Novel Cleavage of Propargylamines by Reaction with Organolithium Compounds

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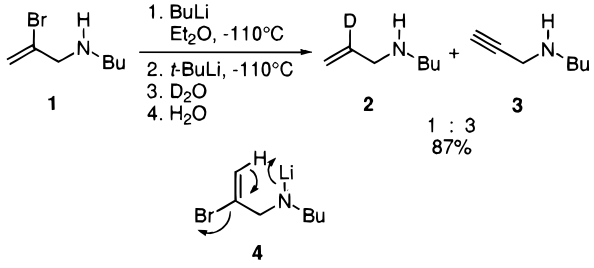
Treatment of secondary aliphatic 2-bromoallylamines with an excess of an organolithium compound led to saturated amines in which the organic group of the organolithium compound is incorporated at the α carbon. On the other hand, the successive reaction of the former amines with BuLi and *t*-BuLi between −80 °C and rt gave 1,3-diamines or hexahydropyrimidines depending on the reaction time. The formation of these unexpected products involves initial generation of lithium propargylamides, which subsequently undergo cleavage of the C propargylic−C acetylenic bond induced by the organolithium present in each case in the reaction medium. A mechanism which takes into account all the different reaction products has been proposed and additionally supported by successful trapping of dilithium acetylide.

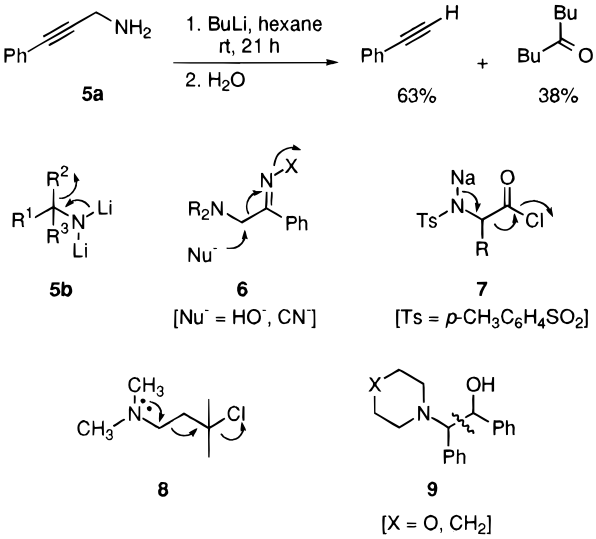
Previous studies in these laboratories showed that successive treatment of 2-bromoallylamine **1** with butyllithium (1 equiv) and *tert*-butyllithium (2 equiv) in ether at −110 °C led, after quenching with D_2O at −110 °C, to an 1:3 mixture of 2-deuterioallylamine **2** and propargylamine **3**, respectively[1] (Scheme 1). The later and major product is formed in the first step due to decomposition of the lithium amide intermediate **4** by elimination of hydrogen bromide. In an attempt to address this reaction to the formation of propargylamine **3** as the only reaction product, it was decided to carry out the experiment either with an excess of BuLi at room temperature, or as indicated in Scheme 1, but allowing the reaction mixture to achieve rt after each organolithium addition. The results of these experiments, which were absolutely unexpected, gave rise to this study; and we now report on a novel cleavage of the Cα−C*β* bond of propargylamines by the action of organolithium compounds, which led to saturated secondary amines or 1,3-diamine derivatives depending on the reaction conditions.

As far as we know, the only precedent of this cleavage reaction has been reported for primary propargylamine **5a**[2a] (Scheme 2). Analogously, lithiated primary amines **5b** having tertiary organic groups have been proposed to undergo ready C−C bond fragmentation on heating with an excess of an organolithium compound which led to formation, among several other reaction products, of α-substituted primary amines.[2b] Other related precedents to this almost unknown displacement-induced Cα−C*β* heterolytic fragmentation of lithium propargylamides in the presence of alkyllithium derivatives can be found in the case of substrates **6**−**9** shown in Scheme 2. α-Aminoacetophenone oxime derivatives **6** undergo nucleophilic substitution at the α carbon atom by strong nucleophiles with formation of benzonitrile, which represents an example of displacement-induced fragmentation.[3] The instability of α-tosylamino acid chlorides **7** in the presence of bases is interpreted in terms of a scission of the α,*β* carbon−carbon bond in the sulfonamido anion.[4] Tertiary *γ*-haloamines **8** can undergo heterolytic fragmentation under solvolytic conditions with release of an iminium ion and an olefin.[3,5] In this context, the reaction of tertiary 1,2-amino alcohols **9** with lead tetraacetate, which involves cleavage of the C−C bond by a mechanism that has been shown to proceed via the iminium ion,[6] or the photoinduced C-C bond cleavage via electron-transfer reactions of some substituted tertiary amines **9**, which

Scheme 1



Scheme 2



⊗ Abstract published in *Advance ACS Abstracts,* May 1, 1996.

(1) Barluenga, J.; Canteli, R. M.; Flórez, J. *J. Org. Chem.* **1994**, *59*, 602.

(2) (a) Richey, H. G., Jr.; Erickson, W. F. *J. Org. Chem.* **1983**, *48*, 4349. (b) Richey, H. G., Jr.; Cabré, S. *J. Org. Chem.* **1983**, *48*, 3822.

(3) Becker, K. B.; Grob, C. A. The Formation of Unsaturated Groups by Heterolytic Fragmentation. In *The Chemistry of Functional Groups*; Patai, S., Ed.; Wiley: London, 1977; Supp. A, p 653.

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(5) Grob, C. A. *Angew. Chem.* **1969**, *81*, 543; *Angew. Chem., Int. Ed. Engl.* **1969,** *8*, 535.

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Scheme 3

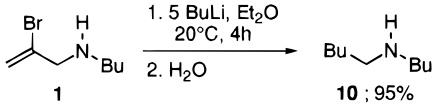
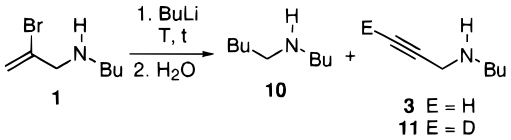


Table 1. Reaction of 1 with an Excess of Butyllithium



entry	no. eq of BuLi	*T* (°C)	*t*	product	ratio[a]	yield (%)[b]
1	5	20	4 h	**10**		95
2	5	20	15 min	**10**		97
3	5	0	1 min	**10, 3**	2:1	94
4	5	−15	5 min	**3**		55
5	5	−30	2 h	**3**		65
6	5	−80	1 h	**11**[c]		50
7	3	−80 to 20	12 h	**10**		73
8	3	−80 to 20	90 min	**10**		74
9	3	−80	30 min	**3**		74

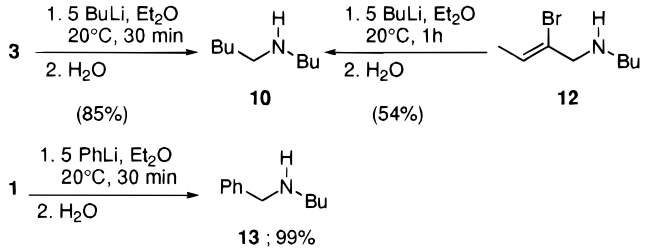
[a] Product ratio determined by ^{1}H NMR. [b] Isolated yields based on compound **1**. [c] The reaction was quenched with D_2O; degree of deuteration >95%.

leads to a neutral free radical and an iminium ion,[7] can also be included.

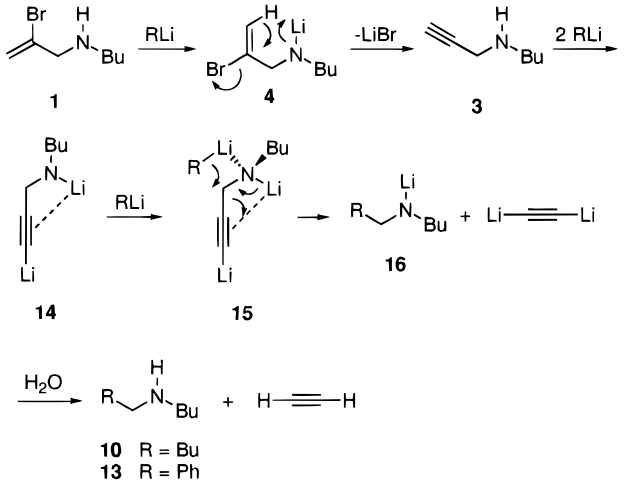
Results and Discussion

A. Reactions of 2-Bromoallylamines with Excess of Alkyllithiums. The reaction between aliphatic secondary 2-bromoallylamine **1** and butyllithium (5 equiv) at rt, unexpectedly led, after hydrolysis, to *N*-butylpentylamine (**10**) as the sole product instead of the initially foreseen propargylamine **3** (Scheme 3). In order to understand this transformation 2-bromoallylamine **1** was treated with butyllithium under several reaction conditions with variations in stoichiometry, temperature and time, and the results are presented in Table 1. The reaction of **1** with 5 equiv of BuLi is indeed very fast and after 15 min at rt the selective formation of **10** was observed almost quantitatively (entry 2). If, however, the reaction is carried out at 0 °C and quenched after 1 min a mixture of saturated amine **10** and propargylamine **3** is isolated in a 2:1 ratio respectively (entry 3). On the other hand, this treatment afforded exclusively propargylamine **3** or its deuterated derivative **11** (formed after quenching with D_2O) when the reaction was run at lower temperatures (−15, −30, −80 °C; entries 4−6). The same reaction conducted with 3 equiv of BuLi provided identical results (entries 7−9), indicating likewise, that propargylamine **3** derivatives are intermediates in the transformation of allylamine **1** to saturated amine **10**. This was proved in an independent experiment in which *N*-butylpropargylamine (**3**) was converted into amine **10** by treatment with BuLi (5 equiv) at rt (Scheme 4). Furthermore, substituted 2-bromoallylamine **12** underwent under similar experimental conditions, an analogous transformation furnishing the same saturated amine **10**. In addition, phenyllithium (5 equiv, rt) efficiently reacted with 2-bromoallylamine **1** in an analogous way to BuLi yielding *N*-butylbenzylamine (**13**).

Scheme 4



Scheme 5



The results presented here may be explained in terms of the mechanism put forth in Scheme 5. As above noticed lithium amide **4** is unstable and decomposes spontaneously, probably by intramolecular elimination of HBr, to **3**, which undergoes further dilithiation with the excess of alkyllithium present in the reaction medium to give dianion **14**. Under these reaction conditions γ-nitrogen-functionalized organolithium compound **14** is stable at low temperatures (ca. −80 to −15 °C), but at temperatures close to 0 °C or rt undergoes a subsequent heterolytic cleavage of the propargylic carbon−acetylenic carbon σ-bond with displacement of 1,2-dilithioethyne induced by a molecule of alkyllithium to furnish lithium amide **16**. Presumably, this fragmentation reaction could take place through complex **15** formed by bonding between the electron pair of the amide group and the lithium atom of the organolithium RLi as well as the possible intramolecular complexation of the triple bond π-system with the lithium amide. This complex **15** places the organolithium in the proximity of the propargylic carbon in which may be considered as an example of a CIPE process.[8] The formation of acetylene after hydrolysis was verified by trapping the 1,2-dilithioethyne with benzaldehyde, which was added to the reaction mixture before hydrolysis as shown in Scheme 6. In this reaction a nearly equimolecular amount of 1,4-diol **17** was obtained in addition to amine **10**. This result lends strong support to the above-postulated mechanism.

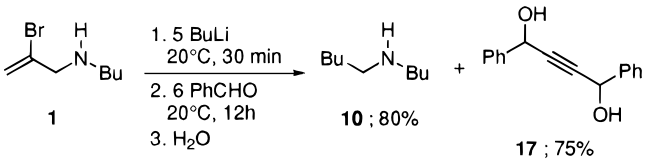
B. Reactions of 2-Bromoallylamines with BuLi and *t*-BuLi at Rt. As depicted in Scheme 7, the

(6) Gladych, J. M. Z.; Hartley, D. Polyfunctional Amines. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon: Oxford, 1979; Vol. 2, p 61.

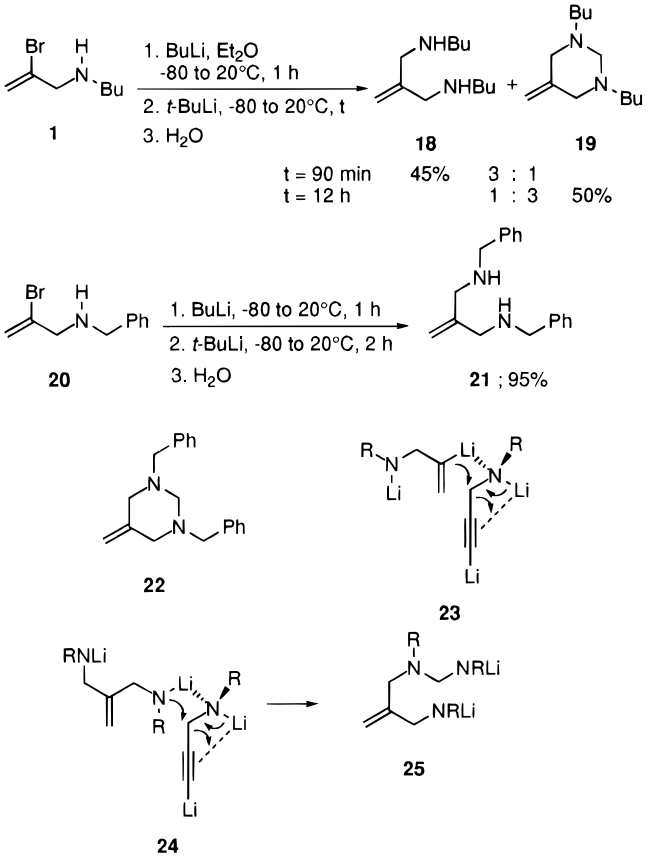
(7) Lee, L. Y. C.; Ci, X.; Giannotti, C.; Whitten, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 175.

(8) (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (b) Although the formation of free CH_2=NBu cannot be ruled out, picture **15** could be a better model for the fragmentation reaction, given that organolithium **14** is stable at rt (does not decompose by β-elimination) in the absence of any other organolithium compound.

Scheme 6

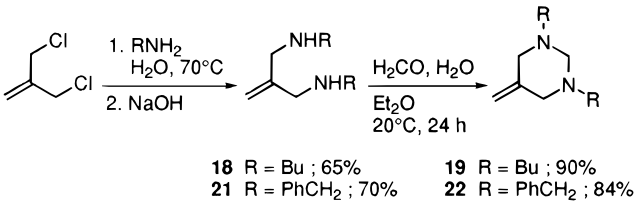


Scheme 7



successive reaction of 2-bromoallylamine **1** with BuLi (1 equiv) and *t*-BuLi (2 equiv) between −80 °C and rt yielded a mixture of compounds **18** and **19**. The ratio of these products was found to be significantly dependent on the reaction time with *t*-BuLi. Thus, 1,3-diamine **18** was the major product observed at shorter reaction times, while the hexahydropyrimidine **19** was formed as the major product on longer reaction times. Under identical conditions, 2-bromoallylamine **20** afforded exclusively 1,3-diamine **21**. In this reaction the formation of the corresponding hexahydropyrimidine **22** was not detected even after 12 h at rt with *t*-BuLi.[9] However, partial transformation of **21** to **22** occurred during silica gel column chromatography and this conversion was complete when purification of 1,3-diamine **21** was attempted by distillation (0.001 mmHg) or when a THF solution of crude **21** was refluxed for 12 h.[10] The structure of these compounds was established by ^{1}H and ^{13}C NMR spectroscopy and in the case of product **19** two-dimensional proton to carbon correlations through $^1J_{CH}$ and $^nJ_{CH}$ experiments were also carried out. Moreover, given the unexpected nature of these compounds their structures

Scheme 8



were further confirmed by comparison with authentic materials prepared from 3-chloro-2-(chloromethyl)-1-propene and the corresponding aliphatic amine[11] to give **18** and **21**, which subsequently were treated with aqueous formaldehyde[12] to yield **19** and **22** (Scheme 8).

These results are readily rationalized by invoking an analogous mechanism to the previously proposed in Scheme 5. At rt the cleavage of the lithium propargylamide generated in the reaction medium could be promoted by formation of complex **23** with the simultaneously originated vinylic organolithium compound to give 1,3-diamines **18** and **21** after hydrolysis (Scheme 7). On longer reaction times complex **24** would account for the generation of hexahydropyrimidine **19** through acyclic aminal intermediate **25**. The transformation of acyclic 1,3-diamines **18** and **21** to the corresponding cyclic diamines **19** and **22** observed in the purification process, could be attributed to the presence in the crude reaction products of some formaldehyde derivative (ca. CH_2=NR, maybe as a trimer) formed in the cleavage process.

In summary, we have found that lithium propargylamides generated *in situ* from secondary aliphatic 2-bromoallylamines either by treatment with an excess of an organolithium compound at rt or by successive reaction with a stoichiometric amount of BuLi and then *t*-BuLi between −80 °C and rt, undergo a novel C−C cleavage reaction with elimination of the corresponding lithium acetylide. This displacement-induced fragmentation led to amine derivatives, which respectively incorporate into their structure the organic group of the organolithium used as reagent or the *β*-nitrogen-functionalized vinylic organolithium compound simultaneously formed in the reaction medium. The successful trapping of dilithium acetylide with benzaldehyde provides evidence for the postulated mechanism.

Experimental Section

General. General experimental techniques and analytical measurements were applied as previously described.[1] The preparation of 2-bromoallylamines **1** and **20** was reported previously.[1] Similarly prepared was (*Z*)-2-bromo-*N*-butyl-2-butenylamine[1] (**12**) from (*Z*)-1,2-dibromo-2-butene and spectral data appear in the supporting information. PhLi was prepared according to the published procedure.[13] The level of purity of compounds is indicated by the inclusion of copies of NMR spectra presented in the supporting information.

General Procedure for the Reaction of 2-Bromoallylamines with Excess of an Alkyllithium. To a solution of the corresponding 2-bromoallylamine **1** or **12** (5 mmol) in Et_2O (30 mL) was added dropwise BuLi (2.5 M in hexane, 25 mmol or 15 mmol) or PhLi (1.25 M in ether, 25 mmol). The resulting solution was stirred at the temperature and for the time indicated in Table 1 or Scheme 4 for each particular case. The reaction mixture was hydrolyzed with H_2O and extracted with

(9) A factor which may contribute to this difference may have to do with the larger size of benzyl group compared to butyl group.

(10) The partial conversion of diamine **18** to hexahydropyrimidine **19,** although was observed in some cases upon silica gel column chromatography or during distillation (0.001 mmHg), seems to be a much less favored process.

(11) D'Amico, J. J.; Harman, M. W.; Cooper, R. H. *J. Am. Chem. Soc.* **1957,** *79*, 5270.

(12) Barluenga, J.; Olano, B.; Fustero, S. *J. Org. Chem.* **1985**, *50*, 4052.

(13) Nobis, J. F.; Moormeier, L. F. *Ind. Eng. Chem.* **1954**, *46*, 539.

ether. The organic phase was dried and concentrated in vacuo (15 mmHg), and the resulting crude material was purified by distillation (bp is given at the corresponding pressure). Yields are listed in Table 1 and Scheme 4. The following compounds were prepared according to this method.

***N*-Butylpentylamine (10)**:[14] Colorless liquid; distilled trap to trap at rt, 0.1 mmHg; ^{1}H NMR δ 0.89 (m, 6H), 1.25−1.55 (m, 11H), 2.57 (m, 4H); ^{13}C NMR δ 13.4, 20.0, 22.1, 29.1, 29.3, 31.8, 49.3, 49.6; MS *m*/*z* 143 (M^+, 4), 100 (70), 86 (100), 44 (82).

***N*-Butylpropargylamine (3)**: Colorless liquid; distilled trap to trap at rt, 0.1 mmHg; ^{1}H NMR δ 0.90 (t, J = 7.2, 3H), 1.25−1.55 (m, 4H), 1.75 (br s, 1H), 2.20 (t, J = 2.5, 1H), 2.67 (t, J = 7, 2H), 3.41 (m, 2H); ^{13}C NMR δ 14.2, 20.6, 32.1, 38.3, 48.5, 71.4, 82.5; MS *m*/*z* 111 (M^+, 2), 69 (17), 68 (100), 41 (8).

***N*-Butyl-3-deuteriopropargylamine (11)**: Colorless liquid; distilled trap to trap at rt, 0.1 mmHg; ^{1}H NMR δ 0.90 (t, J = 7.2, 3H), 1.25−1.55 (m, 4H), 1.75 (br s, 1H), 2.67 (t, J = 7, 2H), 3.41 (s, 2H); ^{13}C NMR δ 14.2, 20.6, 32.1, 38.3, 48.5, 71.4 (t, J = 39), 82.5 (t, J = 7.3); MS *m*/*z* 112 (M^+, 13), 111 (65), 110 (100), 109 (68).

***N*-Butylbenzylamine (13)**:[15] Colorless liquid; bp 69−71 °C, 0.1 mmHg; ^{1}H NMR δ 0.94 (t, J = 7.2, 3H), 1.30−1.55 (m, 4H), 1.85 (br s, 1H), 2.64 (t, J = 7.2, 2H), 3.79 (s, 2H), 7.25−7.65 (m, 5H); ^{13}C NMR δ 13.8, 20.2, 31.9, 48.9, 53.8, 126.6, 127.8, 128.1, 140.1; MS *m*/*z* 163 (M^+, 4), 120 (99), 91 (100), 65 (36).

Reaction of 3 with an Excess of Butyllithium. A solution of amine **3** (5 mmol, 0.55 g) in Et_2O (30 mL) at rt was treated with BuLi (2.5 M in hexane, 25 mmol, 10 mL) dropwise. The solution was stirred at rt for 30 min. The reaction mixture was hydrolyzed with H_2O and extracted with ether. The organic phase was dried and concentrated in vacuo (15 mmHg), and the resulting crude material was distilled trap to trap at rt under reduced pressure (0.1 mmHg) to yield 0.6 g (85%) of *N*-butylpentylamine **10**.

Reaction of 1 with Butyllithium and Benzaldehyde. To a solution of amine **1** (5 mmol, 0.96 g) in Et_2O (30 mL) at rt was added dropwise BuLi (2.5 M in hexane, 25 mmol, 10 mL). The solution was stirred at rt for 30 min. An excess of PhCHO (30 mmol, 3.18 g) was then added at rt and stirring was continued for 12 h at the same temperature. The resulting mixture was hydrolyzed with H_2O and extracted with ether. The organic phase was dried and concentrated in vacuo. From the resulting crude material 0.57 g (80%) of amine **10** was obtained by trap to trap distillation (0.1 mmHg). The corresponding residue was purified by flash column chromatography (CH_2Cl_2/THF, 30:1) to give 0.89 g (75%) of diol **17**.

1,4-Diphenyl-2-butyne-1,4-diol (17): White solid; R_f 0.28 (CH_2Cl_2/THF, 30:1); ^{1}H NMR δ 4.80−5.20 (broad signal, 2H), 5.45 (s, 2H), 7.25−7.55 (m, 10H); ^{13}C NMR δ 68.7, 85.9, 126.4, 127.8, 128.1, 140.2; MS *m*/*z* 238 (M^+, 25), 220 (42), 105 (100), 77 (62).

(14) Elderfield, R. C.; Hageman, H. A. *J. Org. Chem.* **1949**, *14*, 605.
(15) Bortnick, N.; Luskin, L. S.; Hurwitz, M. D.; Craig, W. E.; Exner, L. J.; Mirza, J. *J. Am. Chem. Soc.* **1956**, *78*, 4039.

General Procedure for the Reaction of 2-Bromoallylamines with BuLi and *t*-BuLi at Rt. To a solution of the corresponding 2-bromoallylamine **1** or **20** (5 mmol) in ether (30 mL) cooled at −80 °C was added dropwise BuLi (2.5 M in hexane, 5 mmol). The resulting solution was stirred for 30 min at −80 °C and then 30 min at rt. After the solution was cooled again to −80 °C, *t*-BuLi (1.7 M in pentane, 10 mmol) was added. The mixture was stirred for 1−12 h (the reaction time for each case is indicated in Scheme 7); allowing the temperature to reach rt. The reaction mixture was hydrolyzed with H_2O and extracted with ether. The organic phase was dried and concentrated in vacuo, and the resulting crude material was purified by distillation (in this case bp is given at the corresponding pressure) or flash column chromatography (in this case R_f is reported with the eluent solvent used in the column). The following compounds were prepared according to this method.

***N,N′*-Dibutyl-2-methylene-1,3-propanediamine (18):** Yellow oil; bp 67−69 °C, 0.1 mmHg; ^{1}H NMR δ 0.89 (t, J = 7, 6H), 1.25−1.55 (m, 8H), 1.75 (br s, 2H), 2.56 (t, J = 7.2, 4H), 3.24 (s, 4H), 4.99 (s, 2H); ^{13}C NMR δ 13.9, 20.4, 32.1, 49.0, 53.6, 111.5, 145.9; MS *m*/*z* 198 (M^+, <1), 125 (100), 82 (56).

***N,N′*-Dibenzyl-2-methylene-1,3-propanediamine (21):** Colorless oil; R_f 0.28 (CH_3OH); ^{1}H NMR δ 1.95 (br s, 2H), 3.33 (s, 4H), 3.78 (s, 4H), 5.1 (s, 2H), 7.3 (m, 10H); ^{13}C NMR δ 52.8, 53.1, 112.2, 126.8, 128.0, 128.2, 140.2, 145.6.

***N,N′*-Dibutyl-5-methylenehexahydropyrimidine (19):** Colorless oil; R_f 0.50 (hexane/THF, 5:1); ^{1}H NMR δ 0.83 (t, J = 7, 6H), 1.15−1.45 (m, 8H), 2.30 (t, J = 7.2, 4H), 3.05 (s, 4H), 3.25 (s, 2H), 4.76 (s, 2H); ^{13}C NMR δ 13.8, 20.3, 29.2, 53.6, 58.1, 74.1, 110.2, 139.6; MS *m*/*z* 210 (M^+, 17), 209 (100), 98 (30).

***N,N′*-Dibenzyl-5-methylenehexahydropyrimidine (22):** Colorless oil; R_f 0.41 (hexane/AcOEt, 10:1); ^{1}H NMR δ 3.20 (s, 4H), 3.45 (s, 2H), 3.63 (s, 4H), 4.88 (s, 2H), 7.30 (m, 10H); ^{13}C NMR δ 57.7, 57.9, 73.4, 111.0, 126.8, 128.0, 128.9, 138.3, 139.4; MS *m*/*z* 278 (M^+, 25), 277 (100), 91 (92).

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Supporting Information Available: Analytical data of **12** and copies of ^{1}H and ^{13}C NMR spectra of **3, 10, 11, 13, 17**−**19**, **21** and **22** (10 pages). This material is contained in 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.

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