(±)-44, 102616-22-8; (±)-45, 102616-23-9; (±)-46, 102616-24-0; (±)-47, 109088-00-8; (±)-48, 109088-01-9; (±)-48 (ditosylate), 109088-02-0; (±)-49, 109088-03-1; (±)-pent-3-en-2-ol, 42569-16-4; [4-methoxyphenoxy]acetyl chloride, 42082-29-1; methoxyacetyl chloride, 38870-89-2; benzyloxyacetyl chloride, 19810-31-2; (±)-(Z)-pent-3-en-2-ol, 60102-80-9; (E)-cinnamyl alcohol, 4407-36-7; (Z)-cinnamyl alcohol, 4510-34-3; (E)-3-(1,3-benzodioxol-5-yl)-prop-2-en-1-ol, 58095-76-4; (Z)-3-(1,3-benzodioxol-5-yl)prop-2-en-1-ol, 90359-53-8; (±)-(E)-1-methyl-3-phenylprop-2-en-1-ol, 84519-62-0; (±)-(E)-2-methylhept-5-en-4-ol, 109214-86-0; (±)-(Z)-2-methylhept-5-en-4-ol, 64727-70-4; (±)-(Z)-dec-2-en-4-ol, 109087-97-0; (E)-1-bromopropene, 590-15-8.

Copper(I)-Activated Addition of Grignard Reagents to Nitriles. Synthesis of Ketimines, Ketones, and Amines[1]

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The nucleophilic addition of Grignard reagents to nitriles, especially when using sterically demanding components, is effectively catalyzed by copper(I) salts. Alkyl and aromatic nitriles and a selection of Grignard reagents were employed to prepare sterically hindered ketimines after addition, ketones after a tandem addition–hydrolysis procedure, and branched primary amines after a tandem addition–reduction sequence.

Recently we described a convenient synthesis of branched primary amines using a tandem addition–reduction procedure.[3] Lithium–ammonia reduction was used in situ to reduce ketimines, prepared by addition of Grignard reagents to nitriles. In that study we noted—to our chagrin—that the addition of Grignard reagents to nitriles can be slow and even useless, particularly when the components are sterically hindered. Although the addition of Grignard reagents to nitriles has been known for a long time,[4] synthetically useful preparations using bulky reactants usually required harsh conditions such as refluxing in high boiling solvents (toluene,[5] isoamyl ether,[6] etc.) for extended periods or required large excesses of the Grignard reagent.[5a,b,d]

Early in the tandem addition–reduction study,[3] we realized that the addition of certain Grignard reagents to certain nitriles was slow and varied drastically with the reacting species. Consequently, it was essential to monitor (GLC) the addition step for completeness before proceeding with the reduction sequence.[7] One of the first problems arose with the attempted addition of bulky *tert*-butylmagnesium chloride to benzonitrile. After 1 h in refluxing THF, no ketimine product **1a** could be detected, and after 14 h only 8% was present (see Table I).

Table I. Ketimine 1a from *tert*-Butylmagnesium Chloride and Benzonitrile

	yield,[b] %	
reactn time,[a] h	no CuBr	cat. CuBr[c]
1	0	83
2	1	92
3	2	96
14	8	99

[a] Reaction time in refluxing THF using a 1:1.1 mol ratio of nitrile to Grignard reagent. [b] Percent formation of **1a** relative to unreacted benzonitrile was determined by GLC. [c] Two mole percent of cuprous bromide was immediately added after mixing the reactants, and then the mixture was quickly heated to reflux.

Obviously an activator was required if this nucleophilic addition was to be a synthetically useful reaction.[8] Since copper(I) in catalytic amounts is a known activator of certain Grignard reactions[9]—first noted by Kharasch and Tawney in the cuprous ion catalyzed conjugate addition of organomagnesium compounds to enones[10]—the above reaction was repeated with 2 mol % of CuBr. After only 1 h an 83% yield (GLC) of ketimine **1a** was realized, and the addition was essentially complete after 3–4 h in refluxing THF (see Table I). Clearly copper(I) had a dramatic activating effect.

This reaction between *tert*-butylmagnesium chloride and benzonitrile is now synthetically viable. For example, if the copper-activated addition reaction was worked up after

(1) (a) Initially disclosed at the 192nd National Meeting of the American Chemical Society, Anaheim, CA, Sept 7–12, 1986; Orgn 220. (b) Taken from the Ph.D. Thesis of F. J. W., Rutgers University, January 1987. H. Martin Friedman Thesis Award and Rutgers University Graduate Student Government Award for Excellence in Research, May 1987. (c) Tandem Alkylation–Reduction. 18. Part 17: Farahat, S. E.; Hall, S. S. *J. Heterocycl. Chem.*, in press.

(2) Hoechst-Roussel Pharmaceuticals Inc.

(3) Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1986**, *51*, 5338–5341.

(4) (a) Blaise, E. E. *C. R. Hebd Seances Akad. Sci* **1901**, *132*, 38. (b) Moureu, C.; Mignonac, G. *Ibid.* **1913**, *156*, 1801–1806. (c) Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Non-Metallic Substances*; Prentice-Hall: New York, 1954; pp 767–845.

(5) (a) Willemart, A. *Bull. Soc. Chim. Fr.* **1935**, *2*, 867–882. (b) Lochte, H. L.; Horeczy, J.; Pickard, P. L.; Barton, A. D. *J. Am. Chem. Soc.* **1948**, *70*, 2012–2015. (c) Pickard, P. L.; Vaughan, D. J. *Ibid.* **1950**, *72*, 876–878. (d) Pickard, P. L.; Engles, E. F. *Ibid.* **1952**, *74*, 4607–4608.

(6) Mosher, H. S.; Mooney, W. T. *J. Am. Chem. Soc.* **1951**, *73*, 3948–3949.

(7) Aliquots were injected into water and diluted with Et_2O, and the organic phase was immediately analyzed by GLC.

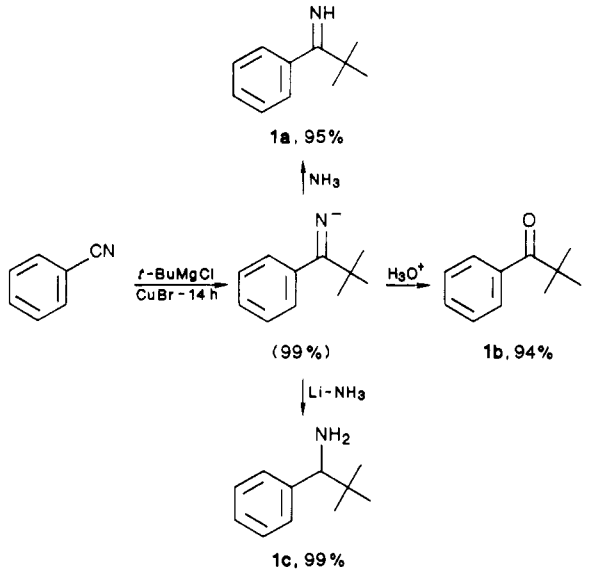
(8) Complexation of the Grignard reagent with $LiClO_4$ prior to the introduction of the nitrile has a modest activating effect on the reaction. Chastrette, M.; Amouroux, R.; Subit, M. *J. Organomet. Chem.* **1975**, *99*, C41–C43.

(9) (a) Erdik, E. *Tetrahedron* **1984**, *40*, 641–657. (b) Normant, J. F. *Pure Appl. Chem.* **1978**, *50*, 709–715. (c) Posner, G. H. *Org. React. (N.Y.)* **1972**, *19*, 1–113. (d) Felkin, H.; Swierczewski, G. *Tetrahedron* **1975**, *31*, 2735–2748. (e) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980; pp 1–9. (f) Normant, J. F. *Synthesis* **1972**, 63–80.

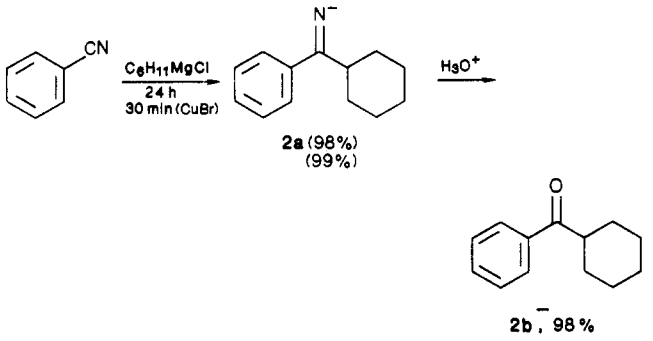
(10) Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308–2315.

0022-3263/87/1952-3901$01.50/0

14 h by the introduction of anhydrous liquid ammonia, using a modified procedure of Pickard and Vaughan,[5c] ketimine **1a** could be isolated (95%). Alternatively, hydrolysis of the ketimine intermediate in a tandem addition–hydrolysis procedure afforded ketone **1b** (94%), and reduction of the ketimine intermediate in a tandem addition–reduction sequence with lithium–ammonia yielded branched primary amine **1c** (99%).[3]



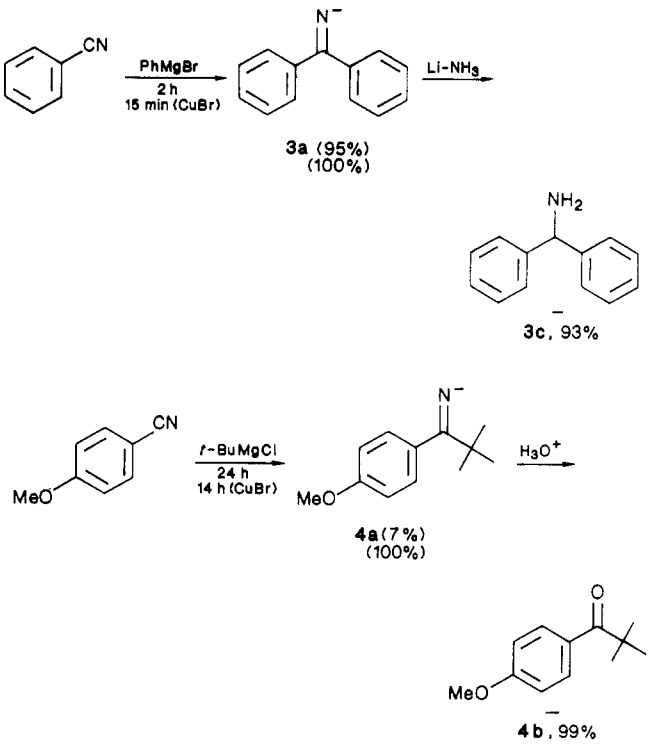
Reaction of bulky cyclohexylmagnesium chloride with benzonitrile was also sluggish and generated the ketimine **2a** in 98% yield (GLC) after 24 h in refluxing THF. However, the reaction was complete (99%) after only 30 min when a catalytic amount of cuprous bromide was interjected. Hydrolytic workup using the tandem addition–hydrolysis protocol afforded cyclohexyl phenyl ketone (**2b**, 98%).



The catalytic process was useful even for more reactive Grignard reagents such as phenylmagnesium bromide. For example, although a 95% yield (GLC) of ketimine **3a**, obtained from phenylmagnesium bromide and benzonitrile, was realized after 2 h in refluxing THF,[11] the addition was complete (100%) in less than 15 min when a catalytic amount of cuprous bromide was present. In this case, subsequent reduction in the tandem addition–reduction sequence afforded diphenylmethylamine (**3c**, 93%).

The reaction of *tert*-butylmagnesium chloride with 4-methoxybenzonitrile was very slow, generating only a 7% yield (GLC) of ketimine **4a** after 24 h in refluxing THF. With a catalytic amount of CuBr the reaction was complete (100%) in 14 h and after tandem hydrolysis a 99% isolated yield of ketone **4b** was achieved.

(11) At 25 °C, an 86% yield of ketimine **3a** was present after 24 h, while with catalytic amounts of CuBr the addition was complete in less than 14 h.



There was no significant difference in the rate of ketimine formation in the copper(I)-catalyzed reaction between *tert*-butylmagnesium chloride and either 4-methoxy- or 2-methoxybenzonitrile in refluxing THF. The percent of ketimine formation after 0.5, 1.0, 1.5, and 2 h was 72%, 82%, 89%, and 92%, respectively, for 4-methoxybenzonitrile, and 70%, 78%, 83%, and 86%, respectively, for 2-methoxybenzonitrile. This comparison suggests that the ortho methoxy group neither directs the Grignard reagent through chelation nor sterically hinders the addition process.

After 23 h in refluxing THF, the reaction between isopropylmagnesium chloride and 2-methoxybenzonitrile was only 76% complete, compared to 97% completion after only 15 min with trace amounts of CuBr. Subsequent workup with ammonia secured ketimine **5a** (92%), tandem hydrolysis of the ketimine intermediate afforded ketone **5b** (98%), and tandem reduction yielded branched primary amine **5c** (89%).

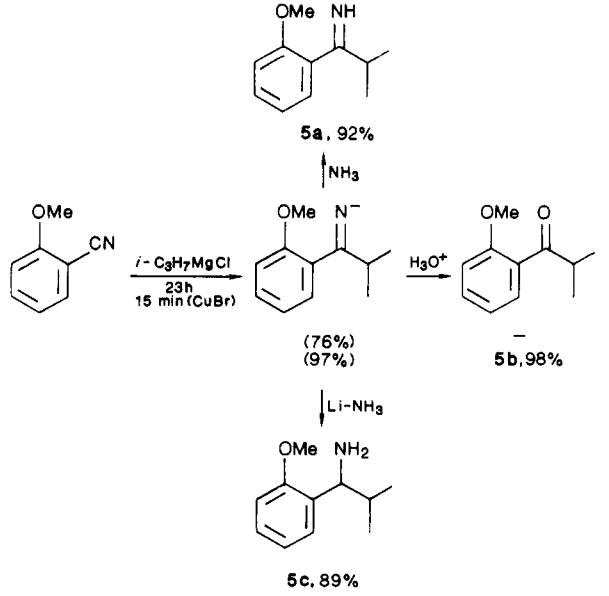
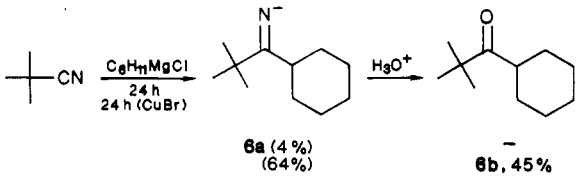


Table II. Copper(I) Salt and Salt Concentration Effects on *tert*-Butylmagnesium Chloride Addition to 4-Methoxybenzonitrile

	yield, %, at reaction time, h					
copper salt (mol %)	0.5	1.0	1.5	2.0	14	24[a]
none	0	0				7[b]
CuBr (2)[c]	72	82	89	92	100	
CuCl (2)[c]	67	77	85	87	100	
CuI (2)[c]	75	86	90	91		
CuCN (2)[c,d]	69	85	90	93	99	99
CuBr·Me_2S (2)[c]	69	81	88	91		
CuBr (50)[e]	4	7	9	11	27	31
CuBr (100)[e]	0	0	0	0	0	0

[a] Reaction time in refluxing THF using a 1:1.1 mol ratio of nitrile to Grignard reagent. [b] Percent formation of ketimine **4a** relative to unreacted nitrile was determined by GLC. [c] The copper(I) salt was immediately added after mixing the reactants and then the mixture was quickly heated to reflux. [d] See footnote 13. [e] The copper salt and Grignard reagent were vigorously premixed for 1 h at ambient temperature before the nitrile was introduced and then the mixture was quickly heated to reflux.

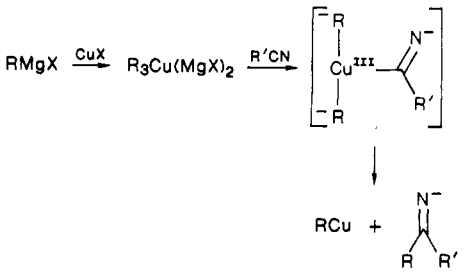
Grignard and nitrile additions that were previously useless become viable in the presence of small amounts of CuBr.[12] For example, with the two very bulky reactants, cyclohexylmagnesium chloride and trimethylacetonitrile, only 4% of the corresponding ketimine was detected (GLC) after 24 h in refluxing THF. In contrast, a 64% conversion to ketimine **6a** had occurred after 24 h in the copper-activated reaction, and a 45% isolated yield of *tert*-butyl cyclohexyl ketone (**6b**) was realized after subsequent tandem hydrolysis.



The copper(I) salt used as the catalyst in these reactions apparently is not critical. For example, in the copper-activated addition of *tert*-butylmagnesium chloride and 4-methoxybenzonitrile to generate ketimine **4a**, various copper salts, which included CuBr, CuCl, CuI, CuCN,[13] and CuBr·Me_2S, were evaluated in catalytic quantities (Table II, entries 2–6). All gave similar results when monitored (ketimine, GLC) over the first 2 h of the reaction. In all of the reactions using catalytic amounts of a copper(I) salt, the Grignard reagent was added to the nitrile in THF at ambient temperature, trace amounts of the copper salt were added, and then the mixture was quickly heated to reflux.

The last two entries in Table II display the results obtained when 0.5 and 1.0 equiv of CuBr were added at ambient temperature to a solution of the Grignard reagent before the nitrile was introduced. These are conditions that favor the formation of homocuprate, *t*-Bu_2CuMgX, and stoichiometric organocopper, *t*-BuCu, respectively,[9b,e] Both reagents are known to be relatively unreactive species, especially with nitriles.[9b,14] After stirring the Grignard reagent and CuBr mixture for 1 h, the nitrile was added and the mixture quickly heated to reflux. The homocuprate conditions (entry 7) produced only 11% of ketimine **4a** after 2 h, and even after 24 h only 31%, while the organocopper conditions (entry 8) afforded no detectable ketimine (GLC), even over the extended time period. It is reasonable to conclude that neither homocuprate nor organocopper is the reactive species in these copper(I)-catalyzed reactions.

Since higher order cuprates[9b,e,15] are suspected of being formed when catalytic amounts of copper(I) salts are added to Grignard reagents, we suggest that a higher order cuprate is generated catalytically and adds to the nitriles in this study. A possible pathway is illustrated where the higher order cuprate reacts with the nitrile by an oxidative addition,[16] followed by an unsymmetrical reductive elimination to generate the product ketimine salt and organocopper. In the presence of excess Grignard reagent, the organocopper recycles to generate more of the reactive higher order cuprate. Similar mechanisms for other copper(I)-activated Grignard reactions have been proposed.[9e,16]



This study demonstrates copper(I)-activated addition of Grignards reagents to nitriles. When the addition reaction is worked up by anhydrous protonation, or coupled with tandem hydrolysis or tandem reduction, the methodology provides efficient synthetic entries to hindered ketimines, hindered ketones, and branched primary amines.

Experimental Section[17]

The apparatus and general experimental procedure previously described for tandem addition–reduction of nitriles to afford branched primary amines was used here for both the synthesis of the ketimines and the amines.[3] For the preparation of the ketones, a Liebig condenser was used rather than a Dewar condenser. Cuprous bromide, cuprous chloride, cuprous iodide, cuprous cyanide, cuprous bromide–dimethyl sulfide complex, and cyclohexylmagnesium chloride (2 M, Et_2O) were from Aldrich Chemical Co. The source of the other fine chemicals and reagents, the analytical and purification techniques used, as well as the preparations of α-*tert*-butylbenzylamine (**1c**), 1,1-diphenylmethylamine (**3c**), and α-isopropyl-*o*-methoxybenzylamine (**5c**) using these techniques, have been described.[3]

α-(1,1-Dimethylethyl)benzenemethanimine (1a). To a stirred solution of 2.00 g (19.4 mmol) of benzonitrile and 10.7 mL (21.4 mmol, 2 M in THF) of *tert*-butylmagnesium chloride in 40 mL of THF was added 50 mg (0.34 mmol) of CuBr, and the mixture was refluxed (under nitrogen) for 14 h. After cooling (0–5

(12) The CuBr-catalyzed reaction between *tert*-butylmagnesium chloride and trimethylacetonitrile was of limited preparative value. Using these conditions, in the absence of catalyst, no ketimine was detected after 24 h. With catalyst, 11% of the ketimine was present after 14 h and 25% after 48 h. Previously only a reduction-derived product (trimethylacetaldehyde, 14%) was isolated (isoamyl ether, 100–110 °C, 8 h) with these reactants (see ref 6).

(13) This reaction was homogeneous at least for the first 3 h of the reaction, while catalytic amounts of the other copper salts immediately produced a minute amount of black particles on mixing.

(14) In fact, benzonitrile is occasionally used as solvent in organocopper reactions (see ref 9f).

(15) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005–5038.

(16) Recent evidence supports a Cu(III)-oxidative addition intermediate. (a) Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7114–7116. (b) Hallnemo, G.; Ullenius, C. *Tetrahedron Lett.* **1986**, *27*, 395–398. (c) Dieter, R. K.; Silks, L. A., III. *J. Org. Chem.* **1986**, *51*, 4687–4701. (d) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015–6018; (e) **1984**, *25*, 3063–3066. (f) Hallnemo, G.; Olsson, T.; Ullenius, C. *J. Organomet. Chem.* **1985**, *282*, 133–144; (g) **1984**, *265*, C22–C24. (h) Krauss, S. R.; Smith, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 141–148.

(17) See footnote 15 in ref 3 for the instrumentation and the analytical procedures.

°C, ice–water bath), the nitrogen inlet tube attached to the condenser was replaced by a soda lime trap and ca. 10 mL of anhydrous ammonia was condensed into the vessel. After allowing the mixture to warm to ambient temperature, it was filtered through Celite and the filtrate concentrated at water-aspirator pressure on a rotary evaporator to afford 3.52 g of a colorless oil. Following Kugelrohr distillation (bp 80–84 °C, 0.6 Torr), 2.97 g (18.4 mmol, 95%) of **1a** was obtained as a colorless oil:[18] IR ($CHCl_3$) 3260 (br), 3100, 3075, 2980, 2920, 2880, 1630, 1615, 1480, 1400, 1360, 1190, 940, 905, 705 cm^{-1}; NMR ($CDCl_3$) δ 9.60–8.76 (1 H, br s, exchanges with D_2O), 7.40–7.30 (3 H, m), 7.30–7.18 (2 H, m), 1.24 (9 H, s); mass spectrum (70 eV), m/z (relative intensity) 161 (M^+, 4), 160 (3), 146 (3), 105 (8), 104 (100), 77 (16).

2,2-Dimethyl-1-phenyl-1-propanone (1b). After the addition mixture described in **1a** had been refluxed for 14 h, it was cooled in ambient temperature and 5 mL of H_2O was cautiously added, followed by 30 mL of 15% H_2SO_4. After stirring for 14 h, 30 mL of ether was added, the phases were separated, and the aqueous layer was extracted twice more with 25-mL portions of ether. The combined organic phase was dried ($MgSO_4$) and the solvent removed at water-aspirator pressure on a rotary evaporator to afford 3.36 g of a brown oil. Following chromatography (silica gel, CH_2Cl_2), 2.96 g (18.3 mmol, 94%) of **1b** was obtained as a colorless oil.[18,19] IR ($CHCl_3$) 3100, 3070, 3040, 2980, 2945, 2925, 2880, 1675, 1600, 1480, 1400, 1370, 1280, 1180, 970, 700 cm^{-1}; NMR (Me_2SO-d_6) δ 7.76–7.64 (2 H, m), 7.60–7.40 (3 H, m), 1.28 (9 H, s); mass spectrum (70 eV), m/z (relative intensity) 162 (M^+, 4), 106 (7), 105 (100), 77 (22), 57 (9).

Cyclohexylphenylmethanone (2b). To a stirred solution of 2.00 g (19.4 mmol) of benzonitrile and 10.7 mL (21.4 mmol, 2 M in Et_2O) of cyclohexylmagnesium chloride in 40 mL of THF was added 50 mg (0.34 mmol) of CuBr, and the mixture was refluxed (under nitrogen) for 30 min. After cooling to 25 °C, 5 mL of H_2O was cautiously added, followed by 30 mL of 15% H_2SO_4. After stirring for 14 h, the mixture was worked up, as described for **1b**, to afford 3.93 g of a pale yellow oil. Following chromatography (silica gel, CH_2Cl_2), 3.57 g (19.0 mmol, 98%) of **2b** was obtained as a colorless oil:[20] IR ($CHCl_3$) 3100, 3070, 3040, 3020, 2945, 2860, 1675, 1600, 1445, 1370, 1250, 970 cm^{-1}; NMR (Me_2SO-d_6) δ 7.98 (2 H, dd, J = 7 and 2 Hz), 7.72–7.49 (3 H, m), 3.50–3.27 (1 H, m), 1.90–1.60 (5 H, m), 1.55–1.05 (5 H, m); mass spectrum (70 eV), m/z (relative intensity) 189 (6), 188 (M^+, 43), 133 (14), 120 (6), 105 (100), 77 (31), 55 (12), 41 (12).

1-(4-Methoxyphenyl)-2,2-dimethyl-1-propanone (4b). Similar treatment of 2.00 g (15.0 mmol) of 4-methoxybenzonitrile, 8.25 mL (16.5 mmol, 2 M in THF) of *tert*-butylmagnesium chloride, and 50 mg (0.34 mmol) of CuBr, as described for **1b**, except that after the aqueous acid was added the hydrolysis mixture was refluxed for 1 h, afforded 3.59 g of an orange oil. Following Kugelruhr distillation (bp 100–101 °C, 0.2 Torr), 2.91 g (14.9 mmol, 99%) of **4b** was obtained as a colorless oil:[21] IR ($CHCl_3$) 3020, 2980, 2945, 2920, 2885, 2850, 1665, 1605, 1590, 1515, 1480, 1465, 1400, 1370, 1310, 1260, 1165, 1040, 1030, 965, 845 cm^{-1}; NMR (Me_2SO-d_6) δ 7.84 (2 H, d, J = 9.0 Hz), 7.00 (2 H, d, J = 9.0 Hz), 3.83 (3 H, s), 1.30 (9 H, s); mass spectrum (70 eV), m/z (relative intensity) 192 (M^+, 6), 135 (100).

2-Methoxy-α-(1-methylethyl)benzenemethanimine (5a). Similar treatment of 2.00 g (15.0 mmol) of 2-methoxybenzonitrile, 9.0 mL (18.0 mmol, 2 M in THF) of isopropylmagnesium chloride, and 50 mg (0.34 mmol) of CuBr, as described for **1a**, except that the mixture was refluxed for only 15 min, afforded 2.83 g of a pale orange oil. Following Kugelrohr distillation (bp 91–94 °C, 0.2 Torr), 2.45 g (13.8 mmol, 92%) of **5a** was obtained as a pale yellow oil: IR ($CHCl_3$) 3280 (br), 3015, 2975, 2950, 2880, 2845, 1620, 1605, 1495, 1470, 1440, 1390, 1365, 1250, 1185, 1115, 1050, 1030, 960, 905 cm^{-1}; NMR ($CDCl_3$) δ 8.00–7.32 (1 H, br s, exchanges with D_2O), 7.31 (1 H, td, J = 7.4 and 1.0 Hz), 7.19 (1 H, dd, J = 7.5 and 1.8 Hz), 6.93 (2 H, m), 3.82 (3 H, s), 3.04 (1 H, septet, J = 6.9 Hz), 1.15 (6 H, d, J = 6.9 Hz); mass spectrum (70 eV), m/z (relative intensity) 177 (M^+, 4), 176 (12), 162 (6), 134 (100), 119 (8), 107 (35), 91 (15), 77 (10), 41 (6). Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.75; H, 8.64; N, 8.06.

1-(2-Methoxyphenyl)-2-methyl-1-propanone (5b). After the addition mixture described in **5a** had been refluxed for 15 min, it was cooled to ambient temperature and 5 mL of H_2O was cautiously added, followed by 30 mL of 15% H_2SO_4. After being refluxed for 1 h, the mixture was worked up, as described for **1b**, to afford 2.90 g of a pale yellow oil. Following Kugelrohr distillation (bp 98–100 °C, 0.2 Torr), 2.63 g (14.7 mmol, 98%) of **5b** was obtained as a colorless oil:[22] IR ($CHCl_3$) 3085, 3020, 2980, 2945, 2880, 2845, 1680, 1600, 1490, 1465, 1440, 1385, 1285, 1245, 1185, 1165, 1025, 980 cm^{-1}; NMR ($CDCl_3$) δ 7.51 (1 H, dd, J = 7.6 and 1.8 Hz), 7.42 (1 H, td, J = 7.4 and 1.9 Hz), 7.02–6.91 (2 H, m), 3.87 (3 H, s), 3.47 (1 H, septet, J = 6.9 Hz), 1.14 (6 H, d, J = 6.8 Hz); mass spectrum (70 eV), m/z (relative intensity) 178 (M^+, 8), 135 (100), 121 (4), 92 (4), 77 (6).

1-Cyclohexyl-2,2-dimethyl-1-propanone (6b). Similar treatment of 1.50 g (18.0 mmol) of 2,2-dimethylpropanenitrile, 10.8 mL (21.6 mmol, 2 M in Et_2O) of cyclohexylmagnesium chloride, and 50 mg (0.34 mmol) of CuBr, as described for **1b**, except that the addition mixtures was refluxed for 24 h, and after the aqueous acid was added the hydrolysis mixture was also refluxed for 24 h, afforded 1.65 g of a pale yellow oil. Following chromatography (silica gel, Et_2O), 1.36 g (8.1 mmol, 45%) of **6b** was obtained as a colorless oil:[20b] IR ($CHCl_3$) 2970, 2940, 2855, 1695, 1450, 1365, 1140, 1070, 980 cm^{-1}; NMR ($CDCl_3$) δ 2.89–2.78 (1 H, m), 1.85–1.55 (5 H, m), 1.55–1.18 (5 H, m), 1.14 (9 H, s); mass spectrum (70 eV), m/z (relative intensity) 169 (5), 168 (M^+, 6), 111 (19), 110 (7), 83 (100), 67 (5), 57 (30), 55 (30), 41 (32).

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Registry No. **1a**, 33611-54-0; **1b**, 938-16-9; **2b**, 712-50-5; **4b**, 2040-26-8; **5a**, 109241-95-4; **5b**, 74786-53-1; **6b**, 15963-60-7; PhCN, 100-47-0; *t*-BuMgCl, 677-22-5; $C_6H_{11}MgCl$, 931-51-1; 4-$MeOC_6H_4CN$, 874-90-8; *i*-C_3H_7MgCl, 1068-55-9; Me_3CCN, 630-18-2; 2-$MeOC_6H_4CN$, 6609-56-9.

(18) Richey, H. G., Jr.; Erickson, W. F. *J. Org. Chem.* **1983**, *48*, 4349–4357.

(19) (a) Stenberg, V. I.; Singh, S. P.; Narain, N. K. *J. Org. Chem.* **1977**, *42*, 2244–2246. (b) Sternerup,H. *Acta Chem. Scand., Ser. B* **1974**, *B28*, 969–980. (c) Posner, G. H.; Brunelle, D. J.; Sinoway, L. *Synthesis* **1974**, 662–663. (d) Posner, G. H.; Whitten, C. E. *Org. Synth.* **1976**, *55*, 122–127.

(20) (a) Kulp, S. S.; McGee, M. J. *J. Org. Chem.* **1983**, *48*, 4097–4098. (b) Kende, A. S.; Scholz, D.; Schneider, J. *Synth. Commun.* **1978**, *8*, 59–63. (c) Solladie-Cavallo, A.; Solladie, G. *Org. Magn. Reson.* **1977**, *10*, 235–237.

(21) Newsoroff, G. P.; Sternhell, S. *Aust. J. Chem.* **1968**, *21*, 747–760.

(22) Malaitong, N.; Thebtaranonth, C. *Chem. Lett.* **1980**, *3*, 305–306.