93 (d, J = 6.5 Hz, 3 H), 0.92 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (53.6 MHz, C_6D_6) δ 171.8, 135.2, 133.5, 131.9, 129.0, 128.9, 128.6, 128.4, 127.8, 126.1, 125.6, 79.5, 61.1, 52.5, 42.3, 39.9, 28.2, 25.3, 23.2, 22.6. Anal. Calcd for $C_{33}H_{37}NO_2$: C, 82.63; H, 7.77; N, 2.92. Found: C, 82.47; H, 7.97; N, 2.93. An 81% yield of **4d** was obtained on a 2 mmol scale.

For reference, a mixture of the diastereomers of **4d** was prepared by heating 212.8 mg (0.720 mmol) of (±)-1, 2.80 g (15.2 mmol) of **3d**, and two drops of triethylamine at 140 °C overnight. Excess **3d** was removed under vacuum, and flash chromatography (10% ether in hexanes) yielded 58.6 mg (17%) of **4d** as a 1:1 mixture of diastereomers. ^1H NMR (250 MHz, C_6D_6) corresponding to the minor diastereomer from above: δ 7.69–7.75 (m, 4 H), 7.55–7.61 (m, 2 H), 7.36–7.45 (m, 2 H), 7.15–7.22 (m, 2 H), 6.94–7.01 (m, 2 H), 3.46 (d, J = 12.1 Hz, 2 H), 3.42–3.62 (m, 3 H), 2.37 (dd, J = 5.6, 13.8 Hz, 1 H), 2.19 (dd, J = 8.4, 13.5 Hz, 1 H), 1.71–1.90 (m, 1 H), 1.28–1.60 (m, 2 H), 1.34 (s, 9 H), 0.97 (d, J = 6.5 Hz, 3 H), 0.95 (d, J = 6.7 Hz, 3 H). ^{13}C NMR (53.6 MHz, C_6D_6) of the 1:1 mixture of diastereomers: δ 171.8, 171.7, 135.2, 135.1, 133.5, 131.93, 131.91, 129.0, 128.93, 128.88, 128.7, 128.3, 127.79, 127.76, 127.7, 126.10, 126.07, 125.6, 79.5, 61.1, 60.4, 52.5, 51.9, 42.7, 42.5, 39.9, 28.2, 28.1, 25.3, 25.2, 23.4, 23.2, 22.6.

Adduct 4e. To a solution of 105.1 mg (0.356 mmol) of (*S*)-1 in 4.5 mL of DME at −63 °C was added 0.160 mL (0.356 mmol) of BuLi (2.23 M in hexanes). After 5 min, a solution of 39.9 mg (0.234 mmol) of **3e** in 4.5 mL of DME at −63 °C was added via cannula. The reaction was stirred for 30 min at −63 °C before quenching with a solution of 19.0 mg (0.356 mmol) of NH_4Cl in 10 mL of water. Most of the DME was removed by rotary evaporation, and the remaining mixture was extracted four times with ether. The combined ether extracts were washed with brine and dried over Na_2SO_4. Flash chromatography (10% ether in hexanes) yielded 75.0 mg (69%) of **4e** as a 34:1 mixture of diastereomers (determined by HPLC: Pirkle column, 5% DME in hexanes, 1.00 mL/min, retention times 26.5 and 28.0 min, first peak predominant). Recrystallization from hexanes gave diastereomerically pure **4e**: mp 204–206 °C; IR (film) 3039, 3002, 2965, 2915, 2872, 2791, 1717, 1648, 1592, 1462, 1437, 1363, 1332, 1270, 1176, 1145, 1090, 1021, 822, 747 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 7.71–7.78 (m, 4 H), 7.52–7.63 (m, 4 H), 7.17–7.23 (m, 2 H), 6.96–7.02 (m, 2 H), 3.63 (d, J = 12.2 Hz, 2 H), 3.53 (d, J = 12.2 Hz, 2 H), 3.24 (ddd, J = 3.8, 7.2, 9.5 Hz, 1 H), 2.38 (dd, J = 3.8, 15.8 Hz, 1 H), 2.05 (dd, J = 7.2, 15.8 Hz, 1 H), 1.62–1.73 (m, 1 H), 1.37 (s, 9 H), 1.06 (d, J = 6.6 Hz, 3 H), 0.91 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (53.6 MHz, C_6D_6) δ 172.6, 135.2, 133.5, 132.0, 128.9, 128.6, 128.3, 127.8, 126.1, 125.6, 125.5, 79.5, 69.0, 53.3, 38.2, 33.3, 28.1, 21.3, 20.1. Anal. Calcd for $C_{32}H_{35}NO_2$: C, 82.54; H, 7.58; N, 3.01. Found: C, 82.78; H, 7.84; N, 2.90. X-ray crystallographic analysis indicated 3*S*-stereochemistry.[22]

For reference, a mixture of the diastereomers of **4e** was prepared by heating 196.3 mg (0.665 mmol) of (±)-1, 2.40 g (14.3 mmol) of **3e**, and 2 drops of triethylamine at 140 °C overnight. Excess **3e** was removed under vacuum, and flash chromatography (10% ether in hexanes) yielded 22.9 mg (7.4%) of **4e** as a 1:1 mixture of diastereomers. ^1H NMR (250 MHz, C_6D_6) corresponding to the minor diastereomer from above: δ 7.70–7.78 (m, 4 H), 7.52–7.63 (m, 2 H), 7.38–7.41 (m, 2 H), 7.22–7.30 (m, 2 H), 6.94–7.00 (m, 2 H), 3.59 (d, J = 12.3 Hz, 2 H), 3.52 (d, J = 12.2 Hz, 2 H), 3.10–3.18 (m, 1 H), 2.44 (dd, J = 4.9, 15.2 Hz, 1 H), 2.31 (dd, J = 7.1, 15.2 Hz, 1 H), 1.53–1.72 (m, 1 H), 1.26 (s, 9 H), 1.01 (d, J = 6.6 Hz, 3 H), 0.93 (d, J = 6.8 Hz, 3 H). ^{13}C NMR (53.6 MHz, C_6D_6) of the 1:1 mixture of diastereomers: δ 172.3, 135.21, 135.18, 135.0, 133.52, 133.46, 132.0, 131.9, 129.0, 128.6, 128.3, 128.1, 127.8, 127.3, 127.22, 127.19, 127.0, 126.1, 126.0, 125.5, 79.5, 67.9, 58.5, 53.3, 52.6, 37.5, 32.7, 28.2, 28.1, 28.0, 21.3, 21.2, 19.9.

Adduct 4f. To a solution of 63.8 mg (0.216 mmol) of (*S*)-1 in 2.5 mL of DME at −63 °C was added 97 μL (0.216 mmol) of BuLi

(21) Hawkins, J. M. Ph.D. Thesis, Massachusetts Institute of Technology, 1986.

(22) Crystal structure analyses were performed by Dr. F. J. Hollander at the UC Berkeley X-ray crystallographic facility.

(2.23 M in hexanes). After 5 min, a solution of 41.8 mg (0.146 mmol) of **3f** in 3 mL of DME at −63 °C was added via cannula. The reaction was stirred at −63 °C for 90 min before quenching with a solution of 11.6 mg (0.216 mmol) of NH_4Cl in 10 mL of water. Most of the DME was removed by rotary evaporation, and the remaining mixture was extracted four times with ether. The combined ether extracts were washed with brine and dried over Na_2SO_4. Flash chromatography (20% ether in hexanes) yielded 72.6 mg (86%) of **4f** as a 43:1 mixture of diastereomers (determined by HPLC: Pirkle column, 5% DME in hexanes, 1.00 mL/min, retention times 24.85 and 27.24 min, second peak predominant): IR (film) 2950, 2905, 2840, 1720, 1455, 1360, 1140 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 7.71–7.74 (m, 4 H), 7.56–7.59 (m, 2 H), 7.40–7.43 (m, 2 H), 7.19–7.23 (m, 2 H), 6.94–7.01 (m, 2 H), 3.61–3.74 (m, 3 H), 3.61 (d, J = 12.3 Hz, 2 H), 3.51 (d, J = 12.2 Hz, 2 H), 2.45 (dd, J = 6.4, 13.9 Hz, 1 H), 2.26 (dd, J = 7.9, 13.9 Hz, 1 H), 1.56–1.80 (m, 2 H), 1.42 (s, 9 H), 0.99 (s, 9 H), 0.07 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (53.6 MHz, C_6D_6) δ 171.6, 135.2, 135.0, 133.5, 131.9, 128.9, 128.6, 128.3, 128.1, 126.1, 125.6, 79.5, 60.9, 60.0, 52.5, 39.9, 35.6, 28.2, 26.2, 18.5, −5.10, −5.15. Anal. Calcd for $C_{37}H_{47}NO_3Si$: C, 76.38; H, 8.14; N, 2.41. Found: C, 76.32; H, 8.18; N, 2.41.

A small amount of the minor diastereomer of **4f** was purified by column chromatography of the combined products from several similar reactions: ^1H NMR (250 MHz, C_6D_6) δ 7.69–7.75 (m, 4 H), 7.56–7.60 (m, 2 H), 7.45–7.49 (m, 2 H), 7.19–7.22 (m, 2 H), 6.94–7.01 (m, 2 H), 3.52–3.73 (m, 3 H), 3.60 (d, J = 12.2 Hz, 2 H), 3.48 (d, J = 12.2 Hz, 2 H), 2.39 (dd, J = 6.4, 13.6 Hz, 2 H), 2.28 (dd, J = 8.1, 13.7 Hz, 1 H), 1.56–1.80 (m, 2 H), 1.35 (s, 9 H), 1.05 (s, 9 H), 0.14 (s, 3 H), 0.10 (s, 3 H).

Adduct 4g. To a solution of 209.4 mg (0.709 mmol) of (*R*)-**1** in 8 mL of DME at −63 °C was added 0.35 mL (0.709 mmol) of BuLi (2.01 M in hexanes). After 5 min, a solution of 142.0 mg (0.473 mmol) of (*R*)-**3g** in 8 mL of DME at −63 °C was added via cannula. The reaction mixture was stirred at −63 °C for 4 h before quenching with a solution of 37.9 mg (0.709 mmol) of NH_4Cl in 10 mL of water. Most of the DME was removed by rotary evaporation, and the remaining mixture was extracted four times with ether. The combined ether extracts were washed with brine and dried over Na_2SO_4. Flash chromatography (5–10% ether in hexanes) yielded 185.2 mg (66%) of **4g** as a 150:1 mixture of diastereomers (determined by HPLC: silica column, 2% THF and 0.5% triethylamine in hexanes, 0.400 mL/min, retention times 16.49 and 17.69 min, second peak predominant), white solidified foam: mp 51–62 °C; IR (film) 2975, 2870, 1730, 1475, 1365, 1135 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 7.70–7.78 (m, 4 H), 7.54–7.61 (m, 4 H), 7.16–7.22 (m, 2 H), 6.95–7.01 (m, 2 H), 3.83 (dd, J = 3.7, 9.5 Hz, 1 H), 3.66 (d, J = 12.3 Hz, 2 H), 3.58 (dd, J = 3.1, 9.5 Hz, 1 H), 3.53 (d, J = 12.2 Hz, 2 H), 3.50–3.68 (m, 1 H), 2.37 (dd, J = 3.8, 15.7 Hz, 1 H), 2.10 (dd, J = 7.4, 15.7 Hz, 1 H), 1.80–1.88 (m, 1 H), 1.37 (s, 9 H), 1.06 (d, J = 6.7 Hz, 3 H), 1.00 (s, 9 H), 0.08 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (53.6 MHz, C_6D_6) δ 172.4, 135.2, 135.1, 133.5, 132.0, 128.9, 128.6, 128.5, 128.1, 126.1, 125.6, 79.5, 66.2, 64.5, 53.3, 40.1, 38.0, 28.1, 26.2, 18.6, 14.8, −5.1, −5.2. Anal. Calcd for $C_{38}H_{49}NO_3Si$: C, 76.59; H, 8.29; N, 2.35. Found: C, 76.27; H, 8.54; N, 2.23.

Adduct 4h. To a solution of 274.1 mg (0.930 mmol) of (*S*)-**1** in 10 mL of DME at −63 °C was added 0.46 mL (0.930 mmol) of BuLi (2.01 M in hexanes). After 5 min, a solution of 185.9 mg (0.619 mmol) of (*R*)-**3g** in 10 mL of DME at −63 °C was added via cannula. The reaction mixture was stirred at −63 °C for 4 h before quenching with a solution of 49.7 mg (0.930 mmol) of NH_4Cl in 10 mL of water. Most of the DME was removed by rotary evaporation, and the remaining mixture was extracted four times with ether. The combined ether extracts were washed with brine and dried over Na_2SO_4. Flash chromatography (5–10% ether in hexanes) yielded 154.2 mg (42%) of **4h** as an 8:1 mixture of diastereomers (determined by HPLC: silica column, 2% THF and 0.05% triethylamine in hexanes, 0.400 mL/min, retention times 16.52 and 19.05 min, first peak predominant), white solidified foam: mp 47–54 °C; IR (film) 2970, 2950, 2915, 2850, 1725, 1460, 1365, 1250 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 7.71–7.78 (m, 4 H), 7.59–7.63 (m, 2 H), 7.51–7.54 (m, 2 H), 7.17–7.23 (m 2 H), 7.00–7.02 (m, 2 H), 3.71 (dd, J = 9.8, 5.2 Hz, 1 H), 3.66 (d, J = 12.0 Hz, 2 H), 3.60–3.66 (m, 1 H), 3.55 (dd, J = 12.1 Hz, 2 H), 3.47 (dd, J = 6.4, 9.7 Hz, 1 H), 2.37 (dd, J = 4.8, 15.5 Hz, 1 H), 2.22 (dd, J = 7.3, 15.4 Hz, 1 H), 1.87–1.96 (m, 1 H), 1.35 (s, 9 H), 1.14 (d, J = 6.7 Hz, 3 H), 1.03 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (53.6 MHz, C_6D_6) δ 172.1, 135.2, 133.5, 131.9, 128.9, 128.6, 128.3, 128.2, 127.8, 126.1, 125.6, 79.5, 66.2, 63.8, 53.9, 41.3, 37.7, 28.1, 26.2, 18.6, 15.2, −5.1. Anal. Calcd for $C_{30}H_{49}NO_3Si$: C, 76.59; H, 8.29; N, 2.35. Found: C, 76.45; H, 8.41; N, 2.29.

The minor diastereomer was purified by additional chromatography: ^1H NMR (250 MHz, C_6D_6) δ 7.69–7.75 (m, 4 H), 7.48–7.60 (m, 4 H), 7.18–7.22 (m, 2 H), 6.94–7.00 (m, 2 H), 3.69 (d, J = 12.3 Hz, 2 H), 3.57 (d, J = 11.7 Hz, 2 H), 3.50–3.72 (m, 3 H), 2.48 (dd, J = 5.8, 14.9 Hz, 1 H), 2.35 (dd, J = 7.1, 14.9 Hz, 1 H), 1.28 (s, 9 H), 1.83–1.93 (m, 1 H), 1.05 (s, 9 H), 1.01 (d, J = 6.9 Hz, 3 H), 0.06 (s, 3 H), 0.12 (s, 3 H).

(*R*)-*tert*-Butyl 3-Aminobutanoate, (*R*)-α-Methoxy-α-(trifluoromethyl)phenylacetamide (5a, (*R*)-MTPA-amide). To 815 mg of dry 20% $Pd(OH)_2/C$ stirred in 5 mL of ethanol at 60 °C was added 1.24 g (9.29 mmol) of morpholinium formate. After 30 min, 162.9 mg (0.372 mmol) of **4a** (66:1 mixture of diastereomers) in 10 mL of ethanol was added. The reaction mixture was stirred for 5 h at 60 °C during which time 200 mg (1.50 mmol) of morpholinium formate was added in four portions. The reaction mixture was filtered, the catalyst was washed with ethanol and $CHCl_3$, and the combined filtrates were concentrated by rotary evaporation. The residue was treated with 10% NaOH (aq) and extracted six times with ether. The combined ether extracts were washed with brine, dried over Na_2SO_4, and concentrated to 50 mL. This solution was treated with triethylamine, 4-(dimethylamino)pyridine (DMAP), and 139 μL (0.743 mmol) of (*R*)-MTPA-Cl. After 12 h, the reaction mixture was diluted with ether and washed with 10% HCl (aq), saturated $NaHCO_3$ (aq), and brine and dried over $MgSO_4$. Flash chromatography (10–50% ether in hexanes) yielded 94.7 mg (68%) of **5a** as the (*R*)-MTPA-amide, >95% de (determined by ^1H NMR integration of the diastereotopic methyl resonances at 1.22 and 1.28 ppm using independently prepared (±)-**5a** as a reference): ^1H NMR (250 MHz, $CDCl_3$) δ 7.50–7.56 (m, 2 H), 7.37–7.42 (m, 3 H), 7.33 (br d, J = 8.3 Hz, 1 H), 4.31–4.43 (m, 1 H), 3.42 (q, J = 1.6 Hz, 3 H), 2.48 (dd, J = 15.3, 5.4 Hz, 1 H), 2.47 (dd, J = 15.3, 5.5 Hz, 1 H), 1.45 (s, 9 H), 1.22 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (53.6 MHz, $CDCl_3$) δ 170.4, 165.3, 132.7, 128.0 (q, J_{C-F} = 46.4 Hz), 83.8 (q, J_{C-F} = 26.2 Hz), 81.3, 54.9, 42.3, 41.1, 28.0, 19.6. Anal. Calcd for $C_{18}H_{24}NO_4F_3$: C, 57.59; H, 6.44; N, 3.73. Found: C, 57.40; H, 6.48; N, 3.60.

***tert*-Butyl 3-Aminodecanoate, 1-Naphthamide (5b, 1-Naphthamide).** To 540 mg of dry 20% $Pd(OH)_2/C$ stirred in 5 mL of ethanol at 60 °C was added 690.9 mg (5.19 mmol) of morpholinium formate. After 20 min, 108.3 mg (0.208 mmol) of **4b** (45:1 mixture of diastereomers) in 10 mL of ethanol was added. After 1 h, 0.150 mL (3.98 mmol) of formic acid (97% aq) was added, and the reaction mixture was stired overnight at 60 °C. The reaction mixture was filtered, the catalyst was washed with ethanol and $CHCl_3$, and the combined filtrates were concentrated by rotary evaporation. The residue was treated with 10% NaOH (aq) and extracted six times with ether. The combined ether extracts were washed with brine, dried over Na_2SO_4, and concentrated to 40 mL. This solution was treated with triethylamine, DMAP, and 39 μL (0.260 mmol) of 1-naphthoyl chloride. After 2 h, the reaction mixture was diluted with ether and washed with 10% HCl (aq), saturated $NaHCO_3$ (aq), and brine, and dried over Na_2SO_4. Flash chromatography (10–50% ether in hexanes) yielded 65.7 mg (80%) of **5b** as the 1-naphthamide, 96% ee (determined by HPLC using independently prepared racemate as a reference: Pirkle column,[23] 10% DME in hexanes, 3.0 mL/min, retention times 40.57 and 45.25 min, second peak predominant): $[\alpha]_D$ 49.1° (*c* 6.36, $CHCl_3$); IR (KBr) 3280, 2976, 3012, 2958, 2927, 2856, 1730, 1635, 1537, 1368, 1322, 1255, 1153, 783 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.29 (m, 1 H), 7.80–7.90 (m, 2 H), 7.38 (m, 4 H), 6.60 (br d, J = 9.2 Hz, 1 H), 4.44–4.58 (m, 1 H), 2.64 (dd, J = 5.0, 15.4 Hz, 1 H), 2.52 (dd, J = 5.6, 15.4 Hz, 1 H), 1.59–1.68 (m, 2 H), 1.44 (s, 9 H), 1.26–1.36 (br m, 10 H), 0.88 (t, J = 6.3, 3 H); ^{13}C NMR (53.6 MHz, $CDCl_3$) δ 171.1, 168.7, 134.7, 133.6, 130.4, 130.1, 128.1, 126.9, 126.3, 125.5, 125.4, 124.7, 81.1, 46.7, 39.9, 34.3, 31.7, 29.3, 29.2, 28.1, 26.3, 22.6, 14.1. For the corresponding racemate: Anal.

(23) Pirkle, W. H.; Welch, C. J. *J. Org. Chem.* **1984**, *49*, 138.

Calcd for $C_{25}H_{35}NO_3$: C, 75.53; H, 8.87; N, 3.52. Found: C, 75.58; H, 8.84; N, 3.51.

***tert*-Butyl 5-Methyl-3-aminohexanoate, 1-Naphthamide (5d, 1-Naphthamide).** To 618 mg of dry 20% $Pd(OH)_2/C$ stirred in 5 mL of ethanol at 60 °C was added 910 mg (6.83 mmol) of morpholinium formate. After 20 min, 122.1 mg (0.255 mmol) of **4d** (60:1 mixture of diastereomers) in 7 mL of ethanol was added, and the reaction was stirred at 60 °C for 2.7 h. The reaction mixture was filtered, the catalyst was washed with ethanol and $CHCl_3$, and the combined filtrates were concentrated by rotary evaporation. The residue was treated with 10% NaOH (aq) and extracted six times with ether. The combined ether extracts were washed with brine, dried over Na_2SO_4, and concentrated to 50 mL. This solution was treated with triethylamine, DMAP, and 48 μL (0.319 mmol) of 1-naphthoyl chloride. After 12 h, the reaction mixture was diluted with ether and washed with water, 10% HCl (aq), saturated $NaHCO_3$ (aq), and brine, and dried over Na_2SO_4. Flash chromatography (10–50% ether in hexanes) yielded 90.5 mg (80%) of **5d** as the 1-naphthamide, 97% ee (determined by HPLC using independently prepared racemate as a reference: Pirkle column,[23] 10% DME in hexanes, 2.0 mL/min, retention times 63.5 and 66.9 min, second peak predominant: $[\alpha]_D$ 47.0° (*c* 7.26, $CHCl_3$): IR (KBr) 3267, 3010, 2957, 2918, 2865, 1738, 1638, 1594, 1580, 1542, 1367, 1311, 1292, 1261, 1161, 786 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ 8.29–8.34 (m, 1 H), 7.80–7.88 (m, 2 H), 7.36–7.59 (m, 4 H), 6.60 (br d, *J* = 9.2 Hz, 1 H), 4.53–4.70 (m, 1 H), 2.63 (dd, *J* = 5.2, 15.5 Hz, 1 H), 2.51 (dd, *J* = 5.3, 15.5 Hz, 1 H), 1.46–1.76 (m, 3 H), 1.44 (s, 9 H), 1.03 (d, *J* = 6.4 Hz, 3 H), 0.96 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (53.6 MHz, $CDCl_3$) δ 171.1, 168.6, 134.6, 133.5, 130.3, 130.1, 128.1, 126.9, 126.2, 125.4, 124.6, 81.1, 44.7, 43.3, 40.3, 28.0, 25.2, 22.9, 22.2. Crystals were obtained from ether: mp 83–85 °C. Anal. Calcd for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.41; H, 8.19; N, 3.89.

(*S*)-*tert*-Butyl 4-Methyl-3-aminopentanoate, 1-Naphthamide (5e, 1-Naphthamide). To 609 mg of dry 20% $Pd(OH)_2/C$ stirred in 5 mL of ethanol at 40 °C was added 371 mg (5.89 mmol) of ammonium formate. After 20 min, 109.6 mg (0.235 mmol) of **4e** (recrystallized, single diastereomer) in 15 mL of ethanol was added. Additional ammonium formate, 50 mg (0.79 mmol), was added after 35 and 70 min of stirring at 40 °C. After a total of 90 min, the reaction mixture was filtered, the catalyst was washed with ethanol and $CHCl_3$, and the combined filtrates were concentrated by rotary evaporation. The residue was treated with 2% NaOH (aq) and extracted six times with ether and four times with $CHCl_3$. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated to 50 mL. This solution was treated with triethylamine, DMAP, and 72 μL (0.48 mmol) of 1-naphthoyl chloride. After 12 h, the reaction mixture was diluted with CH_2Cl_2 and washed with 10% HCl (aq), saturated $NaHCO_3$ (aq), and brine. Flash chromatography (10–50% ether in hexanes) yielded 45.8 mg (57%) of **5e** as the 1-naphthamide, >99% ee (determined by HPLC using independently prepared racemate as a reference: Pirkle column,[23] 10% DME in hexanes, 3.0 mL/min, retention times 54.82 and 56.75 min, only second peak observed): mp 117–119 °C, $[\alpha]_D$ 67.1° (*c* 3.95, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.30–8.35 (m, 1 H), 7.81–7.90 (m, 2 H), 7.38–7.62 (m, 4 H), 6.58 (br d, *J* = 9.4 Hz, 1 H), 4.30–4.46 (m, 1 H), 2.62 (dd, *J* = 4.7, 15.3 Hz, 1 H), 2.51 (dd, *J* = 6.7, 15.3 Hz, 1 H), 1.86–2.03 (m, 1 H), 1.44 (s, 9 H), 1.03 (d, *J* = 6.7 Hz, 3 H), 1.02 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (53.6 MHz, $CDCl_3$) δ 171.3, 168.8, 134.8, 133.6, 130.4, 130.1, 128.1, 127.0, 126.3, 125.5, 125.4, 124.6, 81.1, 52.0, 38.1, 31.9, 28.0, 19.4, 19.0. Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.74; H, 7.98; N, 3.98.

(*R*)-*tert*-Butyl 3-Amino-5-(*tert*-butyldimethylsiloxy)-pentanoate (5f): To 420 mg of dry 20% $Pd(OH)_2/C$ stirred in 5 mL of ethanol was added 227.9 mg (3.61 mmol) of ammonium formate. After 15 min at 45 °C, 84.1 mg (0.145 mmol) of **4f** (chromatographed, single diastereomer) in 7 mL of ethanol was added. Additional ammonium formate, 20 mg (0.32 mmol), was added after 60 min of stirring at 45 °C. After a total of 90 min, the reaction mixture was filtered, the catalyst was washed with ethanol and warm $CHCl_3$, and the combined filtrates were concentrated by rotary evaporation. The residue was treated with 2% NaOH (aq) and extracted six times with ether and four times with $CHCl_3$. The combined organic extracts were washed with brine and dried over Na_2SO_4. Flash chromatography (50% ether in hexanes, 10% triethylamine and 45% ether in hexanes) yielded 35.5 mg (81%) of **5f**: $[\alpha]_D$ −3.9° (*c* 3.55, $CHCl_3$); IR (film) 3392, 2959, 2936, 2866, 1733, 1604, 1464, 1400, 1371, 1254, 1155, 1102, 845, 781 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.70 (dt, *J* = 1.7, 6.1 Hz, 2 H), 3.23–3.36 (m, 1 H), 2.37 (dd, *J* = 4.3, 15.5 Hz, 1 H), 2.18 (dd, *J* = 8.7, 15.5 Hz, 1 H), 1.48–1.73 (m, 4 H), 1.42 (s, 9 H), 0.86 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (53.6 MHz, $CDCl_3$) δ 171.8, 80.4, 60.8, 46.4, 44.1, 39.7, 28.1, 25.9, 18.2, −5.4. A portion of this material was distilled (Kugelrohr, 50 °C (0.15 mmHg)). Anal. Calcd for $C_{15}H_{33}NSiO_3$: C, 59.36; H, 10.96; N, 4.61. Found: C, 59.50; H, 10.81; N, 4.47.

The corresponding 1-naphthamide displayed >99% ee (determined by HPLC using independently prepared racemate as a reference: Pirkle column,[23] 10% DME in hexanes, 3.0 mL/min, retention times 39.39 and 42.44 min, only second peak observed).

Treatment of the corresponding CBZ-amide with trifluoroacetic acid for 90 min gave 3-(carbobenzoxyamino)valerolactone in 40% yield, $[\alpha]_D$ 3.49° (*c* 1.70, $CHCl_3$) indicating 3*R* stereochemistry.[24]

(3*R*,4*R*)-*tert*-Butyl 3-Amino-5-(*tert*-butyldimethylsiloxy)-4-methylpentanoate (5g). To 998 mg of dry 20% $Pd(OH)_2/C$ stirred in 10 mL of ethanol at 40 °C was added 386 mg (6.12 mmol) of ammonium formate. After 20 min, 182.3 mg (0.306 mmol) of **4g** (150:1 mixture of diastereomers) in 20 mL of ethanol was added. After 75 min, the reaction mixture was filtered, the catalyst was washed with warm $CHCl_3$, and the combined filtrates were concentrated by rotary evaporation. The residue was treated with 2% NaOH (aq) and extracted four times with ether. The combined ether extracts were washed with brine and dried over Na_2SO_4. Flash chromatography (10–100% ethyl acetate in hexanes) yielded 76.1 mg (78%) of **5g**: IR (film) 3383 (br), 2964, 2933, 2890, 2858, 1732, 1638, 1463, 1395, 1370, 1263, 1151, 1094, 838, 782 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.55 (dd, *J* = 5.4, 10.0 Hz, 1 H), 3.49 (dd, *J* = 5.8, 10.1 Hz, 1 H), 3.13 (ddd, *J* = 9.5, 5.8, 3.6 Hz, 1 H), 2.39 (dd, *J* = 3.3, 15.5 Hz, 1 H), 2.12 (dd, *J* = 9.8, 15.5 Hz, 1 H), 1.51 (br s, 2 H), 1.54–1.64 (m, 1 H), 1.40 (s, 9 H), 0.83 (s, 9 H), 0.83 (d, *J* = 6.9 Hz, 3 H), −0.01 (s, 6 H); ^{13}C NMR (53.6 MHz, $CDCl_3$) δ 172.3, 80.3, 65.6, 50.6, 40.9, 40.7, 28.0, 25.8, 18.1, 13.3, −5.5. Anal. Calcd for $C_{16}H_{35}SiNO_3$: C, 60.52; H, 11.11; N, 4.41. Found: C, 60.26; H, 11.48; N, 4.69.

The corresponding 1-naphthamide displayed a 147:1 mixture of diastereomers according to HPLC: Pirkle column,[23] 10% DME in hexanes, 3.0 mL/min, retention times 30.40 and 31.80 min, first peak predominant. This material was converted to the 1-naphthamide of 3-amino-4-methylvalerolactone by treatment with trifluoroacetic acid (35% yield from **5g**): mp 156–8 °C; $[\alpha]_D$ 1.54 (*c* 1.56, EtOH); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.92–8.02 (m, 1 H), 7.70–7.75 (m, 2 H), 7.31–7.40 (m, 3 H), 7.17–7.23 (m, 1 H), 6.93 (d, *J* = 8.3 Hz, 1 H), 4.35–4.45 (m, 1 H), 4.06 (dd, *J* = 11.6, 4.3 Hz, 1 H), 3.95 (dd, *J* = 11.5, 7.8 Hz, 1 H), 2.60 (dd, *J* = 18.3, 6.7 Hz, 1 H), 2.40 (dd, *J* = 18.3, 6.3 Hz, 1 H), 2.16–2.24 (m, 1 H), 0.85 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (53.6 MHz, $CDCl_3$) δ 169.6, 169.2, 133.6, 133.4, 130.6, 129.8, 128.23, 128.19, 127.0, 126.4, 124.9, 71.3, 45.7, 34.5, 30.9, 11.2. Crystals from toluene/hexanes were determined to have 3*R*,4*R* stereochemistry by X-ray analysis.[22]

(3*S*,4*R*)-*tert*-Butyl 3-Amino-5-(*tert*-butyldimethylsiloxy)-4-methylpentanoate (5h). To 815 mg of dry 20% $Pd(OH)_2/C$ stirred in 10 mL of ethanol at 40 °C was added 316.8 mg (5.02 mmol) of ammonium formate. After 20 min, 149.7 mg (0.251 mmol) of **4h** (8:1 mixture of diastereomers) in 20 mL of ethanol was added. After 25 min, the reaction mixture was filtered, the catalyst was washed with warm $CHCl_3$, and the combined filtrates were concentrated by rotary evaporation. The residue was treated with 2% NaOH (aq) and extracted four times with ether. The combined ether extracts were washed with brine and dried over Na_2SO_4. Flash chromatography (10–100% ethyl acetate in hexanes) yielded 52.8 mg (66%) of **5h**: IR (film) 3395 (br), 2958, 2931, 2890, 2862, 1732, 1609, 1476, 1467, 1394, 1362, 1257, 1152, 1097, 836, 781 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.55 (dd, *J* = 6.4, 10.1 Hz, 1 H), 3.49 (dd, *J* = 5.7, 10.1 Hz, 1 H), 3.21–3.31 (m, 1 H), 2.32 (dd, *J* = 4.3, 15.3 Hz, 1 H), 2.20 (dd, *J* = 9.3, 15.3 Hz, 1 H), 1.54–1.69 (m, 1 H), 1.45 (br s, 2 H), 1.41 (s, 9 H), 0.85 (s,

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9 H), 0.82 (d, J = 6.9 Hz, 3 H), 0.00 (s, 6 H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 172.1, 80.3, 66.1, 49.7, 41.9, 40.1, 28.1, 25.9, 18.2, 11.1, −5.5. Anal. Calcd for $C_{16}H_{35}SiNO_3$: C, 60.52; H, 11.11; N, 4.41. Found: C, 60.70; H, 11.42; N, 4.49.

The corresponding 1-naphthamide displayed in 8:1 mixture of diastereomers according to HPLC: Pirkle column,[23] 10% DME in hexanes, 3.0 mL/min, retention times 30.27 and 31.63 min, second peak predominant).

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Registry No. (±)-1, 102518-95-6; (*S*)-1, 97551-09-2; **2a** (isomer 1), 138877-95-9; **2a** (isomer 2), 138922-40-4; **2b** (isomer 1), 138877-96-0; **2b** (isomer 2), 138922-41-5; **3a**, 79218-15-8; **3b**, 87947-76-0; **3c**, 87947-77-1; **3d**, 138877-97-1; **3e**, 87776-18-9; **3f**, 138877-98-2; **3g**, 138877-99-3; **4a** (isomer 1), 138878-00-9; **4a** (isomer 2), 138922-42-6; (±)-**4a** (isomer 1), 138922-43-7; (±)-**4a** (isomer 2), 138922-44-8; **4b** (isomer 1), 138878-01-0; **4b** (isomer 2), 138922-45-9; **4d** (isomer 1), 138878-02-1; **4d** (isomer 2), 138922-46-0; (±)-**4d** (isomer 1), 138922-47-1; (±)-**4d** (isomer 2), 138922-48-2; **4e** (isomer 1), 138878-03-2; **4e** (isomer 2), 138922-49-3; (±)-**4e** (isomer 1), 138922-50-6; (±)-**4e** (isomer 2), 138922-51-7; **4f** (isomer 1), 138878-04-3; **4f** (isomer 2), 138922-52-8; **4g** (isomer 1), 138878-05-4; **4g** (isomer 2), 138922-53-9; **4h** (isomer 1), 138922-54-0; **4h** (isomer 2), 138922-55-1; **5a** (*R*-MTPA amide), 138878-07-6; **5b** (1-napthamide), 138878-08-7; **5d** (1-naphthamide), 138878-09-8; **5e**, 138878-10-1; **5f**, 138878-11-2; **5g**, 138878-12-3; **5g** 1-naphthamide derivative, 138878-13-4; **5h**, 138878-14-5; **5h** 1-naphthamide derivative, 138878-15-6; octanal, 124-13-0; *tert*-butyl (triphenylphosphoranylidene)acetate, 35000-38-5; 3-(*tert*-butyldimethylsiloxy)-1-propanol, 73842-99-6; (*S*)-methyl 3-hydroxy-2-methylpropanoate, 80657-57-4; (*S*)-methyl 2-methyl-3-(*tert*-butyldimethylsiloxy)propanoate, 93454-85-4; (*R*)-3-(*tert*-butyldimethylsiloxy)-2-methyl-1-propanol, 112057-64-4; (*E*)-methyl 2-decenoate, 7367-85-3; (*E*)-isopropyl 2-decenoate, 138878-06-5; 1-naphthoyl chloride, 879-18-5; 1,3-propanediol, 504-63-2; *tert*-butyldimethylsilyl chloride, 18162-48-6.

Three-Component Cyclocondensations. An Efficient Synthesis of 4-Amino-2-(methylthio)imidazolium Salts via the Reaction of Methyl Chlorothioimidates with Benzaldimines and Isocyanides. Autoxidation of the Imidazole Derivatives

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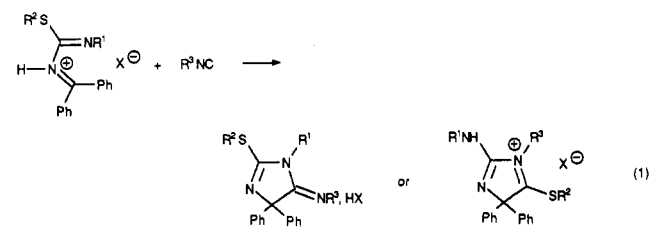
Treatment of imino chlorosulfides **1** with a mixture of benzaldimine and isocyanide provides 4-aminoimidazolium chlorides **5**. Presumably this reaction involves the *N*-imidoylbenzylideniminium chlorides **4** as transient intermediates. 1- and 3-*tert*-Butyl imidazolium salts **5** undergo fast isobutene elimination giving the corresponding imidazole and imidazoline hydrochlorides **10** and **13**. Compounds **13** autoxidize to afford 5-hydroxy derivatives **14** under atmospheric oxygen. The structural assignment of **14** has been confirmed by X-ray diffraction analysis. Under similar conditions, treatment of ketimines **17** with methyl chlorothioimidate **1** and isocyanide gives 2-thioxodiazolidines **19**.

The [1 + 4] cycloaddition of isocyanides to conjugated electron-deficient heterodienes is an effective means to a range of five-membered cyclic systems.[1,2] Also, it has been known for many years that isocyanides react readily with iminium salts.[3-5] To date, however, the use of isocyanides in a ring-closure reaction with N-unsaturated iminium salts has remained limited.[6] The acid-catalyzed conversions of arylidenanilines and *N*-acylimines to 3-aminoindoles[7] and 5-iminooxazolines[8] via [1 + 4] cycloadditions with *tert*-butyl isocyanide have been reported in the literature. Moreover, we have recently disclosed the successful protonation of 2-(alkylthio)- and 2-(arylthio)-1,3-diazabutadienes to give 5-iminoimidazolines or unstable imidazolium salts, upon the addition of isocyanides (eq 1).[9]



(1)

There are several literature reports concerning the participation of unsaturated iminium species as 4π components in hetero-Diels–Alder reactions.[10-13] For example,

(1) See, for instance: Foucaud, A.; Razorilalana-Rabearivony, C.; Loukakou, E.; Person, H. *J. Org. Chem.* **1983**, *48*, 3639. Morel, G.; Marchand, E.; Foucaud, A. *J. Org. Chem.* **1985**, *50*, 771; **1990**, *55*, 1721 and references cited therein.

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