ammonia to evaporate. Once most of the ammonia was gone, wet ether was added followed by saturated NH_4Cl and distilled water to dissolve the salts. Extraction with ether, concentration, and column chromatography (10% EtOAc in hexane) allowed isolation of the desired ketone (95 mg, 95%): IR (CCl_4) 1728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54–7.51 (3 H, m), 7.33 (2 H, br t), 3.97–3.78 (4 H, m), 3.70 (3 H, s), 3.27 (1 H, ABX m, J = 2.98, 8, 11), 2.32–2.00 (4 H, m), 1.81–1.69 (2 H, m), 1.60–1.31 (2 H, m), 1.29–1.16 (2 H, m), 0.96 (1 H, J = 2.98, 14.84, dd), 0.29 (3 H, s), 0.27 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.10 (e), 174.79 (e), 140.00 (e), 133.58 (o), 128.61 (o), 127.58 (o), 107.73 (e), 64.30 (e), 64.24 (e), 51.38 (o), 50.34 (o), 47.51 (e), 47.37 (o), 44.36 (e), 38.38 (e), 37.48 (e), 35.04 (e), 24.23 (e), 12.23 (e), -1.82 (o), -2.15 (o); MS (EI) m/z 416, 401, 339; exact mass for $C_{23}H_{32}O_5Si$ (M) found 416.2017 (calcd 416.2019).

***trans*-1,4,4a,5,6,7,8,8aα-Octahydro-2-(*tert*-butyldimethylsiloxy)-1α-[(dimethylphenylsilyl)methyl]-4aβ-[(methyloxy)carbonyl]-6,6-(ethylenedioxy)naphthalene (16b).** To ketone **15b** (125 mg, 0.29 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added Et_3N (Malinckrodt, 3 mL) followed by dropwise addition of TBDMSOTf. After a total of 40 drops, TLC analysis showed only the desired product. The reaction was quenched with saturated $NaHCO_3$ solution and extracted twice with CH_2Cl_2. Drying with $MgSO_4$, concentration, and column chromatography (5% EtOAc in hexane) yielded the desired silyl enol ether **16b** (144 mg, 90%): IR (CCl_4) 1734, 1714, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (2 H, m), 7.32 (3 H, m), 4.56 (1 H, J = 6.6, bd), 3.88–3.71 (4 H, m), 3.55 (3 H, s), 2.71 (1 H, m), 2.27 (1 H, J = 6.6, br q), 2.18 (1 H, J = 14.17, br dd), 2.45 (2 H, m), 1.83–1.51 (5 H, m), 1.37 (1 H, J = 15.06, 4.8, dd), 1.16 (1 H, J = 4.6, br dd), 1.12 (1 H, m), 1.05 (1 H, overlapping), 0.92 (9 H, s), 0.37 (3 H, s), 0.23 (3 H, s), 0.08 (3 H, s), 0.05 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.26 (e), 154.44 (e), 140.95 (e), 133.48 (o), 128.66 (o), 127.65 (o), 107.93 (e), 99.90 (o), 64.10 (e), 51.20 (o), 45.79 (e), 44.41 (o), 44.01 (e), 39.53 (o), 36.65 (e), 34.70 (e), 25.72 (o), 24.12 (e), 18.01 (e), 16.30 (o), -0.95 (o), -2.39 (o), -4.22 (o), -5.32 (o); MS (EI) m/z 530, 471, 135, 73; exact mass for $C_{29}H_{46}O_5Si_2$ (M) found 530.2867 (calcd 530.2884).

***trans*-1,4,4a,5,6,7,8,8aα-Octahydro-2-(*tert*-butyldimethylsiloxy)-1α-[(dimethylphenylsilyl)methyl]-4aβ-[(methyloxy)methyl]-6,6-(ethylenedioxy)naphthalene (17b).** To silyl enol ether **16b** (20 mg, 37 mmol) in acid-free THF (distilled and stirred with K_2CO_3 over 2 h) at 0 °C was added an excess of LAH and the mixture slowly warmed to room temperature over 8 h. The reaction was then cooled to 0 °C, and Gaubler's salt was added until a white precipitate formed. The solid was filtered and washed with a total of 50 mL of acid-free THF in five portions. Concentration in vacuo allowed the isolation of the desired alcohol. The crude mixture was dissolved in 10 mL of acid-free THF and cooled to 0 °C. Excess NaH (Aldrich) and catalytic amount of KH (Aldrich) were added to the solution. After 10 min, methyl iodide (Malinckrodt, excess) was added and the reaction warmed to room temperature. TLC showed the reaction to be complete after 30 min. After 3 h, the reaction was cooled to 0 °C and quenched with an NH_4Cl saturated solution. The aqueous phase was extracted three times with ether, dried with $MgSO_4$, filtered, and concentrated. Column chromatography (5% EtOAc in hexane) allowed isolation of the desired ether **17b** (9 mg, 47%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.5 (2 H, m), 7.3 (3 H, m), 4.6 (1 H, J = 6.6, bd), 4.0–3.75 (4 H, m), 3.5 (1 H, J = 14, d), 3.25 (3 H, s), 3.2 (1 H, J = 14, d), 2.2–1.0 (remaining protons), 0.95 (9 H, s), 0.37 (3 H, s), 0.23 (3 H, s), 0.08 (3 H, s), 0.05 (3 H, s); MS (EI) m/z 516, 471, 135; exact mass for $C_{29}H_{48}O_4Si_2$ (M) found 516.3094 (calcd 516.3091).

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Supplementary Material Available: ^1H and ^{13}C NMR of all compounds described in the Experimental Section as well as COSY and HETCOR for **15b** and **16b** (19 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

An Improved Method for the Synthesis of Enantiomerically Pure Amino Acid Ester Isocyanates

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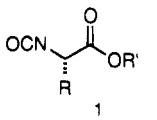
The isocyanate derivatives of amino acid esters (**1**) are useful as precursors to peptides[1] and azapeptides[2] and as synthetic building blocks.[3] These compounds are also



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potentially useful as chiral derivatizing agents[4] and for the preparation of chiral chromatographic media.[5] The most widely used preparation of amino acid ester isocyanates involves the continuous addition of a stream of gaseous phosgene to a refluxing suspension of the amino acid ester hydrochloride in toluene over a period of several hours.[1a,6] The hazards of handling gaseous phosgene, the high temperatures required to drive off the hydrogen chloride byproduct of the reaction, and the harshly acidic reaction conditions detract substantially from this procedure. Alternative procedures for the conversion of amino acid esters to isocyanates require multiple steps, elevated temperatures, or reagents that are expensive or not commercially available.[7,8]

In the course of preparing urea derivatives of amino acids, we required a convenient preparation of amino acid ester isocyanates.[9] We reasoned that elevated temperatures and the continuous addition of gaseous phosgene could be avoided by adding a base to remove hydrogen chloride. We have found that it is possible to generate amino acid ester isocyanates by addition of a commercially available solution of phosgene in toluene[10] to a mixture of an amino acid ester hydrochloride and pyridine (eq 1). The

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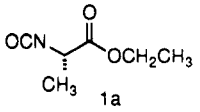
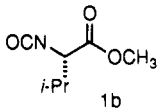
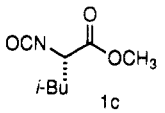
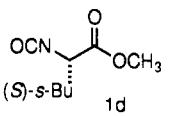
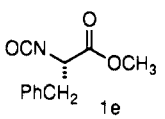
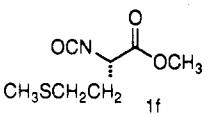
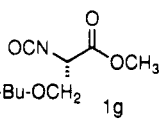
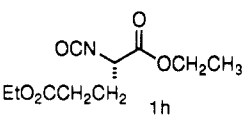
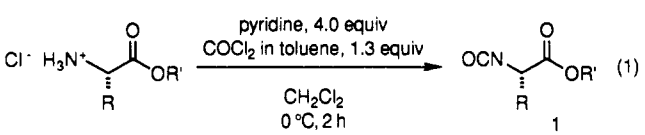
0022-3263/92/1957-7364$03.00/0

Table I. Preparation of Amino Acid Ester Isocyanates

amino acid ester hydrochloride	amino acid ester isocyanate	yield, %[a]
L-alanine ethyl ester hydrochloride	 1a	72
L-valine methyl ester hydrochloride	 1b	87
L-leucine methyl ester hydrochloride	 1c	93
L-isoleucine methyl ester hydrochloride	 1d	90
L-phenylalanine methyl ester hydrochloride	 1e	94
L-methionine methyl ester hydrochloride	 1f	95
L-serine *t*-butyl ether methyl ester hydrochloride	 1g	92
L-glutamic acid diethyl ester hydrochloride	 1h	94

[a] Isolated yields of products purified by kugelrohr distillation.

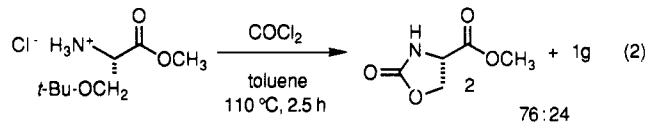
solution of phosgene is easily dispensed by syringe and is less hazardous to handle than the gaseous material. The isocyanates **1** are isolated by rapid aqueous workup at 0 °C to avoid hydrolysis and are formed without significant impurities. Kugelrohr distillation affords analytically pure isocyanates **1** in excellent yields (Table I).



(1)

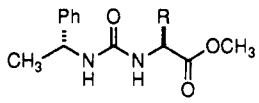
This method for the preparation of isocyanates from amino acid hydrochlorides is compatible with suitably protected functionality in the amino acid side chains. Thus, methionine methyl ester, serine *tert*-butyl ether methyl ester, and glutamic acid diethyl ester are converted to the respective isocyanates (**1f–h**) in high yields.

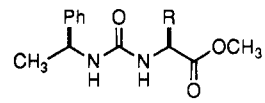
The mild reaction conditions of this procedure allow the preparation of derivatives containing acid-sensitive functionality. For example, serine *tert*-butyl ether methyl ester hydrochloride affords isocyanate **1g** in 92% yield. In contrast, continuous addition of a stream of gaseous phosgene to a refluxing suspension of the amino acid ester hydrochloride in toluene[1a,6] generates a 76:24 mixture of oxazolidinone **2**[11] and the desired isocyanate **1g** (eq 2). Presumably, the hydrogen chloride byproduct of the reaction cleaves the *tert*-butyl ether protective group, thus liberating the hydroxy group and permitting cyclization.



(2)

Isocyanates **1b–g** were determined to be enantiomerically pure (>99% ee) by ^{1}H NMR analysis of the urea adducts **3** with 1-phenylethylamine. Ureas **3a** were prepared by reaction of **1** with (*R*)-1-phenylethylamine. Equimolar mixtures of diastereomers **3a** and **3b** were produced by reaction of **1** with racemic 1-phenylethylamine.[12] The methyl ester resonances of **3a** and **3b** are separated by 0.02–0.03 ppm in the ^{1}H NMR spectra in $CDCl_3$ solution.[13,14] Rigorous 500-MHz ^{1}H NMR analysis of the methyl ester resonances of the (*R*)-1-phenylethylamine adducts **3a** revealed none (<0.5%) of the **3b** diastereomer.[15] On the basis of these observations, we conclude that the isocyanates are formed without racemization.


3a


3b

In summary, the procedure described herein represents an improved method for the preparation of enantiomerically pure amino acid ester isocyanates that avoids the use of gaseous phosgene, elevated temperatures, and strongly acidic conditions. We anticipate that this procedure will have broad utility.

Experimental Section

General. Amino acid ester hydrochlorides were purchased from Aldrich or Bachem and were used without further purification. A 1.93 M solution of phosgene in toluene was obtained from Fluka. Racemic and (*R*)-1-phenylethylamine (*ChiraSelect* grade) were purchased from Fluka and used without further purification. Methylene chloride and pyridine were distilled from calcium hydride. All reactions were performed in flame- or oven-dried glassware under a positive pressure of nitrogen. Reaction product solutions were concentrated using a Büchi rotary evaporator at ca. 10 mmHg.

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(12) Ureas **3** were prepared as follows: A mixture of 1.0 mmol of isocyanate **1** and 1.2 mmol of 1-phenylethylamine in 5 mL of dry CH_2Cl_2 was stirred at room temperature for 18–24 h. The reaction mixture was then extracted with two 10-mL portions of 1 M aqueous HCl and 10 mL of saturated aqueous NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford urea **3**, which was used without further purification.

(13) Substantially greater separations of some of the other resonances occur in the ^{1}H NMR spectra of ureas **3**. For example, valine isocyanate **1b** generates diastereomeric ureas **3** (R = *i*-Pr) in which the methyl resonances of the isopropyl groups appear at 0.66 and 0.77 ppm in diastereomer **3a** and at 0.81 and 0.90 ppm in diastereomer **3b** in 50 mM $CDCl_3$ solution.

(14) In ureas **3** derived from isocyanates **1b–g**, the methyl ester resonances of **3a** consistently appear downfield of those of **3b** in 50 mM $CDCl_3$ solution.

(15) To confirm this level of detection, 1% of an equimolar mixture of **3a** and **3b** was added to each sample of **3a**. In each case, the methyl ester resonance of **3b** could be observed by ^{1}H NMR in the doped sample of **3a**. The methyl ester resonance of **3b** could not be observed in the undoped sample of **3a**.

General Procedure for the Preparation of Amino Acid Ester Isocyanates 1 from Amino Acid Ester Hydrochlorides. A 250-mL, three-necked, round-bottomed flask, fitted with two rubber septa, a nitrogen inlet adapter, and a magnetic stirring bar, was charged with 0.0300 mol of amino acid ester hydrochloride, 100 mL of CH_2Cl_2, and 9.8 mL (0.121 mol) of pyridine. The resulting suspension or solution was cooled in an ice bath for 15 min. A solution of phosgene (1.93 M in toluene, 20.0 mL, 0.0386 mol) [CAUTION: USE HOOD] was added by syringe over 20–30 s, and the resulting light yellow solution was stirred at 0 °C for 2 h. The reaction mixture was extracted two times with 300 mL of cold 0.5 M aqueous HCl and ca. 200 mL of crushed ice. Each aqueous layer was re-extracted with 100 mL of CH_2Cl_2. The combined organic phases were extracted with a mixture of 300 mL of cold saturated aqueous NaCl solution and ca. 200 mL of crused ice, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to afford the crude isocyanate as a light brown oil. (During workup, the isocyanate is only exposed to water for a total of 5–10 min.) The product was purified by Kugelrohr distillation under reduced pressure.

Ethyl (*S*)-2-Isocyanatopropanoate (1a). Reaction of 4.61 g (0.0300 mol) of L-alanine methyl ester hydrochloride followed by Kugelrohr distillation (25 °C, 0.2 mmHg) yielded 3.10 g (72%) of **1a** as a colorless liquid: $[\alpha]^{22}_D$ −24.1° (neat); IR (film) 2270, 2243, 1743, 1215 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (q, *J* = 7.1 Hz, 2 H), 4.07 (q, *J* = 7.1 Hz, 1 H), 1.50 (d, *J* = 7.1 Hz, 3 H), 1.32 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 126.7, 62.4, 52.8, 20.3, 14.1. Anal. Calcd for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.08; H, 6.36; N, 9.69.

Methyl (*S*)-2-Isocyanato-3-methylbutanoate (1b). Reaction of 5.20 g (0.0310 mol) of L-valine methyl ester hydrochloride followed by Kugelrohr distillation (75 °C, 0.04 mmHg) yielded 4.22 g (87%) of **1b** as a colorless liquid: $[\alpha]^{19}_D$ −21.1° (neat); IR (film) 2258, 1743, 1219 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (d, *J* = 3.7 Hz, 1 H), 3.82 (s, 3 H), 2.27–2.22 (m, 1 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 126.9, 63.2, 52.9, 31.8, 19.6, 16.5. Anal. Calcd for $C_7H_{10}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.38; H, 7.14, N, 8.79.

Methyl (*S*)-2-Isocyanato-4-methylpentanoate (1c). Reaction of 5.31 g (0.0293 mol) of L-leucine methyl ester hydrochloride followed by Kugelrohr distillation (90 °C, 0.06 mmHg) yielded 4.65 g (93%) of **1c** as a colorless liquid: $[\alpha]^{21}_D$ −36.1° (neat); IR (film) 2260, 1745, 1213 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (dd, *J* = 8.8, 5.6 Hz, 1 H), 3.81 (s, 3 H), 1.90–1.78 (m, 1 H), 1.68–1.60 (m, 2 H), 0.94 (t, *J* = 6.6 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 126.3, 55.8, 53.0, 42.7, 24.9, 22.8, 21.0. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.23; H, 7.64; N, 8.19.

Methyl (2*S*,3*S*)-2-Isocyanato-3-methylpentanoate (1d). Reaction of 5.28 g (0.0291 mol) of L-isoleucine methyl ester hydrochloride followed by Kugelrohr distillation (85 °C, 3.3 mmHg) yielded 4.48 g (90%) of **1d** as a colorless liquid: $[\alpha]^{19}_D$ −4.3° (neat); IR (film) 2266, 1745, 1217, cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (d, *J* = 3.9 Hz, 1 H), 3.81 (s, 3 H), 2.02–1.92 (m, 1 H), 1.42–1.22 (m, 2 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 0.90 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 126.7, 62.7, 52.9, 38.4, 24.2, 16.3, 11.4. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.24; H, 7.69; N, 8.25.

Methyl (*S*)-2-Isocyanato-3-phenylpropanoate (1e). Reaction of 6.47 g (0.0300 mol) of L-phenylalanine methyl ester hydrochloride followed by Kugelrohr distillation (130 °C, 0.1 mmHg) yielded 5.76 g (94%) of **1e** as a colorless oil, which crystallized upon refrigeration: $[\alpha]^{21}_D$ +71.9° (neat); IR (film) 2258, 1745, 1221 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.23 (m, 3 H), 7.20–7.17 (m, 2 H), 4.26 (dd, *J* = 7.7, 4.6 Hz, 1 H), 3.79 (s, 3 H), 3.15 (dd, ABX pattern, *J* = 13.8, 4.6 Hz, 1 H), 3.01 (dd, ABX pattern, *J* = 13.8, 7.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 135.5, 129.2, 128.6, 127.4, 126.8, 58.5, 53.1, 39.9. Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.11; H, 5.28; N, 6.85.

Methyl (*S*)-2-Isocyanato-4-(methylthio)butanoate (1f). Reaction of 5.99 g (0.0300 mol) of L-methionine methyl ester hydrochloride followed by Kugelrohr distillation (145 °C, 0.8 mmHg) yielded 5.42 g (95%) of **1f** as a colorless liquid: $[\alpha]^{21}_D$ −52.5° (neat); IR (film) 2252, 1745, 1223 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (dd, *J* = 8.6, 4.2 Hz, 1 H), 3.83 (s, 3 H), 2.65–2.57 (m, 2 H), 2.18–1.94 (m, 2 H), 2.11 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 126.8, 55.9, 53.3, 32.8, 30.0, 15.3. Anal. Calcd for $C_7H_{11}NO_3S$: C, 44.43; H, 5.86; N, 7.40. Found: C, 44.42; H, 5.88; N, 7.33.

Methyl (*S*)-2-Isocyanato-3-(1,1-dimethylethoxy)-propanoate (1g). Reaction of 6.35 g (0.0300 mol) of *O*-*tert*-butyl-L-serine methyl ester hydrochloride followed by Kugelrohr distillation (70 °C, 0.15 mmHg) yielded 5.58 g (92%) of **1g** as a colorless liquid: $[\alpha]^{22}_D$ +17.0° (neat); IR (film) 2238, 1753, 1214 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (appar t, *J* = 4.2 Hz, 1 H), 3.81 (s, 3 H), 3.71 (dd, ABX pattern, *J* = 9.3, 4.6 Hz, 1 H), 3.67 (dd, ABX pattern, *J* = 9.0, 3.5 Hz, 1 H), 1.20 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 129.2, 73.9, 62.8, 58.1, 52.9, 27.2. Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.61; H, 7.65; N, 6.96.

Diethyl (*S*)-2-Isocyanatopentanedioate (1h). Reaction of 7.19 g (0.0300 mol) of L-glutamic acid diethyl ester hydrochloride followed by Kugelrohr distillation (108 °C, 0.15 mmHg) yielded 6.46 g (94%) of **1h** as a colorless liquid: $[\alpha]^{23}_D$ −43.9 (neat); IR (film) 2252, 1740, 1213 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (q, *J* = 7.1 Hz, 2 H), 4.19–4.11 (m, 3 H), 2.49–2.43 (m, 2 H), 2.29–2.18 (m, 1 H), 2.07–1.97 (m, 1 H), 1.33 (t, *J* = 7.1 Hz, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 170.8, 127.0, 62.6, 60.6, 56.5, 30.0, 28.8, 14.0. Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.51; H, 6.67; N, 6.15.

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Transmetalation of Disubstituted Alkenyl Groups from Zirconium to Boron Compounds

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The hydrozirconation reaction, developed by Schwartz and co-workers,[1,2] has been used for the preparation of organozirconium compounds. A major drawback of these types of organozirconiums is their inability to undergo general carbon–carbon bond forming reactions. To overcome this limitation, transmetalation of organic groups from zirconium to other metals, which have an established ability to form carbon–carbon bonds, was explored.[3,4]

One of the most widely studied and versatile class of intermediates known to the organic chemist is the organoboranes.[5,6] Although many structurally different types of organoboranes can easily be prepared, there are some limitations to the types of groups that can be placed on boron. By combining the versatility of organoboranes with the unique reactivity and selectivity of the hydro-

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