A Facile Synthesis of γ-Lactams and Secondary Amines from Conjugated Dienes and Imines

Matthew S. Sell, Walter R. Klein, and Reuben D. Rieke*

Department of Chemistry, University of Nebraska–Lincoln, Lincoln, Nebraska 68588-0304

Received November 17, 1994

γ-Lactams are important intermediates in synthetic routes to five-membered heterocyclic compounds. Moreover, tetramic acids and 3-pyrrolin-2-ones represent a diverse and profoundly important family of biologically active secondary metabolites, many of which have potential use in both medicine and agriculture.[1] Synthetic interest in this class of molecules has been intense, particularly in the past decade.[2]

Most approaches to γ-lactams have been dependent on cyclization via acyl–nitrogen bond formation.[3] Cyclization involving carbon–carbon bond formation is an alternative route; however, until recently, this potential methodology has received little attention. Mori and coworkers reported a palladium-catalyzed cyclization of *N*-allyl iodoacetamides, in which the intramolecular addition reaction of the carbon–iodine bond to an olefinic linkage is a key step.[4] A new route to γ-lactams by the ruthenium-catalyzed cyclization of *N*-allyltrichloroacetamides was recently reported.[5] Also, Stork has reported the radical cyclization of *N*-protected haloacetamides to yield *N*-protected lactams.[6] The protecting groups can then be easily removed under a variety of conditions. This efficient radical cyclization route to cis-fused pyrrolidones and piperidones is interesting because of the widespread occurrence of related systems in natural products.[7] We wish to present here a direct method for the one-pot synthesis of γ-lactams and secondary amines utilizing conjugated diene–magnesium complexes.

Previous reports[8] from these laboratories have demonstrated that reactions of diene–magnesium reagents with bis-electrophiles provide a novel approach for annulation, including the generation of complex carbocycles,[9] spiro compounds,[10] and fused ring systems.[11] We have also reported a direct one-pot synthesis of spiro γ-lactones,[12] spiro δ-lactones,[13] and alcohols and 1,2-diols.[14] Recently, we found that γ-lactams and secondary amines can also be synthesized by a variation of this methodology.

Scheme 1 illustrates a route for the synthesis of a γ-lactam from the (2,3-dimethyl-2-butene-1,4-diyl)magnesium complex (**2**). Initially, treatment of **2** with *N*-benzylideneaniline at −78 °C resulted in the formation of the initial adduct (**3**). Significantly, the bis-organomagnesium reagent (**2**) reacted with 100% regioselectivity in the 2-position to give intermediate **3**. Upon warming to 0 °C, **3** reacted with CO_2 to yield the magnesium salt of a γ-amino acid (**5**). Acidic hydrolysis, followed by warming to 40 °C generated β-((1-methylethylene)methyl))-γ-phenyl-*N*-benzyl lactam **7** in 67% isolated yield as a 75:25 mixture of diastereomers (Table 1, entry 2). Importantly, the generation of a highly substituted γ-lactam was accomplished in one-pot and in good overall chemical yield. This approach was equally applicable to a cyclic 1,3-diene (1,2-bis(methylene)cyclohexane) and provided a facile route to a spiro γ-lactam, β-(2-methylenecyclohexyl)-γ-(phenyl)-*N*-benzyl lactam in 36% isolated yield (Table 1, entry 5).

Scheme 1 also illustrates an easy route to secondary amines containing a quaternary carbon center and a vinyl group in the β-position. When the magnesium–diene intermediate **2** was treated with *N*-benzylideneaniline at −78 °C, the initially formed adduct **3** could simply be hydrolyzed at 0 °C to afford *N*-(1-phenyl-2,2,3-trimethyl-3-butenyl)benzylamine (**4**) in 92% isolated yield (Table 2, entry 2). Other secondary amines are shown in Table 2 and all were prepared in high isolated yields.

This facile one-pot transformation of a 1,3-diene–magnesium intermediate provides a new entry for the formation of both secondary amines and β,γ,*N*-trisubstituted γ-lactams in good to high isolated yield. The overall procedure of the γ-lactam synthesis can be thought of as a molecular assembling process in which three independent species, i.e. a conjugated diene, an imine, and carbon dioxide, mediated by Rieke magnesium are transformed into a complex organic molecule in a well-controlled fashion. In the process, the construction of a quaternary carbon center and the introduction of both the amino and carboxyl groups required for lactamization are achieved in one synthetic step. Further studies are underway to define the scope and limitations of the process. It is believed that variations of the initial and/or second electrophile(s) will lead to new types of chemical transformations of 1,3-dienes.

Experimental Section

Infrared spectra were taken on an Analect RFX-65 FTIR spectrophotometer, neat between NaCl or KBr plates, KBr pellets, or KBr powder. Proton NMR spectra were obtained on a General Electric Ω-300 spectrometer. All chemical shifts are reported in parts per million downfield from an internal tetramethylsilane standard. Fully decoupled ^{13}C NMR spectra were obtained on a General Electric Ω-300 spectrometer. The center peak of $CDCl_3$, 77.0 ppm, was used as an internal reference. Elemental analyses were performed by Desert Analytics (Tucson, AZ).

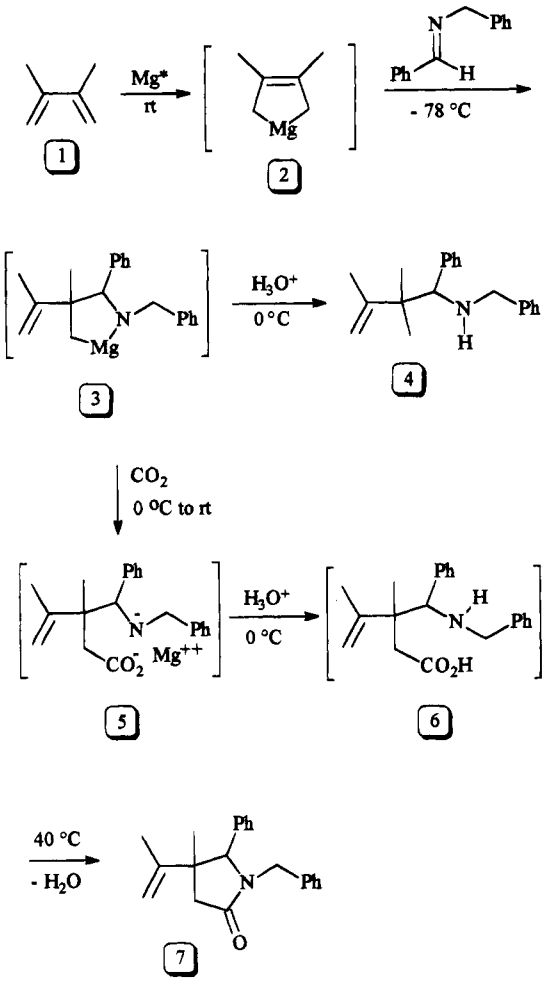
Analytical gas chromatography analyses were performed on a Hewlett-Packard 5890A gas chromatograph using stainless steel columns (12 ft x 1/8 in.) packed with 10% SP-2100 or 10% SP-2250 on Supelcoport.

All inert atmosphere manipulations were carried out on a dual manifold vacuum/argon system. Linde prepurified grade argon was further purified by passing it through several columns containing a 150 °C BASF R3-11 catalyst, phosphorus pentoxide, and granular potassium hydroxide. Tetrahydrofuran was dis-

(1) Laskin, A. I.; Lechevalier, H. A. *CRC Handbook of Microbiology*, 2nd ed., *5*, CRC Press, Inc.: Boca Raton, FL, 1984, and references therein.
(2) Paquette, L. A.; MacDonald, D.; Anderson, L. G.; Wright, J. *J. Am. Chem. Soc.* **1989**, *111*, 8037, and references cited therein.
(3) Frank, R. L.; Schmitz, W. R.; Zeidman, B. *Org. Synth.* **1955**, *3*, 328.
(4) Mori, M.; Oda, I.; Ban, Y. *Tetrahedron Lett.* **1982**, *23*, 5315.
(5) Nagashima, H.; Wakamatsu, H.; Ozaki, N.; Ishii, T.; Watanabe, M.; Tajima, T.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 1682.
(6) Stork, G.; Mah, R. *Heterocycles* **1989**, *28*, 723.
(7) (a) Bachi, M. D.; Frolow, F.; Hornaert, C. *J. Org. Chem.* **1983**, *48*, 1841. (b) Choi, J. K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959. (c) Danishefsky, S. J.; Panek, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 917.
(8) (a) Rieke, R. D. *Crit. Rev. Surf. Chem.* **1991**, *1*, 131. (b) Rieke, R. D. *Science* **1989**, *246*, 1260.
(9) (a) Xiong, H.; Rieke, R. D. *J. Org. Chem.* **1989**, *54*, 3247. (b) Rieke, R. D.; Xiong, H. *J. Org. Chem.* **1991**, *56*, 3109.
(10) Xiong, H.; Rieke, R. D. *Tetrahedron Lett.* **1991**, *32*, 5269.
(11) Xiong, H.; Rieke, R. D. *J. Am. Chem. Soc.* **1992**, *114*, 4415.
(12) Xiong, H.; Rieke, R. D. *J. Org. Chem.* **1992**, *57*, 7007.
(13) Sell, M. S.; Xiong, H.; Rieke, R. D. *Tetrahedron Lett.* **1993**, *34*, 6007.
(14) Sell, M. S.; Xiong, H.; Rieke, R. D. *Tetrahedron Lett.* **1993**, *34*, 6011.

0022-3263/95/1960-1077$09.00/0

Scheme 1



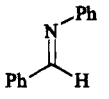
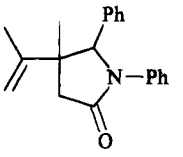
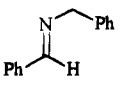
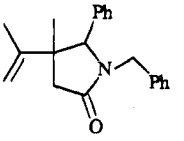
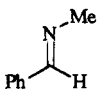
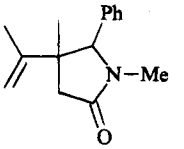
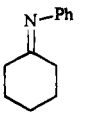
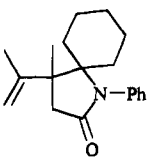
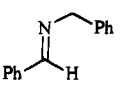
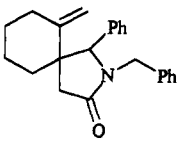
tilled prior to use from sodium/potassium alloy under an argon atmosphere. Commercially available reagents were used as received unless noted.

General Procedure for the Preparation of Highly Reactive Magnesium (The Rieke Method). In an argon drybox, lithium (10.00 mmol), naphthalene (1.50 mmol), and magnesium chloride (4.88 mmol) were weighed into a 50-mL two-neck round-bottom flask equipped with a Teflon stir bar and sealed with a rubber septum and stopcock outlet. The reaction apparatus was removed from the argon drybox, connected to the vacuum/argon manifold, and placed under positive argon pressure. Freshly distilled THF (15 mL) was added via syringe and vigorous stirring commenced. The solution was vigorously stirred at room temperature under argon for 3.5 h, yielding a dark green solution.[15] An additional 10 mL of freshly distilled THF was added to the active magnesium solution, via syringe, and stirring ceased. The active magnesium metal was allowed to settle for 2 h. The supernatant was cannulated off from the active magnesium powder, leaving 4 mL of liquid behind. Freshly distilled THF (10 mL) was added to the active magnesium via syringe. The active magnesium slurry was ready for use.

Typical Procedure for the Formation of (2,3-Dimethyl-2-butene-1,4-diyl)magnesium. Freshly distilled 2,3-dimethyl-1,3-butadiene (1.5 mL, in excess) was syringed into the active magnesium slurry (4.88 mmol, in 10 mL THF) with stirring. The reaction mixture was slowly stirred at room temperature for 8 h, yielding a pale orange solution. Freshly distilled THF (10 mL) was then syringed into the reaction mixture, and the stirring was ceased to allow unreacted active magnesium to settle out of solution, 3 h. The pale orange supernatant was cannulated into another 50-mL two-neck round-bottom flask equipped with a magnetic stir bar, rubber septum, and stopcock outlet. The (2,3-dimethyl-2-butene-1,4-diyl)magnesium solution was then ready for use.

(15) The reaction is vigorously stirred to prevent the coating of the lithium metal. Otherwise, the formation of active magnesium is greatly retarded.

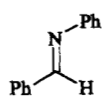
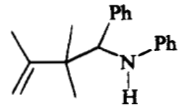
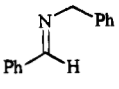
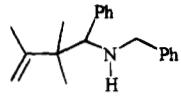
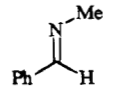
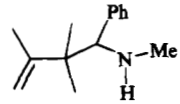
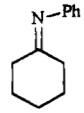
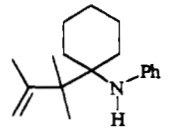
Table 1. Formation of γ-Lactams by Reaction of Conjugated Diene–Magnesium Complexes with Imines Followed by CO_2

Entry	Diene	Imine	Product[a]	% Yield[b]
1	1			47 (80:20)
2	1			67 (75:25)
3	1			58 (70:30)
4	1			39
5	2[c]			36 (57:43)

[a] Elemental analysis, ^1H NMR, ^{13}C NMR, and FTIR were all consistent with the indicated formulation. [b] Isolated yields based on the imine. Diasteriomeric ratios in parenthesis determined by ^1H NMR or by GC analysis. [c] 1,2-Bis(methylene)cyclohexane was utilized as the diene.

Typical Procedure for the Formation of γ-Lactams. The preformed (2,3-dimethyl-2-butene-1,4-diyl)magnesium complex was cooled to −78 °C followed by addition of *N*-benzylideneaniline (3.50 mmol) via syringe and stirred for 30 min at −78 °C. The reaction mixture was warmed to 0 °C and stirred at 0 °C for an additional 30 min. Gaseous carbon dioxide was then bubbled into the solution for 10 min at 0 °C. The reaction was warmed to room temperature, with the continual infusion of carbon dioxide, and stirred at room temperature for an additional 10 min. The carbon dioxide addition was terminated and the reaction cooled to 0 °C. The reaction was quenched at 0 °C with 5 mL of 3 M HCl and warmed to 50 °C for 1 h using a warm water bath. The reaction was allowed to cool to room temperature, and the layers were separated. The water layer was extracted with chloroform (3 × 5 mL). The organic layers were combined, dried over anhydrous magnesium sulfate, and filtered, and the filter cake was washed with chloroform (3 × 15 mL). The solvents were removed under reduced pressure, and the residue was flash chromatographed on silica gel using 20% ethyl acetate/hexanes affording β-((1-methylethylene)-methyl))-γ-phenyl-*N*-benzyl lactam (2.20 mmol) in 67% yield (75:25 mixture of diasteriomers) (Table 1, entry 2): IR (neat) 3085, 3062, 3029, 2967, 2921, 2871, 1695, 1494, 1454, 1440, 1419,

Table 2. Reactions of Conjugated Diene–Magnesium Reagents with Imines Followed by Acidic Hydrolysis

Entry	Diene	Imine	Product[a]	% Yield[b]
1	1			87
2	1			92
3	1			96
4	1			85

[a] Elemental analysis, ^{1}H NMR, ^{13}C NMR, and FTIR were all consistent with the indicated formulation. [b] Isolated yields based on the imine.

1375, 1359, 1255, 1234, 894, 763, 703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.30–6.99 (m, 20 H), 5.17–5.08 (m, 2 H), 4.75–4.73 (m, 2 H), 4.62–4.54 (m, 2 H), 4.17 (s, 1 H), 3.92 (s, 1 H), 3.44–3.39 (m, 1 H), 3.27–3.22 (m, 1 H), 3.16–3.10 (m, 1 H), 2.68–2.63 (m, 1 H), 2.43–2.37 (m, 1 H), 2.21–2.16 (m, 1 H), 1.57 (s, 3 H), 1.24 (s, 3 H), 1.18 (s, 3 H), 0.67 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 173.9, 173.1, 148.3, 145.6, 137.1, 136.4, 135.8, 135.5, 128.3, 128.25, 128.2, 128.0, 127.9, 127.8, 127.7, 127.2, 127.1, 112.0, 110.7, 70.4, 67.9, 44.3, 44.1, 43.9, 42.1, 41.6, 27.5, 22.6, 19.5, 19.3. Anal. Calcd for $C_{21}H_{23}NO$: C, 82.59; H, 7.59; N, 4.59. Found: C, 82.74; H, 7.86; N, 4.58.

β-((1-Methylethylene)methyl))-γ-phenyl-*N*-phenyl lactam (Table 1, entry 1) (80:20 mixture of diasteriomers): IR (neat) 3021, 2965, 2927, 1691, 1599, 1500, 1384, 1377, 1357, 1263, 1223 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.41–7.08 (m, 20 H), 5.04–5.00 (m, 3 H), 4.81 (s, 1 H), 4.74–4.71 (m, 2 H), 3.32–3.27 (m, 1 H), 2.88–2.65 (m, 2 H), 2.36–2.31 (m, 1 H), 2.00 (s, 3 H), 1.55 (s, 3 H), 1.46 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 173.7, 145.3, 138.6, 137.9, 128.7, 128.6, 128.3, 128.0, 127.3, 127.0, 125.1, 124.8, 122.2, 121.7, 113.1, 111.8, 74.4, 71.4, 47.2, 43.3, 42.6, 27.4, 22.5, 20.3. Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.80. Found: C, 82.69; H, 7.20; N, 4.71.

β-((1-Methylethylene)methyl))-γ-phenyl-*N*-methyl lactam (Table 1, entry 3) (70:30 isolable mixture of diasteriomers): major diasteriomer IR (neat) 3475, 3987, 3062, 3031, 2965, 2929, 2238, 1695, 1643, 1601, 1482, 1454, 1425, 1396, 1376, 1349, 1261, 1240, 1166, 1076, 1006, 894, 796, 740, 701, 669, 634 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.20–6.70 (m, 5 H), 4.61–4.56 (m, 2 H), 4.09 (s, 1 H), 3.02–2.97 (m, 1 H), 2.60 (s, 3 H), 2.12–2.06 (m, 1 H), 1.34 (s, 3 H), 1.28 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 173.7, 145.7, 137.2, 128.0, 127.8, 127.5, 112.3, 74.5, 46.7, 41.6, 28.2, 27.9, 19.9.

Minor diasteriomer: ^{1}H NMR (300 MHz, $CDCl_3$) 7.35–7.04 (m, 5 H), 4.88–4.81 (m, 2 H), 4.37 (s, 1 H), 2.71 (s, 3 H), 2.65–2.59 (m, 1 H), 2.37–2.31 (m, 1 H), 1.86 (s, 3 H), 0.74 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 174.6, 148.8, 136.8, 128.5, 128.0, 127.2, 111.2, 72.0, 44.5, 42.5, 28.8, 22.8, 19.9. Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 77.36; H, 8.23; N, 5.95.

β-((1-Methylethylene)methyl))-γ-cyclohexyl-*N*-phenyl lactam (Table 1, entry 4): IR (KBr) 3359, 3087, 3070, 3033, 3023, 3002, 2969, 2938, 2865, 1799, 1697, 1629, 1596, 1498, 1484, 1455, 1427, 1388, 1361, 1346, 1288, 1236, 1226, 1197, 1157, 1145, 1118, 1095, 1072, 1025, 919, 896, 873, 848, 828, 771, 750, 703, 646, 584, 549, 505 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.43–7.27 (m, 5 H), 5.02–4.96 (m, 2 H), 2.95–2.89 (m, 1 H), 2.32–2.27 (m, 1 H), 1.95–0.90 (m, (including singlets at 1.38 (3 H) and 1.94 (3 H)), 16 H); ^{13}C NMR (75 MHz, $CDCl_3$) 174.4, 147.5, 137.8, 130.2, 128.9, 127.9, 114.3, 68.6, 49.8, 43.5, 33.7, 30.8, 24.5, 23.0, 22.4, 22.0, 21.9. Anal. Calcd for $C_{19}H_{25}NO$: C, 80.51; H, 8.90; N, 4.94. Found: C, 80.41; H, 8.73, N, 4.92.

β-(2-Methylenecyclohexyl)-γ-phenyl-*N*-benzyl lactam (Table 1, entry 5) (57:43 mixture of diastereomers): IR (KBr) 3357, 3079, 3054, 3027, 2998, 2979, 2933, 2854, 1687, 1639, 1602, 1583, 1494, 1440, 1419, 1355, 1315, 1294, 1280, 1288, 1234, 1199, 1174, 1078, 1027, 950, 906, 891, 765, 752, 707, 632, 601 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.40–7.06 (m, 20H), 5.15–5.10 (m, 2H), 4.72–4.28 (m, 5H), 3.40–3.25 (m, 3H), 2.70–2.53 (m, 2H), 2.56–0.86 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) 173.5, 150.8, 148.2, 137.0, 136.8, 136.2, 135.8, 128.7, 128.68, 128.6, 128.5, 128.4, 128.3, 128.25, 128.2, 128.1, 128.0, 127.9, 127.5, 127.4, 127.3, 109.6, 108.1, 67.7, 66.4, 47.5, 45.8, 44.5, 44.4, 41.9, 41.8, 39.5, 35.3, 34.0, 33.5, 27.7, 27.2, 22.9. Anal. Calcd for $C_{23}H_{25}NO$: C, 83.34; H, 7.60; N, 4.23. Found: C, 83.19; H, 7.86; N, 4.20.

Typical Procedure for the Formation of Secondary Amines from (2,3-Dimethyl-2-butene-1,4-diyl)magnesium. The preformed (2,3-dimethyl-2-butene-1,4-diyl)magnesium complex was cooled to −78 °C followed by addition of *N*-benzylideneaniline (3.11 mmol) via syringe and stirred for 30 min at −78 °C. The reaction was warmed to 0 °C and stirred at 0 °C for an additional 30 min. The reaction was quenched with 3 mL of 3 M HCl at 0 °C. The layers were separated, and the aqueous layer was extracted with chloroform (3 × 5 mL). The organic layers were combined and dried over anhydrous magnesium sulfate. The dried organic layers were filtered, and the filter cake was washed with chloroform (3 × 15 mL). The solvents were removed in vacuo, and the residue was chromatographed on flash silica gel using 10% ethyl acetate/hexanes giving *N*-(1-phenyl-2,2,3-trimethyl-3-butenyl)benzylamine (2.85 mmol) in 92% yield; Table 2, entry 2): IR (neat) 3324, 3083, 3060, 3025, 2971, 2948, 2921, 2877, 2857, 2792, 1631, 1600, 1492, 1452, 1376, 1361, 1303, 1197, 1170, 1139, 1108, 1072, 1027, 898, 836, 771, 750, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.58–7.32 (m, 10 H), 5.05 (s, 2 H), 3.82–3.79 (m, 1 H), 3.75 (s, 1 H), 3.50–3.48 (m, 1 H), 1.83 (br s, 1 H), 1.77 (s, 3 H), 1.18 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 151.1, 140.8, 140.1, 129.9, 128.1, 127.4, 126.9, 126.6, 112.3, 66.3, 51.7, 43.3, 25.9, 20.3, 18.9. Anal. Calcd for $C_{20}H_{25}N$: C, 85.97; H, 9.02; N, 5.01. Found: C, 86.04; H, 9.12; N, 4.88.

***N*-(1-Phenyl-2,2,3-trimethyl-3-butenyl)aniline** (Table 2, entry 1): IR (neat) 3390, 3085, 3052, 3025, 2969, 2929, 2869, 1633, 1602, 1452, 1428, 1380, 1362, 1317, 1265, 1249, 1205, 1180, 1141, 1078, 1027, 898, 769, 748, 721, 701, 690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.56–7.38 (m, 5 H), 7.19–7.14 (m, 2 H), 6.78–6.73 (m, 1 H), 6.56–6.54 (m, 2 H), 5.16 (s, 2 H), 4.34 (s, 1 H), 4.29 (br s, 1 H), 1.92 (s, 3 H), 1.20 (s, 3 H), 1.17 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 151.3, 147.9, 140.2, 128.9, 128.8, 127.7, 126.9, 117.2, 113.2, 112.2, 63.2, 43.5, 25.9, 20.6, 19.1. Anal. Calcd for $C_{19}H_{23}N$: C, 85.99; H, 8.74; N, 5.28. Found: C, 86.02; H, 9.01; N, 5.25.

***N*-(1-Phenyl-2,2,3-trimethyl-3-butenyl)methylamine** (Table 2, entry 3): IR (neat) 3344, 3085, 3062, 3026, 2972, 2951, 2875, 2842, 2785, 1631, 1601, 1493, 1475, 1452, 1443, 1400, 1377, 1362, 1306, 1176, 1155, 1136, 1119, 1109, 1074, 1030, 987, 897, 874, 820, 773, 723 701, 621 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.36–7.22 (m, 5 H), 4.94–4.92 (m, 2 H), 3.48 (s, 1 H), 2.17 (s, 3 H), 1.83 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 151.1, 139.9, 129.7, 127.3, 126.8, 112.3, 70.3, 43.3, 35.4, 25.9, 20.2, 19.2. Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 81.33; H, 10.52; N, 6.12.

***N*-(1-Cyclohexyl-2,3,3-trimethyl-3-butenyl)aniline** (Table 2, entry 4): IR (neat) 3408, 3086, 3055, 2972, 2929, 2856, 1626, 1569, 1522, 1496, 1468, 1454, 1377, 1358, 1346, 1336, 1325, 1315, 1282, 1252, 1182, 1172, 1153, 1130, 1045, 1034, 995, 980, 920, 897, 864, 841, 744, 712, 690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.10–6.58 (m, 5 H), 5.03–5.02 (m, 1 H), 4.82–4.81 (m, 1 H), 3.27 (s, 1 H), 2.06–2.01 (m, 2 H), 1.83–1.82 (m, 3 H), 1.60–1.40 (m, 7 H), 1.13 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) 151.1,

149.0, 128.9, 116.1, 114.8, 114.2, 62.5, 48.7, 32.0, 25.8, 24.8, 23.9, 22.1. Anal. Calcd for $C_{18}H_{27}N$: C, 83.99; H, 10.57; N, 5.44. Found: C, 83.73; H, 10.49; N, 5.20.

Synthesis of *N*-Cyclohexylidenebenzylamine. The procedure reported by Tsui was followed.[16] To a 500-mL single-neck round-bottom flask fitted with a Dean-Stark condenser and equipped with a magnetic stir bar were placed aniline (0.760 mol), cyclohexanone (0.79 mmol), and toluene (100 mL) as the solvent, with stirring. The reaction mixture was heated to reflux and allowed to reflux for 16 h with the concomitant formation of water. The reaction was cooled to room temperature and the solvent, toluene, removed under reduced pressure. The residue was then vacuum distilled to give *N*-cyclohexylidenebenzylamine in a 71% yield as a yellow oil: bp = 105.0 °C at 2 mm/Hg; IR (neat) 3074, 3059, 3028, 3018, 2931, 2856, 1664, 1593, 1577, 1483, 1448, 1348, 1336, 1313, 1259, 1234, 1196, 1169, 1128, 1070, 1024, 991, 908, 816, 783, 735, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.30–7.24 (m, 2 H), 7.05–6.99 (m, 1 H), 6.73–6.70 (m, 2 H), 2.47–2.43 (m, 2 H), 2.19–2.15 (m, 2 H), 1.87–1.81 (m, 2 H), 1.68–1.59 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) 174.9, 150.7, 128.7, 122.8, 119.7, 39.3, 31.1, 27.7, 27.5, 25.6.

(16) (a) Tsui, F. P.; Chang, Y. H.; Vogel, T. M.; Zon, G. *J. Org. Chem.* **1976**, *41*, 3381. (b) Fukada, M.; Kato, M.; Seki, H.; Kawana, M.; Takeshima, T. *J. Chem. Soc., Perkin Trans. 1* **1978**, *6*, 558.

Acknowledgment. Financial support provided by the National Institutes of Health (Grant GM35153) is gratefully acknowledged.

JO941947K