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Regioselective α-alkylation of ketones with alkyl chlorides and fluorides via highly nucleophilic magnesium enamides

Takuji Hatakeyama,[a] Shingo Ito,[b] Hiroaki Yamane,[a] Masaharu Nakamura[a,*] and Eiichi Nakamura[b,*]

[a]*International Research Center for Elements Science, Institute for Chemical Research, Kyoto University, Uji, Kyoto, 611-0011, Japan*
[b]*Department of Chemistry, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*

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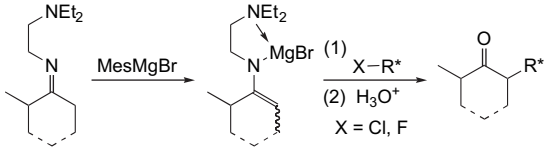
Abstract—A magnesium enamide derived from *N*-2-(*N*′,*N*′-dimethylamino)ethyl imine reacts with primary and secondary alkyl chlorides and fluorides to give an α-alkylated ketone in good to excellent yields upon hydrolysis of the imine moiety. Reactions of the highly nucleophilic magnesium enamide derived from an unsymmetrical ketone take place regioselectively. In addition, the C–C bond formation is stereospecific: a substantial inversion of stereochemistry at the electrophilic carbon center (Walden inversion) was observed, proving its potential utility for the production of optically active compounds.

1. Introduction

Alkylation of a ketone by nucleophilic substitution of an alkyl halide with a metal enolate is a fundamental reaction in organic chemistry.[1] Significant advance was recorded in the 1960's through development of the chemistry of metalloenamines,[2] lithium enolates,[3] and enol silyl ethers.[4] Despite such efforts, problems have remained unsolved since then. For example, the scope of the alkyl halides to be used for intermolecular ketone alkylation has been limited largely to primary alkyl iodides and bromides, and benzylic and allylic chlorides.[5] Regioselectivity in the alkylation of an unsymmetrical ketone is another problem, for example, as we addressed in the 1970's in the course of the fluoride anion promoted reaction between silyl enol ethers and alkyl halides.[4b,c] The regioselectivity of the deprotonation of an unsymmetrical ketone is an additional, underlying issue for the regioselectivity of the α-alkylation reaction.[6] We report here that a magnesium enamide bearing an internal nitrogen coordination site significantly expands the scope of the alkyl halides, allowing the use of alkyl chlorides and fluorides as effective alkylating reagents (Scheme 1).[7] The reaction often takes place regioselectively, and the the S_N2 substitution on the alkyl halide occurs largely with Walden inversion.



Scheme 1. Alkylation of a magnesium enamide derived from *N*-2-(*N*′,*N*′-dimethylamino)ethyl imine with an alkyl chloride or fluoride. Mes represents a 2,4,6-trimethylphenyl group.

2. Results and discussion

2.1. Optimization of the enamide structure and the metal cation

In our previous studies on the addition reaction of a zinc enamide with an olefin,[8,9] we found that the nitrogen substituent on the metal enamide plays a key role for tuning the reactivity and the thermal stability of the nucleophile. Screening of a variety of combinations of the nitrogen substituent and the metal cation in the S_N2 alkylation reaction has been carried out (Chart 1 and Table 1). Thus the reaction between chlorocycloheptane and a variety of metal enamides derived from a 3-pentanone in THF was studied under various conditions as shown in Table 1. The deprotonation of the imine was achieved by treatment with 2,4,6-trimethylphenylmagnesium bromide (MesMgBr) or in a case with *t*-BuMgCl.

We found that the magnesium enamide bearing a 2-(*N*,*N*-diethylamino)ethyl group (entry 1; **1a**) is the best reagent for

* Corresponding authors. Tel.: +81 774 38 3180; fax: +81 774 38 3186 (M.N.); tel./fax: +81 3 5841 4356 (E.N.); e-mail addresses: masaharu@scl.kyoto-u.ac.jp; nakamura@chem.s.u-tokyo.ac.jp

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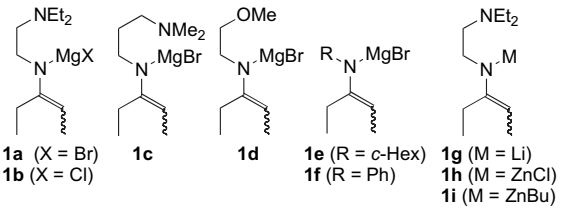
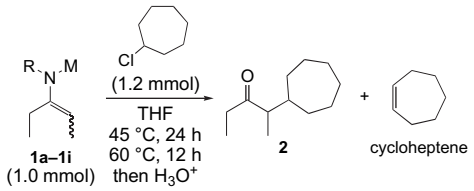


Chart 1. Metal enamides examined for optimization.

Table 1. Screening of the nitrogen substituent and the metal cation



Entry	Metal enamide	Product yield[a] (%)		Recovery of c-$C_7H_{13}Cl$ (mmol)
		2	Cycloheptene	
1	**1a**	88	11	0.25
2[b]	**1a**	69	10	0.34
3	**1b**	60	13	0.35
4	**1c**	79	17	0.29
5	**1d**	4	7	0.85
6[b]	**1e**	47	8	0.66
7	**1e**	51	9	0.60
8	**1f**	1	4	1.07
9	**1g**	23	44	0.41
10	**1h**	21	4	0.95
11	**1i**	3	3	1.03

[a] Yields of **2** and cycloheptene, and recovery of the starting chlorocycloheptane were determined by GC analysis with octane as an internal standard.
[b] The reaction was carried out at 45 °C for 24 h.

the alkylation,[10] and that it gives the desired secondary alkylated ketone **2** in 88% yield after reaction at 45 °C and 60 °C and removal of the imine moiety by acidic workup. The reaction accompanied the formation of cycloheptene in 11% yield suggesting competitive dehydrohalogenation. Lower temperature did not lead to completion of the reaction (e.g., after 24 h at 45 °C, 69% yield of **2**, entry 2). The same enamide possessing a MgCl counter cation (entry 3; **1b**, prepared by imine deprotonation with *t*-BuMgCl) gave the product in lower yield (60%).

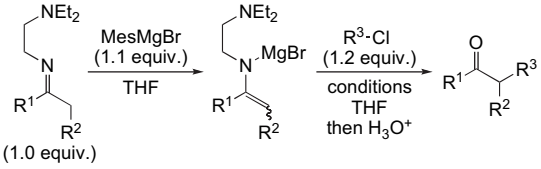
We found then that 3-(*N*,*N*-dimethylamino)propyl reagent **1c** is less nucleophilic than **1a** and gives **2** in 79% yield and cycloheptene (17%, entry 4). The reaction of 2-methoxyethyl reagent **1d** was sluggish and gave the alkylation product only in 4% yield (entry 5). Metal enamides without any chelating side chain behave rather differently. The Stork's original imine, the *N*-cyclohexyl compound **1e** (entry 6), gave **2** in 47% yield after 24 h at 45 °C, and heating at 60 °C did not improve the yield very much (51%, entry 7). The *N*-phenyl compound **1f** (entry 8) was entirely unreactive and gave **2** in only 1% yield. The lithium variant **1g** gave a 1:2 mixture of **2** and cycloheptene (entry 9). The zinc enamides **1h** and **1i** are very unreactive under the same conditions, (entries 10 and 11).

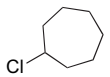
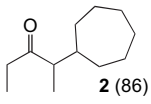
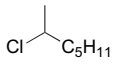
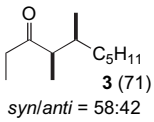
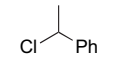
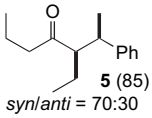
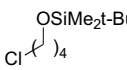
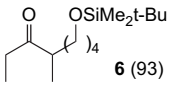
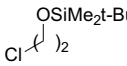
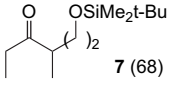
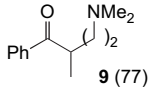
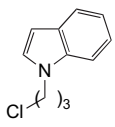
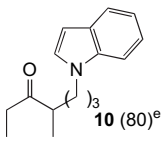
2.2. Alkylation with alkyl chlorides

Having recognized the high nucleophilic reactivity of **1a**, possessing the 2-(*N*,*N*-diethylamino)ethyl group, we investigated the reaction with various alkyl chlorides to examine the scope of the method (Table 2). Entries 1–3 illustrate the viability of the use of secondary alkyl chlorides. The reaction of 2-chloroheptane with **1a** took place in 71% yield to give the product **3**, where we observed a 58:42 *syn*/*anti* diastereoselectivity as to the two secondary carbon centers created by the reaction (entry 2). The acyclic chloride, (1-chloroethyl)benzene, reacted much faster to give the product **5** in 85% yield with a 70:30 *syn*/*anti* selectivity (entry 3). It is yet to be determined if the stereoselectivity is of kinetic or thermodynamic origin.

Certain functionalities can be tolerated under the reaction conditions (entries 4–7). A *tert*-butyldimethylsilyloxy group

Table 2. Alkylation of magnesium enamides with alkyl chlorides



Entry[a]	Enamide	R^3–Cl	Conditions	Product yield[b] (%)
1	**1a**		45 °C, 24 h 60 °C, 12 h	 **2** (86)
2	**1a**		45 °C, 24 h 60 °C, 12 h	 **3** (71) *syn*/*anti* = 58:42
3[c]	 **4**		30 °C, 24 h 50 °C, 12 h	 **5** (85) *syn*/*anti* = 70:30
4	**1a**		50 °C, 24 h 65 °C, 12 h	 **6** (93)
5	**1a**		50 °C, 24 h 65 °C, 12 h	 **7** (68)
6[d]	 **8**		50 °C, 36 h	 **9** (77)
7	**1a**		50 °C, 24 h 65 °C, 12 h	 **10** (80)[e]

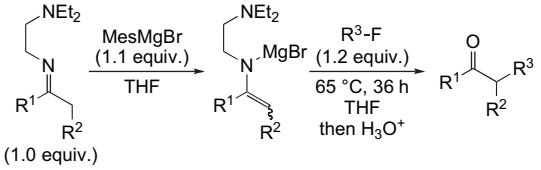
[a] The reaction was carried out in THF (ca. 0.8 M for enamide) on 1.0–2.2-mmol scale unless otherwise noted.
[b] Isolated yield based on imine used.
[c] The use of 1.5 equiv of alkyl chloride.
[d] Enamide **8** (1.4 equiv for alkyl chloride) was prepared by using *t*-BuMgCl. We used a hydrochloric acid salt of the aminoalkyl chloride and used an excess *t*-BuMgCl to prepare in situ the free amine. Yield was determined by GC analysis on the basis of the alkyl chloride.
[e] Double alkylated product was also obtained in 8% yield.

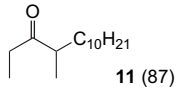
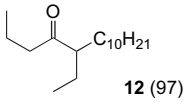
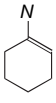
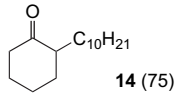
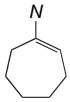
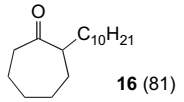
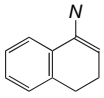
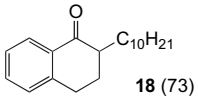
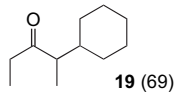
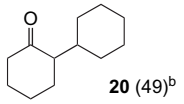
survives the reaction to give the product **6** in 93% yield (entry 4). The success with the ethyl chloride bearing a nearby, electron-withdrawing 2-siloxyethyl group shown in entry 5 provides an illustration of the very high nucleophilicity of the zinc enamide. The neighboring amino function in the chloride does not affect the reaction as shown in entry 6. *N*-Indolyl group remained intact under the conditions to give the product **10** in 80% yield (entry 7). The formation of a double alkylated side product (albeit in 8% yield) was observed only in this case.

2.3. Alkylation with alkyl fluorides

We next investigated the alkylation with alkyl fluorides, which are renowned for the low reactivity in nucleophilic substitution reactions.[5,11] The results summarized in Table 3 suggest that the fluorides are expectedly less reactive than chlorides but still serve as viable alkylating reagents under the present conditions. As shown in entries 1 and 2, acyclic magnesium enamides **1a** and **4** smoothly reacted with 1-fluorodecane at 65 °C to give the products **11** and **12** in 87 and 97% yields, respectively. The reactions of cyclic substrates **13** and **15** with 1-fluorodecane, which are slower than those of acyclic substrates, gave the products **14** and **16** in 75 and 81% yields, respectively (entries 3 and 4).

Table 3. Alkylation of magnesium enamides with alkyl fluorides



Entry	Enamide	R^3–F	Product yield[a] (%)
1	**1a**	F–$C_{10}H_{21}$	 **11** (87)
2	**4**	F–$C_{10}H_{21}$	 **12** (97)
3	 **13**	F–$C_{10}H_{21}$	 **14** (75)
4	 **15**	F–$C_{10}H_{21}$	 **16** (81)
5	 **17**	F–$C_{10}H_{21}$	 **18** (73)
6	**1a**		 **19** (69)
7	**13**		 **20** (49)[b]

[a] The isolated yield.
[b] The reaction was carried out at 80 °C for 40 h.

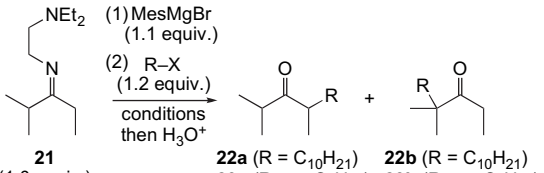
The magnesium enamide **17** derived from α-tetralone also gave the corresponding decylated product **18** in 73% yield (entry 5). To our pleasant surprise, fluorocyclohexane, a secondary alkyl fluoride, also took part in the alkylation reaction to give the product **19** in 69% yield (entry 6). The reaction with the cyclic enamide **13** was slow requiring 80 °C and gave the desired product **20** in 49% yield (entry 7).

2.4. Regioselective alkylation of unsymmetrical ketones

The regioselectivity of the reaction of unsymmetrical imines was briefly examined (Tables 4–6). The magnesium enamide prepared from 3-pentanone imine **21** reacted with 1-chlorodecane to give an 85:15 mixture of **22a** and **22b** in 94% yield (entry 1, Table 4). The reaction with 1-fluorodecane gave the product with slightly higher selectivity (entry 2). The imine deprotonation with alkylmagnesium bromide is known to take place at the less hindered site,[2] but the halide-dependence of the regioselectivity indicates that the regioselectivity is not determined entirely in this imine deprotonation stage. The reaction with chlorocycloheptane took place slowly but very selectively to give the product **23a** with 98% regioselectivity (entry 3). Similarly, the reaction with fluorocyclohexane gave a 91:9 mixture of two regioisomers **24a** and **24b** in 41% yield (entry 4).

The reaction of the magnesium enamide prepared from the 2-methylcyclohexanone imine **25** gave us information on the regioselectivity of the α-alkylation as well as the diastereoselectivity of the newly formed chiral center at C6 against the preexisting chiral center at C2. The regioselectivity was 99–100% for all cases shown in Table 5, but the stereoselectivity was halide-dependent. The reactions with 1-chlorodecane and 1-fluorodecane gave **26** in 92 and 93% yields, respectively (entries 1 and 2, Table 5), and the secondary chloride and fluoride gave lower yields (entries 3 and 4). While 1-chlorodecane gave a 1:1 mixture of cis and trans isomers, other alkyl halides showed slightly improved selectivity and gave a trans isomer as a major product (72, 79, and 89% diastereoselectivities, respectively). The

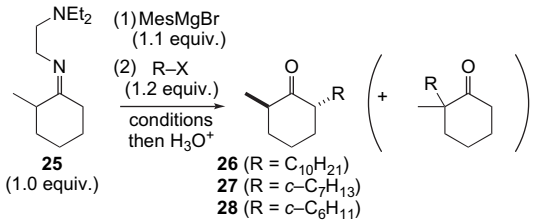
Table 4. Regioselective alkylation of an unsymmetrical magnesium enamide derived from 2-methyl-3-pentanone



Entry	R–X	Conditions	Yield[a] (%)	Regioselectivity[b]
1	Cl–$C_{10}H_{21}$	50 °C, 24 h 65 °C, 12 h	94	**22a/22b**=85:15
2	F–$C_{10}H_{21}$	65 °C, 36 h	90	**22a/22b**=91:9
3		65 °C, 48 h	59	**23a/23b**=98:2
4		80 °C, 48 h	41	**24a/24b**=91:9

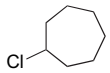
[a] The isolated yield.
[b] Regioselectivity was determined by GC or NMR analysis.

Table 5. Regioselective alkylation of an unsymmetrical magnesium enamide derived from 2-methylcyclohexanone



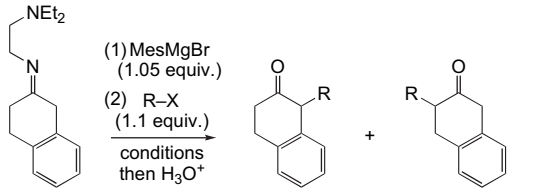
25 (1.0 equiv.)

26 (R = $C_{10}H_{21}$)
27 (R = *c*–C_7H_{13})
28 (R = *c*–C_6H_{11})

Entry	R–X	Conditions	Yield[a] (%)	Diastereoselectivity[b]
1	Cl–$C_{10}H_{21}$	50 °C, 24 h 65 °C, 12 h	92	cis/trans=50:50
2	F–$C_{10}H_{21}$	65 °C, 36 h	93	cis/trans=28:72
3		65 °C, 48 h	52	cis/trans=21:79
4		80 °C, 48 h	42	cis/trans=11:89

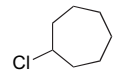
[a] The isolated yield.
[b] Diastereoselectivity was determined by GC or NMR analysis.

Table 6. Regioselective alkylation of an unsymmetrical magnesium enamide derived from β-tetralone



29 (1.0 equiv.)

30a (R = $C_{10}H_{21}$) **30b** (R = $C_{10}H_{21}$)
31a (R = *c*–C_7H_{13}) **31b** (R = *c*–C_7H_{13})

Entry	R–X	Conditions	Yield[a] (%)	Regioselectivity[b]
1	Cl–$C_{10}H_{21}$	50 °C, 48 h	74	**30a/30b**=93:7
2	F–$C_{10}H_{21}$	65 °C, 48 h	89	**30a/30b**>99:1
3		50 °C, 24 h 65 °C, 24 h	71	**31a/31b**=99:1

[a] Isolated yield.
[b] Regioselectivity was determined by GC or NMR analysis.

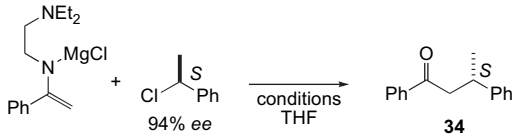
trans selectivity has been considered to reflect the kinetic preference of the reaction.[12] The origin of the halide-dependence is unclear at this time and can be due either to a kinetic or a thermodynamic reason.

The magnesium enamide prepared from β-tetralone imine **29** reacted regioselectively with 1-chlorodecane to give a 93:7 mixture of **30a** and **30b** in 74% yield (Table 6, entry 1). As shown in entries 2 and 3, the reactions with 1-fluorodecane and chlorocycloheptane are slighly more regioselective and gave **30a** and **31a** with 99% selectivity.

2.5. S_N2 substitution of (*S*)-(1-chloroethyl)benzene

In any substitution reaction, the stereochemistry of the carbon atom where the substitution occurs is of general interest. This issue has not been addressed properly in the enolate chemistry however, since secondary (chiral) alkyl halides have not been synthetically useful alkylating agents. The high yielding secondary alkylation now allows us to examine this fundamental issue.

As shown in Scheme 2, the reaction takes place with inversion of stereochemistry at the electrophilic carbon atom. Thus, (*S*)-(1-chloroethyl)benzene **33** (94.0% ee) reacted with the magnesium enamide **32** at 30 °C to give (*S*)-1,3-diphenylbutan-1-one **34** in 64% yield with 89% ee . When the reaction was carried out at more forcing conditions, 50 °C, the enantioselectivity dropped to 85% ee (78% yield). Because the starting benzylic halide **33** undergoes slow racemization under the reaction conditions, we consider that the substitution occurs with a much higher level of inversion of stereochemistry than observed.[13] In the light of availability of optically active alkyl chlorides,[14] the present method was proved to offer a new opportunity for asymmetric C–C bond formation reactions.



32 (1.2 equiv.)
33 (1.0 equiv.)
30 °C, 36 h
50 °C, 12 h
34
64% yield, 89% *ee*
78% yield, 85% *ee*

Scheme 2. Stereoselective nucleophilic substitution of an optically active alkyl chloride.

3. Conclusion

Through the present study, we have examined several issues of general importance in the enolate and enamide alkylation chemistry, and shown that the magnesio 2-aminoethylenamide chemistry provides significant improvement over the conventional chemistry of similar nature. The reaction also provides new opportunities in synthetic chemistry, such as utilization of secondary alkyl halides and alkyl fluorides and the synthesis of optically active ketones by the use of optically active secondary alkyl halides. With the availability of optically active imines of the kind used in this study,[15] we also expect that the present methodology will be useful for the synthesis of optically active ketone derivatives in general.

4. Experimental

4.1. General methods

All reactions dealing with air- or moisture- sensitive compounds were carried out in a dry reaction vessel under positive pressure of argon. Analytical thin-layer chromatography was performed on glass plates coated with 0.25 mm 230–400 mesh silica gel containing a fluorescent indicator (Merck, #1.05715.0009). Flash column chromatography was performed on Kanto Silica gel 60 (spherical, neutral, 140–325 mesh) as described by Still et al.[16] Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on JEOL ECX-400 (400 MHz) or JEOL EX-270 (270.05 MHz) NMR spectrometers. Data are presented as: chemical shift, multiplicity

(s=singlet, d=doublet, t=triplet, q=quartet, quint=quintet, sext=sextet, sept=septet, m=multiplet and/or multiplet resonances, br=broad), coupling constant in hertz (Hz), and signal area integration in natural numbers, assignment (*italic*). IR spectra recorded on a React IR 1000 Reaction Analysis System equipped with DuraSample IR (ASI Applied System) are reported in cm^{-1}. Characteristic IR absorptions are reported in cm^{-1}. High-resolution mass spectra are taken with EI (electron impact) method at a JEOL GC-mate II. Diastereoselectivity (ds) and yield (by using octane, decane, or undecane as an internal standard) were determined for a crude product by GC analyses on a Shimadzu GC-17A instrument equipped with an FID detector and a capillary column, HR-1 (Shinwa, 25 m×0.25 mm i.d., 0.25 mm film thickness). Enantioselectivity was determined by GC analyses on a Shimadzu GC-14B instrument equipped with an FID detector and a capillary column, γ-DEX 225 (Supelco, 30 m×0.25 mm i.d., 0.25 μm film thickness), or by HPLC analyses on a JASCO CD-2095 Plus equipped with chiral column, CHIRALCEL OJ-H (Daicel, 4.6×250 mm). Imines were prepared from corresponding ketones and amines using dry molecular sieves 4 Å.[7] Mesitylmagnesium bromide (MesMgBr) was prepared from bromomesitylene and magnesium (turnings) using a standard method and titrated before use. Florisil® (100–200 mesh) was purchased from Yoneyama Yakuhin Kogyo Co., Ltd.

4.1.1. Typical procedure for alkylation in Table 1; synthesis of 2-cycloheptylpentan-3-one (2). *N′*-(1-Ethylpropylidene)-*N*,*N*-diethyl-1,2-ethanediamine (0.184 g, 1.0 mmol) was added to mesitylmagnesium bromide (MesMgBr, 0.95 M in THF, 1.16 mL, 1.1 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 1 h. After the solvents were removed in vacuo, chlorocycloheptane (0.159 g, 1.2 mmol) was added at room temperature. The reaction was carried out at 45 °C for 24 h and then at 60 °C for 12 h. AcOH in H_2O (50 wt %, 1.0 mL) was added slowly at 0 °C. The reaction mixture was stirred at 50 °C for 1 h and then cooled to room temperature. The reaction mixture was neutralized with saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with Et_2O five times. The combined organic extracts were dried with Na_2SO_4. Gas chromatography analysis was carried out (88% yield) by using octane as an internal standard. After the solvent was removed in vacuo, the crude product was purified by chromatography on silica gel (10 g, pentane and then 2% Et_2O in pentane) to obtain the title compound **2** (0.157 g, 86% yield) as a colorless liquid. R_f=0.38 (10% Et_2O in pentane); IR (neat) 2976, 2922, 2856, 1710 (C=O), 1459, 1378, 1104, 1019, 973, 803; ^{1}H NMR δ 1.00 (d, J=6.9 Hz, 3H, CHCH_3), 1.04 (t, J=7.2 Hz, 3H, CH_2CH_3), 1.13–1.33 (m, 2H, C*H*H$(CH_2)_4$C*H*H), 1.35–1.70 (m, 10H, CH*H*$(CH_2)_4$CH*H*), 1.79–1.88 (m, 1H, C*H*CHCH$_3$), 2.42–2.47 (m, 3H, C*H*CH$_3$, CH_2CH$_3$); ^{13}C NMR δ 7.8, 12.7, 26.6, 26.9, 28.1, 28.2, 30.0, 33.4, 34.7, 41.2, 52.4, 215.5. Anal. Calcd for $C_{12}H_{22}O$ C, 79.06; H, 12.16. Found C, 78.92; H, 11.92.

4.1.2. Typical procedure for alkylation in Tables 2–5; synthesis of 5-ethylpentadecan-4-one (12). *N′*-(1-Propylbutylidene)-*N*,*N*-diethyl-1,2-ethanediamine (0.212 g, 1.0 mmol) was added to mesitylmagnesium bromide (MesMgBr, 0.95 M in THF, 1.16 mL, 1.1 mmol) at room temperature. After stirring at 80 °C for 1 h, 1-fluorodecane (0.192 g, 1.2 mmol) was added at room temperature. The reaction was carried out at 65 °C for 36 h. AcOH in H_2O (50 wt %, 1.0 mL) was added slowly at 0 °C. The reaction mixture was stirred at 50 °C for 1 h and then cooled to room temperature. The reaction mixture was neutralized with saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with Et_2O five times. The combined organic extracts were dried with Na_2SO_4. After the solvent was removed in vacuo, the crude product was purified by chromatography on silica gel (10 g, pentane and then 2% Et_2O in pentane) to obtain the title compound **12** (0.248 g, 97% yield) as a colorless liquid. R_f=0.62 (10% Et_2O in pentane); IR (neat) 2961, 2926, 2856, 1710 (C=O), 1459, 1378, 1123, 1031, 722; ^{1}H NMR δ 0.82–0.93 (m, 9H, C$(CH_2)_2$CH_3, CHCH_2CH_3, $(CH_2)_9$CH_3), 1.15–1.32 (m, 16H, C$(H_2)_8$), 1.30–1.65 (m, 6H, CCH$_2$CH_2, CHCH_2CH$_3$, CHCH_2CH$_2$), 2.33–2.42 (m, 3H, CH_2C(=O)C*H*); ^{13}C NMR δ 11.9, 13.8, 14.1, 16.9, 22.7, 24.6, 27.5, 29.3, 29.4, 29.6 (2C), 29.8, 31.4, 31.9, 44.2, 53.9, 215.0. Anal. Calcd for $C_{17}H_{34}O$ C, 80.24; H, 13.47. Found C, 80.16; H, 13.21.

4.1.2.1. Synthesis of 4,5-dimethyldodecan-3-one[17] (3). The reaction was carried out according to the typical procedure on a 1.0-mmol scale by using *N′*-(1-ethylpropylidene)-*N*,*N*-diethyl-1,2-ethanediamine (0.184 g, 1.0 mmol) and 2-chloroheptane (0.162 g, 1.2 mmol). Conditions: 45 °C, 24 h; 60 °C, 12 h. The title compound **3** (0.131 g, 71% yield, *syn*/*anti*=58:42 determined by ^{1}H NMR analysis) was obtained as a colorless liquid after silica gel column chromatography.

4.1.2.2. Synthesis of 3-ethyl-2-phenylheptan-4-one[8c] (5). The reaction was carried out according to the typical procedure on a 1.0-mmol scale by using *N′*-(1-propylbutylidene)-*N*,*N*-diethyl-1,2-ethanediamine (0.212 g, 1.0 mmol) and (1-chloroethyl)benzene (0.211 g, 1.5 mmol). Conditions: 30 °C, 12 h; 50 °C, 3 h. The title compound **5** (0.186 g, 85% yield, *syn*/*anti*=70:30 determined by ^{1}H NMR analysis) was obtained as a colorless liquid after silica gel column chromatography. R_f=0.50 (10% Et_2O in pentane); IR (neat) 3065 and 3030 (aromatic C–H), 2964, 2934, 2876, 1710 (C=O), 1494, 1455, 1378, 1270, 1127, 1027, 760, 698; *syn*-isomer: ^{1}H NMR δ 0.64 (t, J=7.5 Hz, 3H, $CH_2CH_2CH_3$), 0.81 (t, J=7.5 Hz, 3H, $CHCH_2CH_3$), 1.25 (d, J=6.9 Hz, 3H, $CHCH_3$), 1.18–1.33 (m, 2H, $CH_2CH_2CH_3$), 1.58–1.73 (m, 2H, $CHCH_2CH_3$), 1.79–1.88 (m, 1H, CC*H*HCH$_2$), 2.03–2.12 (m, 1H, CCH*H*CH$_2$), 2.58–2.67 (m, 1H, CC*H*CH$_2$), 2.87–2.97 (m, 1H, C*H*Ph), 7.13–7.18 (m, 3H, C*H*CHC*H*CHC*H*), 7.23–7.27 (m, 2H, CHC*H*CHC*H*CH); ^{13}C NMR δ 11.9, 13.5, 16.2, 18.8, 22.5, 41.7, 46.6, 60.8, 126.2, 127.4 (2C), 128.3 (2C), 145.4, 214.5; *anti*-isomer: ^{1}H NMR δ 0.70 (t, J=7.5 Hz, 3H, $CH_2CH_2CH_3$), 0.93 (t, J=7.5 Hz, 3H, $CHCH_2CH_3$), 1.16 (d, J=6.9 Hz, 3H, $CHCH_3$), 1.25–1.45 (m, 2H, $CH_2CH_2CH_3$), 1.57–1.66 (m, 2H, $CHCH_2CH_3$), 2.37–2.43 (m, 2H, CCH_2CH_2), 2.58–2.67 (m, 1H, CC*H*CH$_2$), 2.87–2.97 (m, 1H, C*H*Ph), 7.17–7.31 (m, 5H, C$(H)_5$); ^{13}C NMR δ 11.6, 13.8, 16.5, 20.4, 24.2, 42.1, 46.5, 60.3, 126.3, 127.4 (2C), 128.4 (2C), 145.1, 214.9.

4.1.2.3. Synthesis of 8-*tert*-butyldimethylsilyloxy-4-methyloctan-3-one[18] (6). The reaction was carried out according to the typical procedure on a 1.0-mmol scale

by using *N*′-(1-ethylpropylidene)-*N*,*N*-diethyl-1,2-ethanediamine (0.184 g, 1.0 mmol) and *tert*-butyl-(4-chlorobutoxy)-dimethylsilane (0.267 g, 1.2 mmol). Conditions: 50 °C, 24 h; 65 °C, 12 h. The title compound **6** (0.253 g, 93% yield) was obtained as a colorless liquid after silica gel column chromatography.

4.1.2.4. Synthesis of 6-*tert*-butyldimethylsilyloxy-4-methylhexan-3-one (7). The reaction was carried out according to the typical procedure on a 1.0-mmol scale by using *N*′-(1-ethylpropylidene)-*N*,*N*-diethyl-1,2-ethanediamine (0.184 g, 1.0 mmol) and *tert*-butyl-(2-chloroethoxy)-dimethylsilane (0.238 g, 1.2 mmol). Conditions: 50 °C, 24 h; 65 °C, 12 h. The title compound **7** (0.131 g, 68% yield) was obtained as a colorless liquid after silica gel column chromatography. R_f=0.35 (10% Et_2O in pentane); IR (neat) 2957, 2934, 2860, 1714 (C=O), 1463, 1254, 1096, 899, 834, 776; ^{1}H NMR δ 0.03 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, $C(CH_3)_3$), 1.04 (t, J=7.2 Hz, 3H, CH_2CH_3), 1.08 (d, J=7.4 Hz, 3H, $CHCH_3$), 1.46–1.54 (m, 1H, CHCHH), 1.87–1.94 (m, 1H, CHCHH), 2.45–2.53 (m, 2H, CCH_2), 2.69–2.78 (m, 1H, CCH), 3.59 (t, J=7.2 Hz, 2H, CH_2OSi); ^{13}C NMR δ −5.5 (2C), 7.8, 16.5, 18.2, 25.9 (3C), 34.3, 35.8, 42.4, 60.7, 215.1. Anal. Calcd for $C_{13}H_{28}O_2Si$ C, 63.87; H, 11.55. Found C, 64.04; H, 11.35.

4.1.2.5. Synthesis of 7-(1*H*-indol-1-yl)-4-methylheptan-3-one (10). The reaction was carried out according to the typical procedure on a 1.0-mmol scale by using *N*′-(1-ethylpropylidene)-*N*,*N*-diethyl-1,2-ethanediamine (0.184 g, 1.0 mmol) and 1-(3-chloropropyl)-1*H*-indole (0.231 g, 1.2 mmol). Conditions: 50 °C, 24 h; 65 °C, 12 h. The title compound **10** (0.193 g, 80% yield) was obtained as a pale yellow liquid after silica gel column chromatography. R_f=0.13 (5% EtOAc in hexane); IR (neat) 2971, 2936, 2875, 1707 (C=O), 1461, 1313, 738; ^{1}H NMR δ 0.99 (t, J=7.1 Hz, 3H, CH_2CH_3), 1.03 (d, J=7.1 Hz, 1H, $CHCH_3$), 1.21–1.41 (m, 1H, C(=O)CHCHH), 1.57–1.87 (m, 3H, NCH_2CH_2, C(=O)CHCHH), 2.18–2.54 (m, 3H, CH_3CH_2, CH_3CH), 4.09 (dt, J=2.7, 6.9 Hz, 2H, CH_2N), 6.48 (d, J=3.0 Hz, 1H, NCHCH), 7.06 (d, J=3.0 Hz, 1H, NCH), 7.09 (t, J=7.6 Hz, 1H, NCCHCHCH), 7.20 (t, J=7.6 Hz, 1H, NCCHCH), 7.31 (d, J=8.1 Hz, 1H, NCCH), 7.62 (d, J=7.8 Hz, 1H, NCCCH); ^{13}C NMR δ 7.8, 16.8, 28.0, 30.2, 34.3, 45.6, 46.3, 101.0, 109.2, 119.1, 120.9, 121.3, 127.6, 128.5, 135.7, 214.5. The double alkylated product, 1,9-di(1*H*-indol-1-yl)-4,6-dimethylnonan-5-one was also obtained in 8% yield (0.030 g) as a 6:4 mixture of diastereomers. R_f=0.07 (5% EtOAc in hexane); the major diastereomer: ^{1}H NMR δ 0.95 (t, J=6.5 Hz, 6H, CH_3), 1.10–1.81 (m, 8H, $NCH_2CH_2CH_2$), 2.34–2.55 (m, 2H, C(=O)CH), 3.92–4.16 (m, 4H, NCH_2), 6.46 (d, J=3.0 Hz, NCHCH), 7.01 (d, J=3.2 Hz, NCH), 7.08 (t, J=7.8 Hz, NCCCHCHCH), 7.19 (t, J=7.8 Hz, NCCHCH), 7.28 (d, J=7.6 Hz, NCCH), 7.61 (d, J=7.8 Hz, NCCCHCHCHCH); ^{13}C NMR δ 16.5 (2C), 27.8 (2C), 29.9 (2C), 44.5 (2C), 46.2 (2C), 101.0 (2C), 109.3 (2C), 119.2 (2C), 121.0 (2C), 121.4 (2C), 127.7 (2C), 128.5 (2C), 135.9 (2C), 217.0; the minor diastereomer: ^{1}H NMR δ 0.95 (t, J=6.5 Hz, 6H, CH_3), 1.10–1.81 (m, 8H, $NCH_2CH_2CH_2$), 2.34–2.55 (m, 2H, C(=O)CH), 3.92–4.16 (m, 4H, NCH_2), 6.47 (d, J=3.0 Hz, NCHCH), 7.04 (d, J=3.2 Hz, NCH), 7.08 (t, J=7.8 Hz, NCCCHCHCH), 7.18 (t, J=7.8 Hz, NCCHCH), 7.30 (d, J=8.1 Hz, NCCH), 7.61 (d, J=7.8 Hz, NCCCHCHCHCH); ^{13}C NMR δ 16.8 (2C), 28.0 (2C), 29.8 (2C), 44.5 (2C), 46.3 (2C), 101.0 (2C), 109.3 (2C), 119.2 (2C), 121.0 (2C), 121.4 (2C), 127.7 (2C), 128.5 (2C), 135.9 (2C), 216.9.

4.1.2.6. Synthesis of 2-decylcyclohexanone[19] (14). The reaction was carried out according to the typical procedure on a 1.0-mmol scale by using *N*′-cyclohexylidene-*N*,*N*-diethyl-1,2-ethanediamine (0.196 g, 1.0 mmol) and 1-fluorodecane (0.192 g, 1.2 mmol). Conditions: 65 °C, 36 h. The title compound **14** (0.178 g, 75% yield) was obtained as a colorless liquid after silica gel column chromatography.

4.1.2.7. Synthesis of 2-decylcycloheptanone (16). The reaction was carried out according to the typical procedure on a 1.0-mmol scale by using *N*′-cycloheptylidene-*N*,*N*-diethyl-1,2-ethanediamine (0.210 g, 1.0 mmol) and 1-fluorodecane (0.192 g, 1.2 mmol). Conditions: 65 °C, 36 h. The title compound **16** (0.205 g, 81% yield) was obtained as a colorless liquid after silica gel column chromatography. R_f=0.15 (5% EtOAc in hexane); IR (neat) 2922, 2853, 1702 (C=O), 1455, 934, 733; ^{1}H NMR δ 0.88 (t, J=6.6 Hz, 3H, CH_3), 1.15–1.95 (m, 26H, $(CH_2)_9CH_3$, $C(=O)CH_2CH_2CH_2CH_2CH_2$), 2.34–2.58 (m, 3H, $CH_2C(=O)CH$); ^{13}C NMR δ 14.2, 22.7, 24.7, 27.3, 28.5, 29.4, 29.6, 29.7 (3C), 29.8, 31.3, 31.9, 32.5, 42.7, 52.4, 216.4.

4.1.2.8. Synthesis of 2-decyl-1-tetralone (18). The reaction was carried out according to the typical procedure on a 1.0-mmol scale by using *N*′-(3,4-dihydronaphthalen-1(2*H*)-ylidene)-*N*,*N*-diethyl-1,2-ethanediamine (0.244 g, 1.0 mmol) and 1-fluorodecane (0.192 g, 1.2 mmol). Conditions: 65 °C, 36 h. The title compound **18** (0.209 g, 73% yield) was obtained as a colorless liquid after silica gel column chromatography. R_f=0.69 (10% EtOAc in hexane); IR (neat) 2922, 2853, 1683 (C=O), 1601, 1455, 1357, 1288, 1221, 909, 740; ^{1}H NMR δ 0.88 (t, J=6.6 Hz, 3H, CH_3), 1.20–1.60 (m, 17H, $CH(CH_2)_8CH_3$), 1.80–2.02 (m, 2H, C(=O)CHCHH, C(=O)CCCH$_2$CHH), 2.16–2.31 (dq, J=4.9, 13.5 Hz, 1H, C(=O)CCCH$_2$CHH), 2.39–2.54 (m, 1H, C(=O)CCCHH), 2.93–3.03 (m, 2H, C(=O)CH, C(=O)CCCHH), 7.22 (d, J=7.8 Hz, 1H, CH_2CCH), 7.29 (t, J=7.8 Hz, 1H, C(=O)CCHCH), 7.44 (td, J=1.4, 7.2 Hz, 1H, C(=O)CHCHCH), 8.01 (dd, J=1.4, 8.4 Hz, 1H, C(=O)CCH); ^{13}C NMR δ 14.2, 22.8, 27.1, 28.3, 28.4, 29.4, 29.5, 29.7, 29.7 (2C), 29.9, 32.0, 47.5, 126.4, 127.4, 128.5, 132.5, 132.9, 143.8, 200.3.

4.1.2.9. Synthesis of 2,4-dimethyl-3-tetradodecanone (22a) and 4,4-dimethyl-3-tetradodecanone (22b). The reaction was carried out according to the typical procedure on a 1.0-mmol scale by using *N*′-(1-isopropylpropylidene)-*N*,*N*-diethyl-1,2-ethanediamine **21** (0.198 g, 1.0 mmol) and 1-fluorodecane (0.192 g, 1.2 mmol). Conditions: 65 °C; 36 h. The title compounds (0.216 g, 90% yield, **22a**/**22b**=91:9 determined by ^{1}H NMR analysis) were obtained as a colorless liquid after silica gel column chromatography. R_f=0.31 (3% Et_2O in pentane); IR (neat) 2964, 2926, 2856, 1714 (C=O), 1463, 1382, 1015, 722. Anal. Calcd for $C_{16}H_{32}O$ C, 79.93; H, 13.42. Found C, 79.77; H, 13.35; 2,4-dimethyl-3-tetradodecanone: ^{1}H NMR δ 0.88 (t, J=7.2 Hz, 3H, CH_2CH_3), 1.00–1.11 (m, 9H, $CH(CH_3)_2$,

$CHCH_3$), 1.32–1.43 (m, 18H, $(CH_2)_9$), 2.63–2.77 (m, 2H, $CHC(=O)CH$); ^{13}C NMR δ 14.1, 16.8, 18.2, 18.4, 22.7, 27.5, 29.4, 29.5, 29.6 (2C), 29.7, 31.9, 33.2, 39.6, 44.6, 218.7.

The reaction was carried out according to the typical procedure on a 1.0-mmol scale by using *N*′-(1-isopropylpropylidene)-*N*,*N*-diethyl-1,2-ethanediamine **21** (0.198 g, 1.0 mmol) and 1-chlorodecane (0.212 g, 1.2 mmol). Conditions: 50 °C, 24 h; 65 °C, 12 h. The title compound (0.226 g, 94% yield, **22a/22b**=85:15, determined by ^1H NMR analysis) was obtained as a colorless liquid after silica gel column chromatography.

4.1.2.10. Synthesis of 2-decyl-5-methylcyclohexanone (26). The reaction was carried out according to the typical procedure on a 1.0-mmol scale by using *N*′-(2-methylcyclohexylidene)-*N*,*N*-diethyl-1,2-ethanediamine **25** (0.210 g, 1.0 mmol) and 1-fluorodecane (0.192 g, 1.2 mmol). Conditions: 65 °C, 36 h. The title compound **26** (0.235 g, 93% yield, cis/trans=28:72 determined by ^1H NMR analysis) was obtained as a colorless liquid after silica gel column chromatography. R_f=0.47 (trans isomer), 0.65 (cis isomer) (10% Et_2O in pentane); IR (neat) 2922, 2853, 1714 (C=O), 1455, 1378, 1127, 984, 857, 722. Anal. Calcd for $C_{17}H_{32}O$ C, 80.88; H, 12.78. Found C, 80.76; H, 12.96; trans isomer: ^1H NMR δ 0.88 (t, J=6.9 Hz, 3H, CH_2CH_3), 1.00 (d, J=6.3 Hz, 3H, $CHCH_3$), 1.08–1.18 (m, 1H, $CHCHH(CH_2)_8$), 1.18–1.40 (m, 18H, $CHCHHCH_2CHHCH$), $(CH_2)_8CH_3$), 1.65–1.86 (m, 3H, $CHCH_2CH_2CH_2CH$, $CHH(CH_2)_8CH_3$), 2.18–2.18 (m, 2H, $CHCHHCH_2CHHCH$), 2.19–2.28 (m, 1H, $CH(CH_2)_9$), 2.34–2.44 (m, 1H, $CHCH_3$); ^{13}C NMR δ 14.1, 14.5, 22.7, 25.6, 27.3, 29.1, 29.3, 29.5, 29.6 (2C), 29.9, 31.9, 35.2, 37.5, 45.6, 50.8, 214.4; cis isomer: ^1H NMR δ 0.88 (t, J=6.9 Hz, 3H, CH_2CH_3), 1.05 (d, J=6.3 Hz, 3H, $CHCH_3$), 1.10–1.20 (m, 1H, $CHH(CH_2)_8CH_3$), 1.18–1.33 (m, 16H, $(CH_2)_8CH_3$), 1.33–1.48 (m, 2H, $CHCHHCH_2CHHCH$), 1.64–1.88 (m, 4H, $CH_3CHCH_2CH_2CHHCH$, $CHH(CH_2)_8CH_3$), 1.94–2.02 (m, 1H, $CH(CH_3)CHH$), 2.37–2.44 (m, 1H, $CH(CH_2)_9$), 2.49–2.57 (m, 1H, $CHCH_3$); ^{13}C NMR δ 14.1, 15.3, 20.5, 22.7, 27.3, 29.3, 29.5, 29.6 (3C), 30.9, 31.9, 32.4, 35.6, 42.2, 49.5, 217.0.

The reaction was carried out according to the typical procedure on a 1.0-mmol scale by using *N*′-(2-methylcyclohexylidene)-*N*,*N*-diethyl-1,2-ethanediamine **25** (0.210 g, 1.0 mmol) and 1-chlorodecane (0.212 g, 1.2 mmol). Conditions: 50 °C, 24 h; 65 °C, 12 h. The title compound **26** (0.233 g, 92% yield, cis/trans=50:50 determined by ^1H NMR analysis) was obtained as a colorless liquid after silica gel column chromatography.

4.1.3. Typical procedure for alkylation in Tables 2–6; synthesis of 2-cyclohexylcyclohexanone[20] (20). To *N*′-cyclohexylidene-*N*,*N*-diethyl-1,2-ethanediamine (0.196 g, 1.0 mmol) was added mesitylmagnesium bromide (MesMgBr, 1.18 M in THF, 0.932 mL, 1.1 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 1 h. Fluorocyclohexane (0.122 g, 1.2 mmol) was added at room temperature. The reaction was carried out at 80 °C for 40 h. AcOH in H_2O (10 wt %, 2.0 mL) was added slowly at 0 °C. The reaction mixture was stirred at room temperature for 0.5 h and then neutralized with saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with pentane five times. The combined organic extracts were dried over Na_2SO_4. After the solvents were removed in vacuo, the crude product was purified by chromatography on silica gel (12 g, pentane and then 2% Et_2O in pentane) to obtain the title compound **20** (0.089 g, 49% yield) as a colorless liquid.

4.1.3.1. Synthesis of 2-cyclohexylpentan-3-one[21] (19). The reaction was carried out according to the typical procedure on a 1.0-mmol scale by using *N*′-(1-ethylpropylidene)-*N*,*N*-diethyl-1,2-ethanediamine (0.184 g, 1.0 mmol) and fluorocyclohexane (0.122 g, 1.2 mmol). Conditions: 65 °C, 36 h. The title compound **19** (0.116 g, 69% yield) was obtained as a colorless liquid after silica gel column chromatography.

4.1.3.2. Synthesis of 2-cycloheptyl-4-methyl-3-pentanone (23a) and 2-cycloheptyl-2-methyl-3-pentanone (23b). The reaction was carried out according to the typical procedure on a 1.0-mmol scale by using *N*′-(1-isopropylpropylidene)-*N*,*N*-diethyl-1,2-ethanediamine **21** (0.198 g, 1.0 mmol) and chlorocycloheptane (0.159 g, 1.2 mmol). Conditions: 65 °C, 48 h. The title compounds (0.116 g, 59% yield, **23a/23b**=98:2 determined by ^1H NMR analysis) were obtained as a colorless liquid after silica gel column chromatography; IR (neat) 2918, 2854, 1708 (C=O), 1460, 1381, 1098, 1015, 1000, 801; 2-Cycloheptyl-4-methyl-3-pentanone (major): ^1H NMR δ 0.92 (d, J=7.5 Hz, 3H, $CHCHCH_3$), 0.98 (d, J=7.2 Hz, 3H, CH_3CHCH_3), 1.00 (d, J=7.5 Hz, 3H, CH_3CHCH_3), 1.04–1.60 (m, 12H, $(CH_2)_6$), 1.70–1.79 (m, 1H, CH_2CH), 2.57 (quint, J=7.8 Hz, 1H, $CHCHCH_3$), 2.72 (sept, J=7.8 Hz, 1H, CH_3CHCH_3); ^{13}C NMR δ 13.0, 18.0, 18.8, 26.5, 26.9, 28.1, 28.2, 30.0, 33.5, 39.8, 41.0, 50.7, 218.5. Anal. Calcd for $C_{13}H_{24}O$ C, 79.53; H, 12.32. Found C, 79.41; H, 12.50.

4.1.3.3. Synthesis of 2-cyclohexyl-4-methyl-3-pentanone (24a) and 2-cyclohexyl-2-methyl-3-pentanone (24b). The reaction was carried out according to the typical procedure on a 1.0-mmol scale by using *N*′-(1-isopropylpropylidene)-*N*,*N*-diethyl-1,2-ethanediamine **21** (0.198 g, 1.0 mmol). Conditions: 80 °C, 48 h. The title compounds (0.074 g, 41% yield, **24a/24b**=91:9 determined by ^1H NMR analysis) were obtained as a colorless liquid after silica gel column chromatography.

4.1.3.4. Synthesis of 2-cycloheptyl-6-methylcyclohexanone (27). The reaction was carried out according to the typical procedure on a 1.0-mmol scale by using *N*′-(2-methylcyclohexylidene)-*N*,*N*-diethyl-1,2-ethanediamine **25** (0.210 g, 1.0 mmol), MesMgBr (1.18 M in THF, 1.69 mL, 2.0 mmol), and chlorocycloheptane (0.159 g, 1.2 mmol). Conditions: 65 °C, 48 h. The title compound **27** (0.104 g, 52% yield, cis/trans=21:79 determined by ^1H, ^{13}C NMR analyses) was obtained as a colorless liquid after silica gel column chromatography; IR (neat) 2918, 2852, 1705 (C=O), 1451, 1375, 1123, 992, 855; trans isomer: ^1H NMR δ 1.01 (d, J=6.6 Hz, 3H, CH_3), 1.08–1.89 (m, 16H, $CHCHHCH_2CHHCH$, $(CH_2)_6$), 1.92–2.05 (m, 3H, $CHCHHCH_2CHHCH$, $CCHCH$), 2.14 (dt, J=4.6, 9.2 Hz, 1H, $CCHCH$), 2.47 (dquint, J=6.5, 10.5 Hz, 1H, CH_3CH);

^{13}C NMR δ 15.1, 20.6, 26.1, 26.4, 28.2, 28.6, 29.3, 31.0, 32.2, 36.1, 37.8, 42.6, 56.3, 216.9. Anal. Calcd for $C_{14}H_{24}O$ C, 80.71; H, 11.61. Found C, 80.75; H, 11.78.

4.1.3.5. Synthesis of 2-cyclohexyl-6-methylcyclohexanone (28). The reaction was carried out according to the typical procedure on a 1.0-mmol scale by using *N*′-(2-methylcyclohexylidene)-*N*,*N*-diethyl-1,2-ethanediamine **25** (0.210 g, 1.0 mmol). Conditions: 80 °C, 48 h. The title compound **28** (0.082 g, 42% yield, cis/trans=11:89 determined by ^{1}H, ^{13}C NMR analyses[22]) was obtained as a colorless liquid after silica gel column chromatography; IR (neat) 2923, 2852, 1705 (C=O), 1449, 1376, 1123, 864; trans isomer: ^{1}H NMR δ 0.74–1.41 (m, 8H, CH*H*(CH_2)$_3$CH*H*), 1.00 (d, 3H, *J*=6.6 Hz, CH_3), 1.55–1.91 (m, 7H, CH*H*(CH_2)$_3$CH*H*, CHC*H*HCH_2C*H*HCH, CCHC*H*), 1.98–2.11 (m, 3H, CHCH*H*CH_2CH*H*CH, CC*H*CH), 2.47 (dquint, *J*=6.5, 11.0 Hz, 1H, CH_3C*H*); ^{13}C NMR δ 14.8, 20.7, 26.2 (2C), 28.9 (2C), 30.3, 31.2, 36.3, 36.5, 42.5, 56.7, 216.7. Anal. Calcd for $C_{13}H_{22}O$ C, 80.35; H, 11.41. Found C, 80.08; H, 11.15.

4.1.3.6. Synthesis of 1-decyl-2-tetralone (30a) and 3-decyl-2-tetralone (30b). The reaction was carried out according to the typical procedure on a 1.0-mmol scale by using *N*′-(3,4-dihydronaphthalen-2(2*H*)-ylidene)-*N*,*N*-diethyl-1,2-ethanediamine **29** (0.244 g, 1.0 mmol), MesMgBr (1.18 M in THF, 0.889 mL, 1.05 mmol), and 1-chlorodecane (0.194 g, 1.1 mmol). Conditions: 50 °C, 48 h. The title compounds (0.212 g, 74% yield, **30a/30b**=93:7 determined by ^{1}H NMR analysis) were obtained as a colorless liquid after silica gel column chromatography; IR (neat) 3019 (aromatic C–H), 2922, 2852, 1709 (C=O), 1457, 1207, 1039, 754; 1-decyl-2-tetralone (major): ^{1}H NMR δ 0.87 (t, *J*=6.6 Hz, 3H, CH_3), 1.17–1.27 (m, 16H, (CH_2)$_8$), 1.80–1.83 (m, 2H, CH_2CH), 2.50 (ddd, *J*=6.6, 9.9, 17.4 Hz, 1H, C(=O)CH_2C*H*H), 2.65 (ddd, *J*=5.4, 6.0, 17.4 Hz, 1H, C(=O)CH_2CH*H*), 2.99 (ddd, *J*=5.4, 6.6, 15.6 Hz, 1H, C(=O)C*H*HCH_2), 3.18 (ddd, *J*=6.0, 9.9, 15.6 Hz, 1H, C(=O)CH*H*CH_2), 3.38 (t, *J*=6.9 Hz, 1H, CC*H*), 7.09–7.33 (m, 4H, (*CH*)$_4$); ^{13}C NMR δ 14.0, 22.6, 26.9, 27.8, 29.2, 29.3, 29.5 (3C), 31.8, 32.2, 37.5, 54.0, 126.6, 126.7, 127.8, 128.1, 136.3, 137.6, 212.8. Anal. Calcd for $C_{20}H_{30}O$ C, 83.86; H, 10.56. Found C, 83.31; H, 10.50.

4.1.3.7. Synthesis of 1-cycloheptyl-2-tetralone (31a) and 3-cycloheptyl-2-tetralone (31b). The reaction was carried out according to the typical procedure on a 0.45-mmol scale by using *N*′-(3,4-dihydronaphthalen-2(2*H*)-ylidene)-*N*,*N*-diethyl-1,2-ethanediamine **29** (0.110 g, 0.45 mmol), MesMgBr (1.18 M in THF, 0.400 mL, 0.47 mmol), and chlorocycloheptane (0.066 g, 0.50 mmol). Conditions: 50 °C, 24 h; 65 °C, 24 h. The title compounds (0.071 g, 71% yield, **31a/31b**=99:1 determined by ^{1}H NMR analysis) were obtained as a colorless liquid after silica gel column chromatography; IR (neat) 3019 (aromatic C–H), 2923, 2852, 1708 (C=O), 1457, 1220, 1178, 970, 739; 1-cycloheptyl-2-tetralone (major): ^{1}H NMR δ 1.22–1.84 (m, 12H, (CH_2)$_6$), 2.12–2.21 (m, 1H, CH_2C*H*), 2.52 (ddd, *J*=6.9, 11.4, 11.8 Hz, 1H, C(=O)CH_2C*H*H), 2.75 (ddd, *J*=2.7, 6.3, 18.3 Hz, 1H, C(=O)CH_2CH*H*), 2.96 (ddd, *J*=2.7, 6.9, 15.9 Hz, 1H, C(=O)*CH*H), 3.26 (d, *J*=8.1 Hz, 1H, CC*H*), 3.38 (ddd, *J*=6.3, 11.4, 15.9 Hz, 1H, C(=O)CH*H*); ^{13}C NMR δ 25.8, 26.0, 27.6, 27.9, 28.2, 32.1, 32.5, 37.1, 41.8, 61.9, 126.4, 126.7, 127.9, 129.8, 136.6, 137.0, 212.9. Anal. Calcd for $C_{17}H_{22}O$ C, 84.25; H, 9.15. Found C, 84.22; H, 9.22.

4.1.4. Synthesis of 4-dimethylamino-2-methyl-1-phenylbutan-1-one (9). *N*′-(1-Phenylpropylidene)-*N*,*N*-diethyl-1,2-ethanediamine (0.629 g, 3.08 mmol) was added to *t*-BuMgCl (2.12 M in THF, 1.44 mL, 3.08 mmol) at −78 °C. The mixture was stirred at 0 °C for 1 h, and then warmed to room temperature. The reaction mixture was transferred to the alkyl chloride, prepared from *t*-BuMgCl (2.12 M in THF, 1.04 mL, 2.2 mmol) and 2-dimethylaminoethylchloride hydrochloride (0.317 g, 2.2 mmol) in THF (1.0 mL), via cannula at room temperature and rinsed with THF (0.5 mL) twice. The reaction mixture was heated at 50 °C for 36 h. AcOH in H_2O (50 wt %, 2.0 mL) was added slowly at 0 °C. The reaction mixture was stirred at 50 °C for 1 h and then cooled to room temperature. H_2O (8.0 mL) was added and the aqueous layer was washed with pentane three times to remove propiophenone. To the aqueous layer was added 3 N NaOH until pH >12. The aqueous layer was extracted with Et_2O five times. The combined extracts were filtered with a pad of Na_2SO_4 by using Et_2O as an eluent. Gas chromatography analysis was carried out (77% yield) by using undecane as an internal standard. The solvent was removed in vacuo. The title compound **9** (0.310 g, 69% yield) was obtained as a colorless liquid after Kugelrohr distillation; bp 140 °C/5 mmHg. R_f=0.17 (100% MeOH); IR (neat) 3065 (aromatic C–H), 2968, 2941, 2860, 2818, 2768, 1679 (C=O), 1598, 1579, 1447, 1370, 1220, 1177, 1042, 973, 795, 703; ^{1}H NMR δ 1.21 (d, *J*=6.9 Hz, 3H, CHCH_3), 1.54–1.61 (m, 1H, CHCH*H*), 1.99–2.06 (m, 1H, CHC*H*H), 2.17 (s, 6H, N(CH_3)$_2$), 2.22–2.39 (m, 2H, NCH_2), 3.57 (sext, *J*=6.9 Hz, 1H, C*H*CH_3), 7.46 (br t, *J*=7.5 Hz, 2H, C*H*(CH)$_3$C*H*), 7.55 (br t, *J*=7.5 Hz, 1H, (CH)$_2$C*H*(CH)$_2$), 7.97 (br d, *J*=7.5 Hz, 2H, CHC*H*CHC*H*CH); ^{13}C NMR δ 17.5, 31.6, 38.6, 45.4 (2C), 57.4, 128.2 (2C), 128.5 (2C), 132.7, 136.8, 204.2. Anal. Calcd for $C_{13}H_{19}NO$ C, 76.06; H, 9.33; N, 6.82. Found C, 75.99; H, 9.39; N, 6.77.

4.1.5. Synthesis of (3*S*)-1,3-diphenylbutan-1-one[23] (34). The starting alkyl halide, (1*S*)-(1-chloroethyl)benzene **33**, was prepared according to the literature procedure[24] from (1*R*)-1-phenylethanol in 46% yield. The enantiomeric excess of the chloride was determined as 94.0% by GC analysis.

N′-(1-Phenylethylidene)-*N*,*N*-diethyl-1,2-ethanediamine (0.131 g, 0.6 mmol) was added to *t*-BuMgCl (2.06 M in THF, 0.29 mL, 0.6 mmol) at −78 °C. The mixture was stirred at 0 °C for 1 h, and then warmed to room temperature. After 1 h, (1*S*)-(1-chloroethyl)benzene **33** (0.070 g, 0.5 mmol, 94% ee) was added at room temperature. The reaction mixture was stirred at 30 °C for 36 h. AcOH in H_2O (50 wt %, 0.5 mL) was added slowly at 0 °C. The reaction mixture was stirred at 50 °C for 1 h and then cooled to room temperature. The reaction mixture was neutralized with saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with Et_2O five times. The combined organic extracts were dried with Na_2SO_4. After the solvents were removed in vacuo, the crude product was chromatographed on

silica gel (5 g, pentane and then 3% Et_2O in pentane) to obtain the title compound **34** (0.072 g, 64% yield, 89% ee) as a colorless liquid. The enantiomeric excess of the compound was determined by HPLC analysis (CHIRALCEL OJ-H, Daicel, 4.6×250 mm; column temperature, 15 °C; eluent, hexane/*i*-PrOH=99:1; flow rate, 0.3 mL/min; detector, 254 nm (UV)). Peaks at the retention times of 49.3 and 63.8 min; $[\alpha]_D^{26}$ +12.43 (*c* 0.58, CCl_4). The starting alkyl chloride was recovered (30% ^{1}H NMR yield, 81% ee). Similarly, the reaction at 50 °C for 12 h gave **34** in 78% yield with 85% ee (0.088 g).

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