Tandem Alkylation-Reduction of Nitriles. Synthesis of Branched Primary Amines[1,2]

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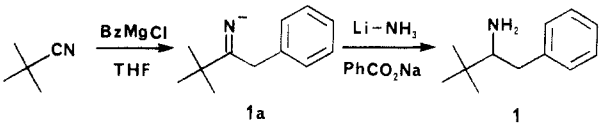
Tandem alkylation-reduction of a series of nitriles by alkylating with Grignard reagents followed by reducing with lithium-ammonia afforded the corresponding branched primary amines in reasonable isolated yields. Alkyl and aromatic nitriles and a variety of Grignard reagents have been employed in this convenient procedure. A mechanism for the reduction of the imine intermediate is suggested.

In ongoing studies[2] in this laboratory the usefulness of tandem alkylation-reduction of carbonyls for the preparation of complex aromatic alkanes,[4a] aromatic alkenes,[4b] α-cyclopropyl aromatic hydrocarbons,[4c] dienes,[4d,e] and (*E*)-propenyl ethers[4f] has been demonstrated. The advantage of the method is that the reactions are performed in the same reaction vessel without isolation of intermediates, thereby usually resulting in high yields. Heretofore, the examples utilizing the tandem alkylation-reduction method involved carbonyl groups as the electrophile, e.g., aldehydes[4a-c,f] ketones,[4a-e] esters and lactones.[4g] In continuing development studies, extension of the method to other electrophiles was sought. Herein is described a convenient preparation of branched primary amines by tandem alkylation-reduction of nitriles.

An example of this tandem reaction sequence is as follows. After refluxing a solution of 2,2-dimethylpropanenitrile and benzylmagnesium chloride in THF in a metal-ammonia reaction assembly until all of the nitrile was consumed,[5] anhydrous liquid ammonia was condensed into the reaction vessel and then an excess of lithium wire added, which turned the mixture dark blue after 1-5 min. The reluctance of the blue color to establish itself immediately indicated that a reduction had occurred. The excess reducing agent was then destroyed by introduction of the aprotic quenching agent sodium benzoate, and after normal workup and purification afforded α-*tert*-butylphenethylamine (**1**, 84%).



1a **1**

Table I is a listing of the nitriles and the Grignard reagents that were subjected to this tandem alkylation-reduction procedure and the structures and yields of the branched primary amine products.[6] The indicated yields are the isolated yields after purification and are based on the starting nitrile. Satisfactory yields of amines **1** and **3** indicate that the imine intermediate does not have to be in conjugation with an aromatic group for the reduction of the carbon-nitrogen double bond to occur and that an added proton source, such as MeOH, is not necessary for the reduction of aliphatic imines.[7] The alkylation-reduction sequence does not appear to be sensitive to steric effects since many of the nitriles and Grignard reagents are sterically congested and yet reasonable isolated yields were realized for most reactions using the conditions described. In fact, metal-ammonia has been utilized in the reduction of sterically hindered imines where other methods of reduction failed.[8] The aromatic rings of the amines **1**, **2**, and **4-9** survived the mild reduction conditions; however, the terminal olefin functionality that was introduced by the alkylation of 3-methylbenzonitrile with allylmagnesium bromide was reduced during the reduction sequence.[9] The alkylations of benzonitrile with *tert*-butylmagnesium chloride and 2-methoxybenzonitrile with isopropylmagnesium chloride were sluggish and incomplete. Subsequently, it was found that the alkylation step could be catalyzed by trace amounts of CuBr.[10] Using these alkylation conditions in the tandem sequence afforded excellent isolated yields of the corresponding amines **5** and **8**, respectively.

A suggested mechanism for the reduction of the in situ generated imine in the tandem alkylation-reduction sequence is as follows,[11,12] and is similar to the mechanism

(1) Disclosed in part at the 191st National Meeting of the American Chemical Society, New York, April 13-18, 1986; Orgn 222. Taken in part from the Ph.D. Thesis of F.J.W., Rutgers University, January 1987.

(2) Tandem Alkylation-Reduction. 16. Part 15: Flisak, J. R.; Hall, S. S. *Synth. Commun.* **1986**, *16*, 1217-1228.

(3) Address: Hoechst-Roussel Pharmaceuticals Inc., Somerville, NJ 08876.

(4) (a) Hall, S. S.; Lipsky, S. D. *J. Org. Chem.* **1973**, *38*, 1735-1738. (b) McEnroe, F. J.; Sha, C.-K.; Hall, S. S. *J. Org. Chem.* **1976**, *41*, 3465-3468. (c) Hall, S. S.; Sha, C.-K.; Jordan, F. *J. Org. Chem.* **1976**, *41* 1494-1498. (d) Ryan Zilenovski, J. S.; Hall, S. S. *J. Org. Chem.* **1979**, *44*, 1159-1161. (e) Ryan Zilenovski, J. S.; Hall, S. S. *J. Org. Chem.* **1981**, *46*, 4139-4142. (f) Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1985**, *50*, 5308-5314. (g) Srisethnil, S. T.; Hall, S. S. *J. Org. Chem.* **1977**, *42*, 4266-4268.

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

(6) As indicated in Table I, 1,1-diphenylmethylamine (**6**) is the product when the alkylation-reduction mixture is quenched with the aprotic agent sodium benzoate after the insoluble imine salt is protonated by adding 0.97 equiv of MeOH. In contrast, when the reduction is interjected with 1.29 g (25.3 mmol, 1.31 equiv) of MeOH as an added proton source diphenylmethane is the major product. This is not unexpected since the latter are conditions utilized to cleave benzyl groups of protected amines. See: Green, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1981; p 272.

(7) Smith, M. In *Reduction*; Augustine, R. L., Ed.; Marcel Dekker: New York, 1968; p 117.

(8) Lochte, H. L.; Horeczy, J.; Pickard, P. L.; Barton, A. D. *J. Am. Chem. Soc.* **1948**, *70*, 2012-2015.

(9) In this particular example 533 mg (76.9 mmol, 4.5 equiv) of lithium had to be added before the mixture turned blue. When the normal amount of lithium was added a complex mixture of products resulted.

(10) Weiberth, F. J.; Hall, S. S. *Abstracts of Papers*, 192nd National Meeting of the American Chemical Society, Anaheim, CA, Sept 7-12, 1986; Orgn 220.

(11) Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Non-Metallic Substances*; Prentice-Hall: New York, 1954; p 767 and references cited therein.

(12) The reductive dimerization of imines by alkali metals in ether solvents and by electrochemical methods have been shown to proceed by the carbon-carbon coupling of radical-anion intermediates such as **1c**. See: (a) Giri, B. P.; Mehrotra, K. N. *Synthesis* **1977**, 489-490. (b) Eisch, J. J.; Kaska, D. D.; Peterson, C. J. *J. Org. Chem.* **1966**, *31*, 453-456. (c) Smith, J. G.; Veach, C. D. *Can. J. Chem.* **1966**, *44*, 2497-2502. (d) Smith, J. G.; Ho, I. *J. Org. Chem.* **1972**, *37*, 653-656. (e) Horner, L.; Skaletz, D. H. *Tetrahedron Lett.* **1970**, 1103-1106, (f) 3679-3681.

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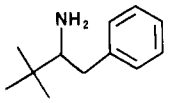
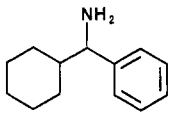
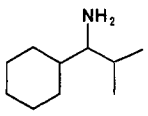
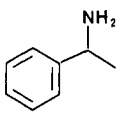
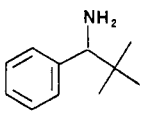
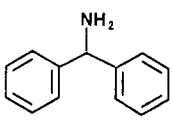
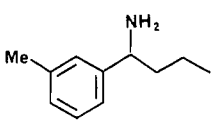
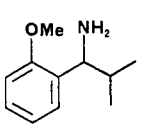
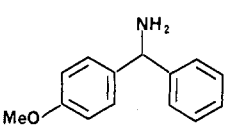
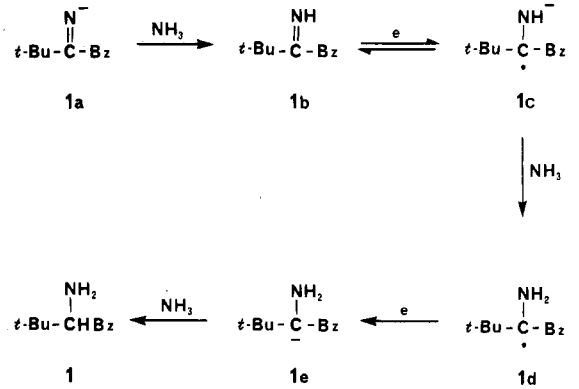
Table I. Tandem Alkylation–Reduction of Nitriles[a]

nitrile	reagent	product (% yield)[b]
2,2-dimethylpropanenitrile	benzylmagnesium chloride	 1 (84)[c]
cyclohexanecarbonitrile	phenylmagnesium bromide	 2 (92)[d]
cyclohexanecarbonitrile	isopropylmagnesium chloride	 3 (60)[d]
benzonitrile	methylmagnesium chloride	 4 (32)[e]
benzonitrile	*tert*-butylmagnesium chloride	 5 (99)[d,f]
benzonitrile	phenylmagnesium bromide	 6 (93)[d,f,g]
3-methylbenzonitrile	allylmagnesium bromide	 7 (78)[d,h]
2-methoxybenzonitrile	isopropylmagnesium chloride	 8 (89)[d,f]
4-methoxybenzonitrile	phenylmagnesium bromide	 9 (80)[d]

[a] Details are in the Experimental Section. [b] Isolated yields are based on the nitrile. [c] Purified by column chromatography. [d] Purified by Kugelrohr distillation. [e] Purified by short-path distillation. [f] The alkylation step was catalyzed by a trace of CuBr. [g] See ref 6 and 20. [h] See ref 9.

proposed for the electrochemical reduction of substituted imines.[13]



This study shows that branched primary amines can be prepared from nitriles by tandem alkylation–reduction. The satisfactory isolated yields and the availability of the starting materials, coupled with the simplicity of this one-pot procedure, makes this another expedient method for the synthesis of branched primary amines.[14]

Experimental Section[15]

All glassware was assembled, dried using a heat gun, and then allowed to cool to ambient temperature under a static nitrogen atmosphere. The alkylations were performed under a static nitrogen atmosphere with a Firestone oil bubbler valve. When ammonia was to be introduced, the N_2 source was disconnected, and the reaction was protected by attaching a soda lime trap to the side arm of the Dewar condenser for the duration of the reduction. Anhydrous THF was stored over 3-Å molecular sieves. 2,2-Dimethylpropanenitrile, cyclohexanecarbonitrile, benzonitrile, 3-methylbenzonitrile, 2-methoxybenzonitrile, and 4-methoxybenzonitrile from Aldrich Chemical Co. were used without further purification. Benzylmagnesium chloride (2 M, THF), phenylmagnesium bromide (3 M, Et_2O), isopropylmagnesium chloride (2 M, THF), methylmagnesium chloride (2.8 M, THF), *tert*-butylmagnesium chloride (2 M, THF), and allylmagnesium bromide (1 M, Et_2O) were from Aldrich Chemical Co. Cuprous bromide was from Research Organic/Inorganic Chemical Corporation (ROC/RIC). Anhydrous ammonia was distilled through a tower of potassium hydroxide pellets directly into the reaction vessel. Lithium wire (0.32-cm diameter, high purity, Foote Mineral Co.) was wiped free of oil, rinsed in hexane, and cut into 0.5-cm pieces just prior to use. Gas–liquid chromatographic analysis were performed on a 180 cm × 4 mm (i.d.) glass column packed with 3% OV-17 (50% phenyl, methyl) supported on 60–80-mesh Gas-Chrom Q or on a 12 m × 0.22 mm (i.d.) fused silica gel capillary column coated with BP10 (7% cyanopropyl, 7% phenylmethylsiloxane) from Scientific Glass Engineering Inc. Purification by column chromatography was accomplished on 70–230-mesh silica gel 60 (E. Merck). Kugelrohr and short-path distillation boiling points are uncorrected.

α-*tert*-Butylphenethylamine (1). A stirred solution of 1.50 g (18.0 mmol) of 2,2-dimethylpropanenitrile and 9.9 mL (19.8

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(14) A complementary one-pot method using lithium aluminum hydride as the reducing agent has been described: Pohland, A.; Sullivan, H. R. *J. Am. Chem. Soc.* **1953**, *75*, 5898–5899.

(15) GLC analyses were performed on a Perkin-Elmer Model 2920B chromatograph (flame ionization detector) using a 30 mL/min helium gas flow rate or on a Perkin-Elmer Model Sigma 3B chromatograph (flame ionization detector) using a 12 psi helium head pressure. The IR spectra were determined with a Pye Unicam Model SP3-200 or a Perkin-Elmer Model 1420 spectrophotometer. The NMR spectra were determined in $CDCl_3$ or Me_2SO-d_6 at 200 MHz with a Varian Model XL-200 Fourier transform spectrometer and the chemical shifts are expressed in δ values (ppm) relative to a Me_4Si internal standard. Mass spectra were determined at 17 eV or 70 eV on a Finnigan Model 4023 spectrometer with an INCOS data system attachment. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, IL.

mmol, 2 M in THF) of benzylmagnesium chloride in 45 mL of anhydrous THF was refluxed under a nitrogen atmosphere for 22 h. After cooling, the N_2 source was replaced with a soda lime trap and ca. 175 mL of ammonia was condensed into the reaction vessel followed by the addition of 337 mg (48.6 mmol, 18 pieces) of lithium wire. After 20 min, 3.0 g of sodium benzoate was added to discharge the dark blue reaction mixture to produce a yellow slurry. After allowing the ammonia to evaporate, the residue was diluted with 60 mL of ether and then the stirred, cooled (ice–water bath) mixture was adjusted to pH 8.5 by the slow addition of 56 mL of 2 N HCl. After the phases were separated, the aqueous layer was saturated with NaCl and extracted with 30 mL of ether, and the combined organic phase was washed with 15 mL of saturated NaCl. The organic phase was then extracted with 40 mL of 0.5 N HCl, and the acidic aqueous phase was separated, washed with 20 mL of ether, and adjusted to pH 11 by the addition of 8 mL of 10% NaOH. This basic aqueous phase was partitioned with 60 mL of ether, and the separated aqueous phase was then saturated with NaCl and extracted twice more with 30-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 3.29 g of a colorless oil. Following chromatography (silica gel, Et_2O–hexane 1:3), 2.68 g (15.2 mmol, 84%) of **1** was obtained as a colorless oil:[16] IR ($CHCl_3$) 3380, 3310, 3080, 3060, 2960, 2870, 1600, 1580, 1485, 1470, 1450, 1385, 1360, 1075, 1020, 935, 860, 835 cm^{-1}; NMR (Me_2SO-d_6) δ 7.32–7.16 (5 H, m), 2.85 (1 H, dd, J = 13.1 and 2.0 Hz), 2.49 (1 H, dd, J = 10.6 and 2.2 Hz), 2.10 (1 H, dd, J = 13.0 and 10.8 Hz), 0.92 (9 H, s) superimposed on 1.04–0.89 (2 H, br s, exchanges with D_2O); mass spectrum (17 eV), m/z (relative intensity) 179 (4), 178 (M^+ + 1, 33), 176 (2), 175 (2), 162 (6), 121 (10), 120 (100), 106 (2), 87 (3), 86 (49), 69 (2).

α-Phenyl-α-cyclohexylmethylamine (2). Similar treatment of 2.00 g (18.3 mmol) of cyclohexanecarbonitrile and 7.6 mL (22.8 mmol, 3 M in THF) of phenylmagnesium bromide, as described for **1** except that the alkylation mixture was heated at 52 °C for 22 h, afforded 3.76 g of an orange oil. Following Kugelrohr distillation (bp 99–102 °C, 0.5 torr), 3.18 g (16.8 mmol, 92%) of **2** was obtained as a colorless oil:[17] IR ($CHCl_3$) 3390, 3360, 3090, 3070, 3005, 2950, 2930, 2850, 1605, 1580, 1490, 1445, 1260, 1025, 900, 870, 835 cm^{-1}; NMR ($CDCl_3$) δ 7.35–7.16 (5 H, m), 3.58 (1 H, d, J = 7.4 Hz), 1.95 (1 H, d with further splitting, J = 7.3 Hz), 0.81 (12 H, m, 2 H exchange with D_2O); mass spectrum (17 eV), m/z (relative intensity) 191 (5), 190 (35), 189 (M^+, 2), 173 (9), 120 (4), 107 (7), 106 (100), 86 (2).

1-Cyclohexyl-1-isopropylmethylamine (3). Similar treatment of 2.00 g (18.3 mmol) of cyclohexanecarbonitrile and 11.0 mL (22.0 mmol, 2 M in THF) of isopropylmagnesium chloride, as described for **1** except that the alkylation mixture was refluxed for 72 h, afforded 2.25 g of an orange oil. Following Kugelrohr distillation (bp 173–175 °C, 30 torr), 1.70 g (10.9 mmol, 60%) of **3** was obtained as a colorless oil: IR ($CHCl_3$) 3390, 2940, 2860, 1585, 1470, 1450, 1390, 1370, 1270, 1090, 975, 890, 870, 845 cm^{-1}; NMR ($CDCl_3$) δ 2.18 (1 H, t, J = 5.8 Hz), 1.88–1.52 (6 H, m), 1.40–0.94 (8 H, m, 2 H exchange with D_2O), 0.92 (3 H, d, J = 6.8 Hz), 0.86 (3 H, d, J = 6.7 Hz); mass spectrum (17 eV), m/z (relative intensity) 157 (10), 156 (M^+ + 1, 86), 154 (2), 139 (2), 113 (8), 112 (100), 95 (14), 73 (4), 72 (88), 55 (2). Anal. Calcd for $C_{10}H_{21}N$: C, 77.35; H, 13.63; N, 9.02. Found: C, 77.22; H, 13.48; N, 8.95.

α-Methylbenzylamine (4). Similar treatment of 2.00 g (19.4 mmol) of benzonitrile and 7.2 mL (20.2 mmol, 2.8 M in THF) of methylmagnesium chloride, as described for **1** except that the alkylation mixture was refluxed for only 14 h, afforded 1.80 g of an orange oil. Following short-path distillation (bp 185–188 °C), 0.75 g (6.2 mmol, 32%) of **4** was obtained as a colorless oil:[18] NMR (Me_2SO-d_6) δ 7.39–7.12 (5 H, m), 3.97 (1 H, q, J = 6.6 Hz), 1.79 (2 H, br s, exchanges with D_2O), 1.23 (3 H, d, J = 6.5 Hz); mass spectrum (70 eV), m/z (relative intensity) 123 (1), 122 (11), 121 (M^+, 2), 120 (5), 107 (9), 106 (100), 105 (16), 91 (2), 79 (14), 77 (7).

α-*tert*-Butylbenzylamine (5). Similar treatment of 2.00 g (19.4 mmol) of benzonitrile and 10.7 mL (21.4 mmol, 2 M in THF) of *tert*-butylmagnesium chloride, as described for **1** except that 56 mg (0.39 mmol) of CuBr was added as catalyst[10] and this alkylation mixture was refluxed for only 14 h, afforded 3.45 g of a yellow oil. Following Kugelrohr distillation (bp 103–105 °C, 0.2 torr), 3.15 g (19.3 mmol, 99%) of **5** was obtained as a colorless oil:[18a,19] IR ($CHCl_3$) 3390, 3330, 3100, 3080, 3040, 3020, 2980, 2920, 2870, 1605, 1585, 1495, 1480, 1455, 1395, 1370, 1065, 1030, 920, 880 cm^{-1}; NMR (Me_2SO-d_6) δ 7.40–7.18 (5 H, m), 3.57 (1 H, s), 1.69 (2 H, br s, exchanges with D_2O), 0.82 (9 H, s); mass spectrum (17 eV), m/z (relative intensity) 165 (1), 164 (M^+ + 1, 11), 148 (2), 147 (4), 107 (8), 106 (100).

1,1-Diphenylmethylamine (6). A stirred mixture of 2.00 g (19.4 mmol) of benzonitrile, 7.1 mL (21.3 mmol, 3 M in Et_2O) of phenylmagnesium bromide, and 56 mg (0.39 mmol) of CuBr as catalyst[10] in 45 mL of anhydrous THF was refluxed under a nitrogen atmosphere for 15 min. After cooling, the N_2 source was replaced with a soda lime trap and ca. 175 mL of ammonia was condensed into the reaction vessel followed by the sequential addition of 0.60 g (18.8 mmol) of MeOH[20] and 337 mg (48.6 mmol, 18 pieces) of lithium wire. After 20 min, 2.0 g of sodium benzoate was added to discharge the dark blue reaction mixture to produce an orange slurry. Similar workup, as described for **1**, afforded 3.95 g of an orange oil. Following Kugelrohr distillation (bp 158–161 °C, 0.6 torr), 3.29 g (18.0 mmol, 93%) of **6** was obtained as a colorless oil:[18a–c,21] NMR ($CDCl_3$) δ 7.36–7.12 (10 H, m), 5.13 (1 H, s), 1.70 (2 H, s, exchanges with D_2O); mass spectrum (17 eV), m/z (relative intensity) 185 (1), 184 (15), 183 (M^+, 100), 182 (20), 168 (2), 167 (5), 166 (4), 106 (57), 105 (54).

α-Propyl-*m*-methylbenzylamine (7). Similar treatment of 2.00 g (17.1 mmol) of 3-methylbenzonitrile and 18.8 mL (18.8 mmol, 1 M in Et_2O) of allylmagnesium bromide, as described for **1** except that the alkylation mixture was heated at 50 °C for only 15 min and 533 mg (76.9 mmol, 28 pieces) of lithium was used for the reduction,[9] afforded 2.91 g of an orange oil. Following Kugelrohr distillation (bp 98–101 °C, 0.4 torr), 2.18 g (13.3 mmol, 78%) of **7** was obtained on a colorless oil: IR ($CHCl_3$) 3390, 3050, 2970, 2945, 2875, 1610, 1590, 1485, 1460, 1380, 920, 860, 830 cm^{-1}; NMR (Me_2SO-d_6) δ 7.19–7.04 (3 H, m), 6.98 (1 H, d, J = 7.1 Hz), 3.66 (1 H, t, J = 6.8 Hz), 2.26 (3 H, s), 1.7 (2 H, br s, exchanges with D_2O), 1.56–1.36 (2 H, complex m), 1.36–1.04 (2 H, complex m), 0.81 (3 H, t, J = 7.1 Hz); mass spectrum (17 eV), m/z (relative intensity) 165 (2), 164 (M^+ + 1, 18), 147 (8), 121 (10), 120 (100). Anal. Calcd for $C_{11}H_{17}N$: C, 80.93; H, 10.50; N, 8.57. Found: C, 81.09; H, 10.65; N, 8.62.

α-Isopropyl-*o*-methoxybenzylamine (8). Similar treatment of 1.50 g (11.3 mmol) of 2-methoxybenzonitrile and 10.5 mL (21.0 mmol, 2 M in THF) of isopropylmagnesium chloride, as described for **1** except that 33 mg (0.23 mmol) of CuBr was added as catalyst[10] and this alkylation mixture was refluxed for only 15 min and only 243 mg (35.1 mmol, 13 pieces) of lithium was used for the reduction, afforded 2.10 of an orange oil. Following Kugelrohr distillation (bp 105–108 °C, 0.3 torr), 1.79 g (10.0 mmol, 89%) of **8** was obtained as a colorless oil: IR ($CHCl_3$) 3390, 3330, 3080, 3010, 2975, 2875, 2840, 1595, 1580, 1485, 1465, 1440, 1385, 1365, 1290, 1240, 1210, 1050, 1030, 930 cm^{-1}; NMR (Me_2SO-d_6) δ 7.32 (1 H, dd, J = 7.5 and 1.9 Hz), 7.16 (1 H, td, J = 7.8 and 1.8 Hz), 6.92 (1 H, d, J = 7.8 Hz) superimposed on 6.90 (1 H, t, J = 7.3 Hz), 3.86 (1 H, d, J = 6.6 Hz), 3.75 (3 H, s), 1.79 (1 H, octet, J = 6.7 Hz), 1.58 (2 H, br s, exchanges with D_2O), 0.84 (3 H, d, J = 6.8 Hz), 0.74 (3 H, d, J = 6.7 Hz); mass spectrum (17 eV), m/z (relative intensity) 180 (M^+ + 1, 1), 163 (1), 137 (9), 136 (100), 122 (3), 106 (1). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.49; H, 9.29, N, 7.73.

(16) Lindeke, B.; Jonsson, J.; Hallstrom, G.; Paulsen, U. *Biol. Oxid. Nitrogen, Proc. Int. Symp., 2nd* **1978**, 47–52.
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p-Methoxy-α-phenylbenzylamine (9). Similar treatment of 2.00 g (15.0 mmol) of 4-methoxybenzonitrile and 6.0 mL (18.0 mmol, 3 M in THF) of phenylmagnesium bromide, as described for **1** except that the alkylation mixture was refluxed for only 14 h and only 285 mg (41.3 mmol, 15 pieces) of lithium was used for the reduction, afforded 2.95 g of a yellow oil. Following Kugelrohr distillation (bp 132–138 °C, 0.1 torr), 2.56 g (12.0 mmol, 80%) of **9** was obtained as a colorless oil:[22] IR ($CHCl_3$) 3440, 3400, 3080, 3040, 3025, 2980, 2960, 2930, 2855, 1685, 1620, 1595, 1515, 1500, 1470, 1460, 1310, 1250, 1180, 1040, 915, 845, 710 cm^{-1}; NMR (Me_2SO-d_6) δ 7.40–7.14 (7 H, m), 6.83 (2 H, dd, J = 6.7 and 2.1 Hz), 5.03 (1 H, s), 3.69 (3 H, s), 2.16 (2 H, br s, exchanges with D_2O); mass spectrum (17 eV), m/z (relative intensity) 214 (6), 213 (M^+, 51), 212 (14), 197 (23), 182 (10), 137 (8), 136 (100), 135 (31), 121 (9), 106 (9), 105 (40).

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Regioselectivity of Electrophilic Additions to 7-Oxabicyclo[2.2.1]heptenes Controlled by Remote Substituents. Arenesulfonyl Substituted 7-Oxabicyclo[2.2.1]heptenes as Stereo- and Regioselective Chiral Dienophiles[1]

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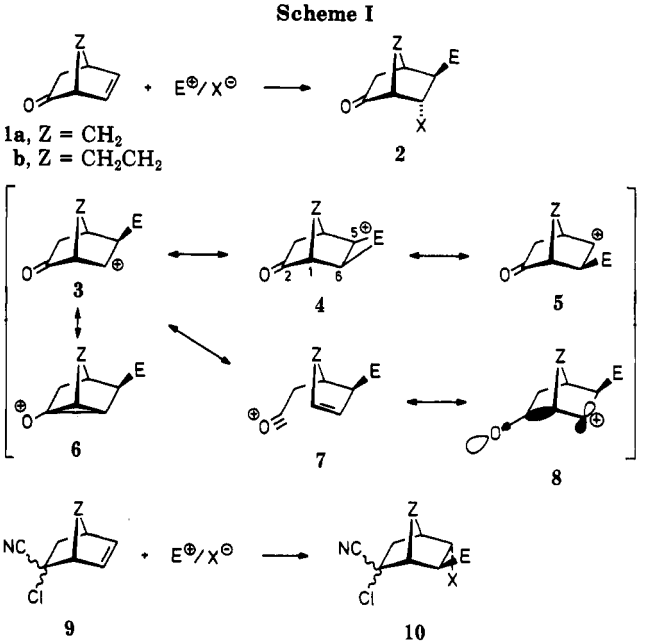
Benzeneselenenyl, 2-nitrobenzenesulfenyl, and 2,4-dinitrobenzenesulfenyl chlorides added to 2-*endo*-acetoxy-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*-carbonitrile (**11**) in an anti fashion with complete stereo- and regioselectivity, giving the adducts **13a–c** in which the chlorine substituent occupies the endo position at C(5). Opposite regioselectivity was observed when the same electrophilic reagents were allowed to react with the closely related enone **12** (7-oxabicyclo[2.2.1]hept-5-en-2-one), leading to adducts **14a–c** in which the chloride substituent is endo at position C(6). This stereo- and regiochemical control was used in the preparation of the new chiral bicyclic dienophiles **30** (6-(2-nitrobenzenesulfonyl)-2-*endo*-acetoxy-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*-carbonitrile) and **33** (5-benzenesulfonyl-7-oxabicyclo[2.2.1]hept-5-en-2-one), whose cycloadditions to the Danishefsky diene **22** were found to be highly regio- and stereoselective. This allowed the facile preparation of complex bicyclo[4.4.0]decane derivatives in a stereocontrolled fashion.

Under kinetic control, 2-bicyclo[2.2.1]hept-5-enone (**1a**) and 2-bicyclo[2.2.2]oct-5-enone (**1b**) add soft electrophiles, EX, to give the corresponding adducts **2** with high regioselectivity.[3] The nucleophile's (X^-) preference to attack

Scheme I



carbon center C(6) of intermediate **4** can be understood by recognizing that limiting structure **3** is favored over structure **5**. Structure **3** is stabilized due to the carbonyl group's polarizability, which can be interpreted in terms

(1) A preliminary communication of this work has been presented at the 179th ACS Meeting, Sept 8–13, Chicago, Abstr. No. 62, ORGN. For other examples of chiral dienophiles, see, for instance: (a) Walborsky, H. M.; Barash, L.; Davis, T. C. *J. Org. Chem.* **1961**, *26*, 4778–4779. Evans, D. A.; Chapman, K. T. *J. Am. Chem. Soc.* **1984**, *106*, 4261–4263, and references cited therein. Mann, J.; Thomas, A. *J. Chem. Soc., Chem. Commun.* **1985**, 737–738. Posner, G. H.; Harrison, W. *Ibid.* **1985**, 1786–1787. Horton, D.; Machinami, T.; Takagi, Y.; Bergmann, C. W.; Christoph, G. C. *Ibid.* **1983**, 1164–1166. De Lucchi, O.; Marchioro, C.; Valle, G.; Modena, G. *Ibid.* **1985**, 878–880. Maignan, C.; Guessous, A.; Rouessac, F. *Tetrahedron Lett.* **1984**, *25*, 1727–1728. Sundin, A.; Frejd, T.; Magnusson, G. *Ibid.* **1985**, *26*, 5605–5608. Fitzsimmons, B. J.; Fraser-Reid, B. *Tetrahedron* **1984**, *40*, 1279 and references cited therein. Franck, R. W.; John, T. V.; Olejniczak, K. *J. Am. Chem. Soc.* **1982**, *104*, 1106–1107. (b) Grieco, P. A.; Zelle, R. E.; Lis, R.; Finn, J. *J. Am. Chem. Soc.* **1983**, *105*, 1403–1404. (c) Tolbert, L. M.; Mahfuza, B. A. *Ibid.* **1984**, *106*, 3806–3810. Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 112–114. Ortuno, R. M.; Corbera, J.; Font, J. *Tetrahedron Lett.* **1986**, *27*, 1801–1804. Oppolzer, W.; Chapuis, C. *Ibid.* **1983**, *24*, 4665–4668. Angell, E. C.; Fringuelli, F.; Minuti, L.; Pizzo, F.; Porter, B.; Tattichi, A.; Wenkert, E. *J. Org. Chem.* **1985**, *50*, 4686–4690. Angell, E. C.; Fringuelli, F.; Halls, T. D. J.; Pizzo, F.; Porter, B.; Taticchi, A.; Tourris, A. P.; Wenkert, E. *Ibid.* **1985**, *50*, 4691–4696. Angell, E. C.; Fringuelli, F.; Pizzo, F.; Poster, B.; Taticchi, A.; Wenkert, E. *Ibid.* **1985**, *50*, 4696–4698. Arai, Y.; Kuwayama, S.-i.; Takeuchi, Y.; Kuizimi, T. *Tetrahedron Lett.* **1985**, *26*, 6205–6208.

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