Metalloaldimines. 4. Reaction of Lithium Aldimines with Carbonyl Compounds and with Activated Alkyl Halides[1,2]

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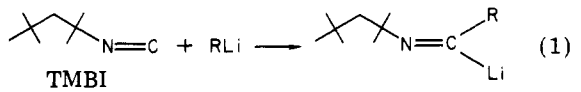
Lithium aldimines, acyl anions derived from isocyanides and organolithium reagents, add to aldehydes to give, after quenching with water, α-amino ketones. These products result from an Almadori rearrangement of the α-hydroxy imine precursor. The intermediate alkoxides are trapped by trimethylsilyl chloride to give α-trimethylsiloxy imines. Lithium aldimines add exclusively 1,2 to acrolein but add exclusively 1,4 to methyl acrylate. Hydrolysis of these imine products gives the corresponding carbonyl compounds. Lithium aldimines also couple with benzyl bromide to give upon hydrolysis the benzyl ketone. Coupling of lithium aldimines with allyl bromide yields an *E,Z* mixture of α,β-unsaturated imines.

Lithium aldimines (1) are useful synthetic intermediates prepared by the addition of organolithium reagents (eq 1, R = cyclic or acyclic aliphatic) to 1,1,3,3-tetramethylbutyl



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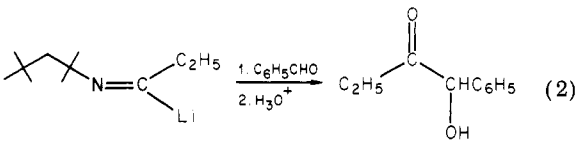
isocyanides (TMBI). Lithium aldimines were shown to react with a wide range of electrophiles, including primary alkyl halides, carbon dioxide, ethyl chloroformate, and benzaldehyde.[3] We now report further studies on the reactivity of lithium aldimines with other carbonyl compounds and with allyl and benzyl halides.

The reaction of ethyl lithium aldimine with benzaldehyde gave an 81% yield of 1-hydroxy-1-phenylbutanone after acid hydrolysis (eq 2). The imine intermediate was not isolated. The addition of lithium aldimines to enolizable aldehydes and ketones was not successful in earlier work.[3]



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Results and Discussion

Addition of a lithium aldimine (1) to enolizable aldehydes is achieved by the inverse addition of the lithium aldimine solution at −78 °C to a solution of the aldehyde at −78 °C (Scheme I, Table I).

Addition of *tert*-butyllithium aldimine 1 (R = *t*-Bu) to pentanal gives alkoxide 2, but quenching with water gives a 58% yield of α-amino ketone 3. Alkoxide 2 is trapped by treatment with trimethylsilyl chloride to give a 58% yield of α-siloxy imine 4. α-Hydroxy ketone 5 is readily obtained by hydrolysis of α-siloxy imine 4 by steam distillation from oxalic acid (45% overall yield).

Scheme I. Reaction of Lithium Aldimines with Aldehydes

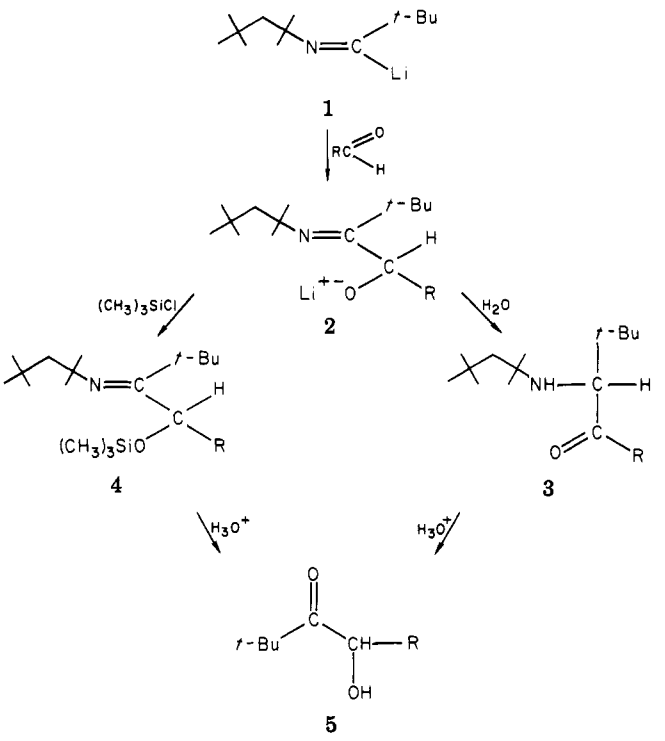

Table I. Reaction of Lithium Aldimines with Aldehydes

	R (aldehyde)	% yield 3	4	5
a	*n*-butyl (pentanal)	58	58	45
b	phenyl (benzaldehyde)	54	57	
c	vinyl (acrolein)	47	46	21

α-Amino ketone 3 results from a double tautomerization of α-hydroxy imine 6 formed initially after quenching the reaction with water. Imine 6 isomerizes to enolamine 7 (eq 3) which in turn tautomerizes to the observed product. An analogous reaction has been observed in the rearrangement of a glycosylamine to an amino sugar and is referred to as the Amadori rearrangement.

Double tautomerization also occurs in the product from the condensation of 1 with benzaldehyde. α-Amino ketone 3 is formed in 54% yield upon quenching of the reaction with water while trapping with trimethylsilylchloride gives a 57% yield of α-siloxy imine 4. Acid hydrolysis of either 3 or 4 leads to the formation of 5. In our early work[3] no

(1) Support of this work by a grant from the National Science Foundation is gratefully acknowledged.

(2) Previous paper in this series: Marks, Maurice J.; Walborsky, Harry M. *J. Org. Chem.*, in press.

(3) Niznik, G. E.; Morrison, W. H.; Walborsky, H. M. *J. Org. Chem.* **1974**, *39*, 600.

(4) We are grateful to a reviewer who directed our attention to this earlier work. Amadori, M. *Atti. Accad. Naz. Lincei, Cl. Sci. Fis. Mat. Nat. Rend.* **1925**, *2* (6), 337; **1929**, *9* (6), 68, 226. For a review see: Lemieux, R. U. In "Molecular Rearrangements"; de Mayo, P., Ed.; Wiley: New York, 1964; Part 2, p 753.

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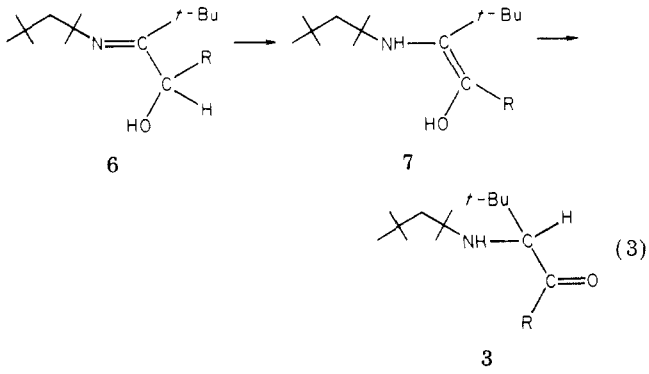

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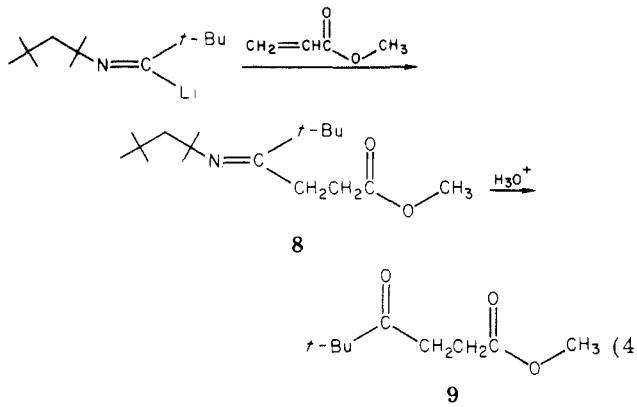
attempt was made to isolate intermediate products, but instead the reaction mixture was subjected to acid hydrolysis after quenching with water. Therefore, only the α-hydroxy ketone was observed as the product of the reaction.

Addition of a lithium aldimine (1) to acrolein occurs exclusively 1,2 to yield alkoxide **2** which after quenching of the reaction with water undergoes double tautomerization to give 2-amino enone **3** in 47% yield (Scheme I, R = CH_2=CH). Trapping with trimethylsilyl chloride gives a 46% yield of α-siloxy imine **4**. The sensitive α-hydroxy β,γ-enone **5** is obtained in 21% overall yield from steam distillation of **4** from aqueous oxalic acid followed by treatment with acetic acid in methanol to remove the byproduct hexamethyldisiloxane.

tert-Butyllithium aldimine 1 (R = *t*-Bu) adds 1,4 to methyl acrylate to give a 39% yield of γ-imino ester **8** (eq 4). The imino group is selectively hydrolyzed by aqueous



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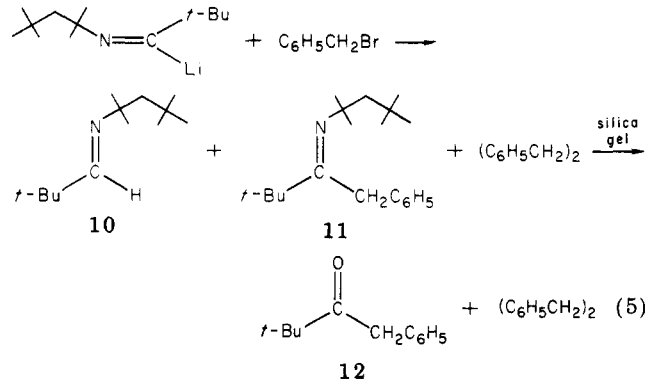
ammonium chloride in THF to give γ-keto ester **9** in 35% overall yield. The major side reaction is polymerization of methyl acrylate. No addition of the lithium aldimine occurs to α- or β-substituted acrylates or to acrylonitrile.

Lithium aldimines do not add to enolizable ketones or α,β-unsaturated enones, even on using the inverse addition technique. Proton abstraction by **1** occurs exclusively.

The reaction of lithium aldimines with activated alkyl halides was found to be of little synthetic value. The coupling of benzyl bromide with lithium aldimines (1) yields aldimine[2] **10** (ca. 50% yield) and a mixture of bibenzyl and benzyl imine **11** (eq 5). Bibenzyl and benzyl imine **11** codistilled; separation of these compounds by column chromatography on silica gel occurred with hydrolysis to give bibenzyl (23%) and benzyl ketone **12** (22%).

The reaction of *tert*-butyllithium aldimine 1 (R = *t*-Bu) with allyl bromide does not give the expected β,γ-unsaturated imine **13**, but produces a mixture of the *E* and *Z* α,β-unsaturated imine isomers **14** (eq 6). The β,γ-unsaturated isomer **13** is presumably rapidly isomerized to **14** by deprotonation at the methylene carbon by *tert*-butyl-



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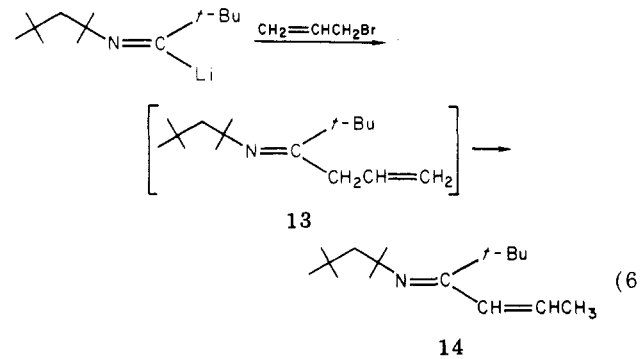
lithium aldimine 1 (R = *t*-Bu). Again the major byproduct is aldimine **10**.



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Although lithium aldimines undergo a number of useful reactions, some of which are unique among acyl anion equivalents, their high basicity limits their utility as synthetic intermediates.

Experimental Section

Melting points were determined with a Mel-Temp apparatus and open capillaries. Melting points and boiling points are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Model 257 spectrophotometer; band positions are reported in wave numbers (cm^{-1}). Nuclear magnetic resonance spectra were obtained on a JEOL C-60-HL Model spectrometer (proton). Microanalyses were performed by Beller Laboratories.

Quantitative GLC analyses were performed on a Hewlett-Packard Model 571A gas chromatograph (thermal-conductivity detector with helium as the carrier gas) by using packed columns (15% Lexan on acid-washed 60/80 Chromosorb P, 10 ft × $^1/_8$ in.). Thin-layer chromatography (TLC) was performed by using glass plates coated with Merck silica gel 60 PF-254 + 366. Column chromatography was carried out by using silica gel 60 F_{254} (70–230 mesh, E. Merck No. 10757).

All bulk solvents were distilled before use. Tetrahydrofuran (THF) and diethyl ether were dried by being refluxed and distilled from sodium benzophenone dianion. Hexane and cyclohexane were dried by being refluxed and distilled from phosphorous pentoxide.

1,1,3,3-Tetramethylbutyl isocyanide (TMBI) was prepared according to the procedure of Niznik and Walborsky.[5] *tert*-Butyllithium and *n*-butyllithium, purchased from Aldrich Chemical Co., were titrated before use.[6]

All glassware was flame-dried under nitrogen before use. Syringes, needles and pipets were dried in a 110 °C oven before use.

2,2-Dimethyl-3-[(2,4,4-trimethyl-2-pentyl)amino]-4-octanone (3a). A solution of 5 mmol of *tert*-butyllithium aldimine 1 (R = *t*-Bu) in 20 mL of THF at −70 °C was added to a solution of 0.53 mL (0.43 g, 5 mmol) of pentanal in 20 mL of THF at −70 °C. After 1 h at −70 °C, 10 mL of water was added, and the

(5) Niznik, G. E.; Morrison, W. H., III; Walborsky, H. M. *Org. Synth.* **1971**, *51*, 31.
(6) Eppley, R. L.; Dixson, J. A. *J. Organomet. Chem.* **1967**, *8*, 1976.

mixture was extracted with diethyl ether. The organic layer was separated, dried (Na_2SO_4 and $MgSO_4$), and evaporated (standard workup) to give 0.83 g (58%) of the distilled ketone: bp 95–97 °C (0.05 mm); IR (neat) 3300 (w), 1705, 1660 (m), 1470, 1370, 1230 cm^{-1}; ^1H NMR (CCl_4) δ 0.7–1.55 (3 s and m, 33), 1.85 (s, 1), 2.4 (m, 2), 2.88 (s, 1).

Anal. Calcd for $C_{18}H_{37}NO$: C, 76.24; H, 13.15; N, 4.96. Found: C, 76.45; H, 13.05; N, 4.93.

2-[[2,2-Dimethyl-4-(trimethylsiloxy)-3-octylidene]amino]-2,4,4-trimethylpentane (4a). A solution of 5 mmol of the *tert*-butyllithium aldimine 1 (R = *t*-Bu) in 20 mL of THF at −70 °C was added to a solution of 0.53 mL (0.43 g, 5 mmol) of pentanal in 20 mL of THF at −70 °C. After 1 h at −70 °C, 0.70 mL (0.6 g, 5.5 mmol) of trimethylsilyl chloride was added. After 30 min of gradual warming, a standard workup gave 1.02 g (58%) of the distilled ketimine: bp 108–110 °C (0.25 mm); IR (neat) 1640 (m), 1260, 1090, 850 cm^{-1}; ^1H NMR (CCl_4) δ 0.12 (s, 9), 0.80–1.56 (m and 3 s, 35), 4.60–4.85 (m, 1).

Anal. Calcd for $C_{21}H_{45}NOSi$: C, 70.91; H, 12.75; N, 3.94. Found: C, 71.02; H, 12.79; N, 3.84.

2,2-Dimethyl-4-hydroxy-3-octanone (5a). Hydrolysis of 1.02 g of **5** was accomplished by steam distillation from oxalic acid followed by treatment with 50% acetic acid in refluxing methanol (for 30 min). Extraction with diethyl ether, drying (Na_2SO_4), and evaporation gave 0.4 g (81%, 45% overall) of the hydroxy ketone: bp 85 °C (1 mm, bulb to bulb); IR (neat) 3480, 1700, 1480, 1470, 1370, 1060 cm^{-1}; ^1H NMR (CCl_4) δ 0.85–1.65 (m), 1.15 (s, 18), 3.41 (s, 1), 4.44 (m, 1).

Anal. Calcd for $C_{10}H_{20}O$: C, 69.72; H, 11.70. Found: C, 69.99; H, 11.85.

3,3-Dimethyl-2-[(2,4,4-trimethyl-2-pentyl)amino]-1-phenyl-1-butanone (3b). To a solution of 20 mmol of the *tert*-butyllithium aldimine 1 (R = *t*-Bu) was added at −70 °C a solution of 2.03 mL (2.12 g, 20 mmol) of benzaldehyde in 10 mL of THF. After 1 h of gradual warming, a standard workup gave 3.3 g (54%) of the distilled ketone which crystallized on standing. Recrystallization from chloroform gave colorless needles: mp 57–60 °C; IR ($CHCl_3$) 3310 (w), 1660 (m), 1370, 990 (m), 840 (m); ^1H NMR ($CDCl_3$) δ 0.90 (s, 9), 1.03 (s, 9), 1.20 (s, 6), 1.4 (s, 2), 2.2 (s, 1), 4.10 (s, 1), 7.50–8.20 (m, 5).

Anal. Calcd for $C_{20}H_{33}NO$: C, 79.15; H, 10.96; N, 4.61. Found: C, 79.28; H, 10.98; N, 4.5.

2-[[3,3-Dimethyl-1-phenyl-1-(trimethylsiloxy)-2-butylidene]amino]-2,4,4-trimethylpentane (4b). To a solution of 10 mmol of the *tert*-butyllithium aldimine 1 (R = *t*-Bu) in 20 mL of THF at −70 °c was added 1.01 mL (1.06 g, 10 mmol) of benzaldehyde. After 1 h at −70 °C, 1.4 mL (1.20 g, 11 mmol) of trimethylsilyl chloride was added. After 30 min of gradual warming, a standard workup gave 2.13 g (57%) of distilled ketimine: bp 115–117 °C (0.15 mm); IR (neat) 1640 (m), 1260, 1080, 900, 840 cm^{-1}; ^1H NMR (CCl_4) δ 0.26 (s, 9), 0.84 (s, 3), 1.00 (s, 6), 1.06 (s, 9), 1.33 (s, 6), 1.65 (s, 2), 5.94 (s, 1), 7.15 (s, 5).

Anal. Calcd for $C_{23}H_{41}NOSi$: C, 73.53; H, 11.00; N, 3.73. Found: C, 73.52; H, 11.11; N, 3.80.

2,2-Dimethyl-3-[(2,4,4-trimethyl-2-pentyl)amino]-hex-5-en-4-one (3c). To a solution of 5 mmol of the *tert*-butyllithium aldimine 1 (R = *t*-Bu) in 20 mL of THF at −70 °C was added 0.34 mL (0.28 g, 5 mmol) of acrolein. After 30 min at −70 °C, 10 mL of water was added. A standard workup gave 0.6 g (47%) of distilled enone: bp 85–87 °C (0.2 mm); IR (neat) 1700, 1620 (m), 1370 cm^{-1}; ^1H NMR (CCl_4) δ 0.85–1.12 (m, 6), 0.88 (s, 9), 1.00 (s, 9), 1.30 (s, 2), 2.00 (s, 1), 3.15 (s, 1), 5.60 (dd, J = 2.5, 9 Hz, 1), 5.94–6.80 (m, 2).

Anal. Calcd for $C_{16}H_{29}NO$: C, 76.44; H, 11.63; N, 5.57. Found: C, 76.37; H, 11.77; N, 5.74.

2-[[2,2-Dimethyl-4-(trimethylsiloxy)-3-hex-5-en-3-ylidene]amino]-2,4,4-trimethylpentane (4c). To a solution of 10 mmol of the *tert*-butyllithium aldimine 1 (R = *t*-Bu) in 25 mL of THF at −70 °C was added 0.68 mL (0.56 g, 10 mmol) of acrolein. After 2 h at −70 °C, 1.4 mL (1.20 g, 11 mmol) of trimethylsilyl chloride was added. After 30 min of gradual warming, a standard workup gave 1.49 g (46%) of the distilled ketimine: bp 84–87 °C (0.1 mm); IR (neat) 1650 (m), 1260, 890, 840 cm^{-1}; ^1H NMR (CCl_4) δ 0.20 (s, 9), 1.00 (s, 9), 1.10 (s, 9), 1.30 (s, 6), 1.70 (s, 2), 5.10–5.62 (m, 3), 5.85 (d, J = 5 Hz, 1).

Anal. Calcd for $C_{19}H_{37}NOSi$: C, 70.52; H, 11.53; N, 4.33. Found: C, 70.33; H, 11.50; N, 4.47.

2,2-Dimethyl-4-hydroxyhex-5-en-3-one (5c). Hydrolysis of 1.49 g of **4c** by steam distillation from oxalic acid gave a mixture of hydroxy ketone and hexamethyldisiloxane. This mixture was dissolved in 20 mL of methanol and treated with 5 mL of glacial acetic acid and 5 mL of water. After the mixture was refluxed for 30 min, the organic layer was separated, dried (Na_2SO_4), and evaporated to give 0.3 g (46%, 21% overall) of the hydroxy ketone: bp 58–60 °C (1 mm); IR (neat) 3450, 1710, 1490, 1370, 1000 cm^{-1}; ^1H NMR (CCl_4) δ 1.15 (s, 9), 3.56 (br s, 1), 4.97 (d, J = 6 Hz, 1), 5.18–6.00 (m, 3).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.67; H, 10.00.

2-[[5-(Carbomethoxy)-2,2-dimethyl-3-pentylidene]amino]-2,4,4-trimethylpentane (8). To a solution of 5 mmol of the *tert*-butyllithium aldimine 1 (R = *t*-Bu) in 20 mL of THF at −70 °C, was added 0.45 mL (0.43 g, 5 mmol) of methyl acrylate. After 30 min at −70 °C, 10 mL of water was added. Standard workup gave 1.1 g (39%) of distilled ketimine: bp 123–125 °C (0.2 mm); IR (neat) 1740, 1640 (m), 790 cm^{-1}; ^1H NMR (CCl_4) δ 0.96 (s, 9), 1.1 (s, 9), 1.25 (s, 6), 1.56 (s, 2), 2.10–2.85 (m, 4), 3.56 (s, 3).

Anal. Calcd for $C_{17}H_{31}NO_2$: C, 72.55; H, 11.10; N, 4.98. Found: C, 72.26; H, 11.12; N, 4.67.

Methyl 5,5-Dimethyl-4-oxohexanoate (9). Hydrolysis of 1.1 g of **8** with 20 mL of saturated ammonium chloride in 50 mL of THF at the reflux for 1 h gave 0.3 g (67%, 35% overall) of the keto ester: bp 100–103 (1.0 mm) [lit.[7] bp 180 °C (9 mm)]; IR (neat) 1740, 1720 cm^{-1}; ^1H NMR (CCl_4) δ 1.15 (s, 9), 1.5–2.95 (m, 4), 3.6 (s, 3).

2,2-Dimethyl-4-phenyl-3-butanone (12). To a solution of 20 mmol of the *tert*-butyllithium aldimine 1 (R = *t*-Bu) in 50 mL of THF at −70 °C was added a solution of 2.4 mL (3.4 g, 20 mmol) of benzyl bromide in 15 mL of THF. After 1 h of gradual warming, a standard workup gave a mixture of three compounds (TLC and GLC). Vacuum distillation gave 1.8 g (46%) of the *tert*-butyllithium aldimine and a mixture of two compounds, bp 85–93 °C (0.05 mm). This mixture was indicated by its spectral properties (IR 1650 cm^{-1}) to contain the benzyl ketimine. Column chromatography on 50 g of silica gel with hexane as the eluant gave 0.4 g (22%) of bibenzyl [mp 48–50 °C (lit.[8] mp 50–53 °C); ^1H NMR (CCl_4) δ 2.8 (s, 2), 7.2 (s, 5)] and 0.8 g (23%) of the ketone, bp 63–67 °C (0.2 mm) [lit.[9] bp 65–66 °C (0.2 mm)].

(*E*,*Z*)-3-[(2,2-Dimethyl-4-ene-3-hexylidene)amino]-2,4,4-trimethylpentane (14). To a solution of 20 mmol of the *tert*-butyllithium aldimine 1 (R = *t*-Bu) in 50 mL of THF at −70 °C was added 1.76 mL (2.40 g, 20 mmol) of allyl bromide. After 1 h of gradual warming, a standard workup gave 2.2 g (46%) of the distilled ketimines: bp 74 °C (0.55 mm); IR (neat) 1660 (m), 1640 (m), 1490, 1380, 1240, 980 (m) cm^{-1}; ^1H NMR (CCl_4) δ 0.94 (s, 9), 1.00 (s, 9), 1.15 (s, 6), 1.53 (s, 2), 1.64 (d, J = 1.5 Hz, 1.5), 1.8 (d, J = 1.5 Hz, 1.5), 5.0–6.0 (m, 2).

Anal. Calcd for $C_{16}H_{31}N$: C, 80.94; H, 13.16; H, 5.90. Found: C, 80.89; H, 13.16; N, 5.90.

Registry No. 1 (R = *t*-Bu), 79618-24-9; **3a**, 79593-96-7; **3b**, 79593-97-8; **3c**, 79593-98-9; **4a**, 79593-99-0; **4b**, 79594-00-6; **4c**, 79594-01-7; **5a**, 79594-02-8; **5c**, 79594-03-9; **8**, 79594-04-0; **9**, 34553-32-7; **10**, 49707-49-5; **11**, 79594-05-1; **12**, 6721-67-1; (*E*)-**14**, 79594-06-2; (*Z*)-**14**, 79594-07-3; pentanal, 110-62-3; benzaldehyde, 100-52-7; acrolein, 107-02-8; methyl acrylate, 96-33-3; benzyl bromide, 100-39-0; bibenzyl, 103-29-7; allyl bromide, 106-95-6.

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