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Synthesis of Tertiary *sec*-Alkylamines by the Addition of Grignard Reagents to *N*,*N*-Dialkylformamides Mediated by Ti(O*i*Pr)$_4$ and Me$_3$SiCl

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A number of tertiary *sec*-alkylamines (22 examples, 29–80 % yield) have been prepared according to a simple one-pot procedure by the addition of Grignard reagents to *N*,*N*-dialkylformamides in the presence of Ti(O*i*Pr)$_4$ and Me$_3$SiCl.

Introduction

Simple tertiary *sec*-alkylamines are easily available by the reaction of ketones with secondary amines under weakly acidic conditions in the presence of sodium cyanoborohydride.[1] However, this reductive amination gives poor yields or fails completely in the case of sterically congested ketones and diaryl ketones.[1] Only a few general methods are known for the synthesis of tertiary *sec*-alkylamines utilizing organometallic reagents. For example, such amines can be prepared according to a one-pot protocol based on the alkylation of *N*,*N*-disubstituted amides with organolithium compounds followed by reduction of the intermediates with lithium aluminum hydride,[2] by treatment of *N*,*N*-dialkylformamide dimethylacetal with Grignard reagents[3] or by dialkylation of iminium salts, obtained from *N*,*N*-dialkylformamides and phosgene, with organometallic reagents.[4] In the reaction of non-enolizable aldehydes with alkyltris(diethylamino)titanium such tertiary amines result by way of an overall direct replacement of the carbonyl *O*-atom by an alkyl and a diethylamino group.[5]

Results and Discussion

As we described previously, primary *tert*-alkylamines can be prepared by addition of organometallic reagents to nitriles under mediation of Ti(O*i*Pr)$_4$.[6] This led us to check whether tertiary *sec*-alkylamines can be obtained by addition of two equivalents of an organometallic reagent to *N*,*N*-dialkylcarboxamides in the presence of Ti(O*i*Pr)$_4$, starting with the most reactive *N*,*N*-dialkylformamides. When one equiv. of Ti(O*i*Pr)$_4$ and three equiv. of *p*-tolylmagnesium bromide (**2n**) were employed as in the protocol for the synthesis of primary *tert*-alkylamines from nitriles,[6] *N*,*N*-dimethylformamide (DMF, **1a**) gave the corresponding amine **3an** in low yield and accompanied by hardly removable impurities, while *N*-formylpyrrolidine (**1b**) or *N*-formylpiperidine (**1c**) and the same Grignard reagent did not provide any of the corresponding tertiary amine.

It is literature knowledge that in some reactions employing transition metal reagents, such as McMurry or Nozaki–Hiyama–Kishi couplings, the addition of chlorotrimethylsilane (Me$_3$SiCl) makes it possible to use catalytic instead of stoichiometric amounts of titanium or chromium reagents.[7,8] Following these literature precedents, the protocol for the reaction of *N*,*N*-dialkylformamides with arylmagnesium bromides was adjusted, and indeed, DMF (**1a**) in the presence of one equiv. of Me$_3$SiCl and 0.03 equiv. of Ti(O*i*Pr)$_4$ reacted with two equiv. of phenylmagnesium bromide (**2m**) to furnish the corresponding amine **3am** in 66% yield (Scheme 1, Table 1).[9] Under the same conditions, various tertiary amines each with one diarylmethyl substituent, were obtained in yields ranging from 29 to 80%.

In a control experiment, treatment of DMF (**1a**) with *p*-tolylmagnesium bromide (**2n**) in the presence of Me$_3$SiCl, but without Ti(O*i*Pr)$_4$, not even a trace of the amine **3an** was isolated. When Me$_3$SiCl and Ti(O*i*Pr)$_4$ were both employed in catalytic quantities (0.03 equiv.), the reaction failed as well.

Ethylmagnesium bromide (**2q**) upon reaction with *N*,*N*-dialkylformamides in the presence of a stoichiometric amount of Ti(O*i*Pr)$_4$ is known to furnish *N*,*N*-dialkylcy-

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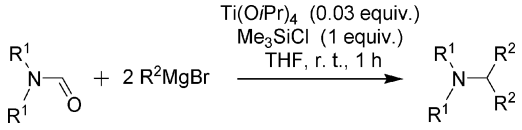


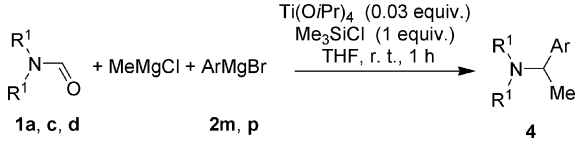
Scheme 1. Tertiary *sec*-alkylamines from *N*,*N*-dialkylformamides and Grignard reagents in the presence of $Ti(OiPr)_4$ and Me_3SiCl. For details see Table 1.

Table 1. Tertiary amines from *N*,*N*-dialkylformamides and Grignard reagents in the presence of $Ti(OiPr)_4$ and Me_3SiCl (see Scheme 1).

$R^1{}_2$ in formamide **1**	R^2 in R^2MgBr **2**	Product	% Yield
a Me_2	**m** Ph	**3am**	66
a Me_2	**n** 4-MeC_6H_4	**3an**	40
a Me_2	**o** 4-$MeOC_6H_4$	**3ao**	80
b $-(CH_2)_4-$	**m** Ph	**3bm**	41
b $-(CH_2)_4-$	**n** 4-MeC_6H_4	**3bn**	29
b $-(CH_2)_4-$	**o** 4-$MeOC_6H_4$	**3bo**	50
b $-(CH_2)_4-$	**p** 4-FC_6H_4	**3bp**	46
b $-(CH_2)_4-$	**q** Et	**3bq**	42
c $-(CH_2)_5-$	**m** Ph	**3cm**	76
c $-(CH_2)_5-$	**n** 4-MeC_6H_4	**3cn**	45
c $-(CH_2)_5-$	**o** 4-$MeOC_6H_4$	**3co**	52
c $-(CH_2)_5-$	**p** 4-FC_6H_4	**3cp**	62
c $-(CH_2)_5-$	**q** Et	**3cq**	35
d $-(CH_2)_2O(CH_2)_2-$	**m** Ph	**3dm**	43
d $-(CH_2)_2O(CH_2)_2-$	**n** 4-MeC_6H_4	**3dn**	45
d $-(CH_2)_2O(CH_2)_2-$	**o** 4-$MeOC_6H_4$	**3do**	40
d $-(CH_2)_2O(CH_2)_2-$	**p** 4-FC_6H_4	**3dp**	41

clopropylamines in good to very good yields.[10,11] Yet, under the current conditions, i.e. with $Ti(OiPr)_4$ in catalytic quantities, it reacted with *N*-formylpyrrolidine (**1b**) and *N*-formylpiperidine (**1c**) to give the corresponding tertiary *sec*-pentylamines **3bq** and **3cq**, albeit only in moderate yields of 35 and 42%, respectively.

The successive addition of two different Grignard reagents to *N*,*N*-dialkylformamides turned out to also be possible to provide tertiary amines with two different substituents at the secondary carbon atom (Scheme 2, Table 2). The two Grignard reagents were added to the reaction mixture simultanously,[9] but they could also be added one after the other. In all these cases a combination of an alkyl and an aryl Grignard reagent was employed. The use of two similar alkyl Grignard reagents turned out to be unfavorable due to difficulties in separating the products.

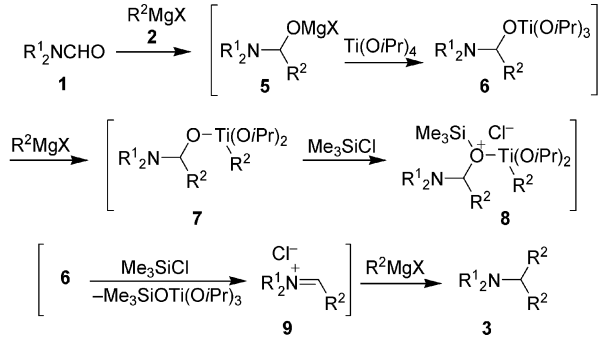


Scheme 2. Tertiary sec-alkylamines with two different substituents at the α-carbon from *N*,*N*-dialkylformamides and two different Grignard reagents. For details see Table 2.

The role of titanium tetraisopropoxide and chlorotrimethylsilane in the successive addition of the two molecules of a Grignard reagent to an *N*,*N*-dialkylformamide is not clear. The addition of the first entity is known to proceed without any catalyst to give the tetrahedral intermediate **5** (Scheme 3), which usually is quite stable. It presumably undergoes magnesium to titanium exchange with $Ti(OiPr)_4$ to form **6**, and the latter may then react with a second molecule of the Grignard reagent R^2MgX exchanging one of its isopropoxy groups for an R^2 group to give **7**. Chlorotrimethylsilane would then act as a Lewis acid coordinating at the oxygen of the *O*,*N*-acetal moiety and thus facilitate the intramolecular transfer of the residue R^2 in **8** from the titanium to the carbon atom next to the nitrogen. Alternatively, Me_3SiCl might react with the intermediate **6** to yield an aldimmonium chloride **9** with recovery of the catalytically active titanium tetraalkoxide, and the immonium salt **9** would then undergo addition of the second molecule of the Grignard reagent. Considering the relative concentrations of the various intermediates in the postulated mechanisms and the corresponding relative rates of their succeeding bimolecular reactions, the latter version is the more likely one.

Table 2. Tertiary *sec*-alkylamines with two different substituents at the α-carbon from *N*,*N*-dialkylformamides and two different Grignard reagents (see Scheme 2).

$R^1{}_2$ in formamide **1**	Ar in **2**	Product	% Yield
a Me_2	**m** Ph	**4am**	60
c $-(CH_2)_5-$	**m** Ph	**4cm**	46
d $-(CH_2)_2O(CH_2)_2-$	**m** Ph	**4dm**	52
c $-(CH_2)_5-$	**p** 4-FC_6H_4	**4cp**	43
a Me_2	**r** Bn	**4ar**	31



Scheme 3. Mechanistic rationalization of the formation of tertiary *sec*-alkylamines from *N*,*N*-dialkylformamides and two equivalents of a Grignard reagent in the presence of $Ti(OiPr)_4$ and Me_3SiCl.

Unfortunately, this transformation is limited to *N*,*N*-dialkylformamides. Even *N*,*N*-dialkylacetamides and *N*-(trifluoracetyl)pyrrolidine did not yield the amines under the same conditions. It is an open question, whether this is due to an electronic or a steric effect.

Conclusions

This new approach to tertiary amines with secondary alkyl groups essentially leads to structures that have significant importance as pharmacologically active compounds as for example the amphetamines.[12]

Experimental Section

General Remarks: NMR spectra were recorded with a Bruker DPX 300 instrument at 300 (^{1}H) and 75 (^{13}C and DEPT) MHz. All spectra were calibrated against tetramethylsilane as an internal standard (δ = 0 ppm) or the signals of the residual protons of deuterated solvents: δ = 7.26 for $CHCl_3$, δ = 2.50 for [D_5]DMSO. Multiplicities of signals are described as follows: s = singlet, d = doublet, t = triplet, q = quadruplet, m_c = centered multiplet. Coupling constants (J) are given in Hz; J values in ^{13}C NMR spectra refer to ^{13}C-^{19}F couplings. EI-MS (70 eV) data were recorded with a Finnigan MAT 95 spectrometer. HRMS data were acquired with a Micromass LCT (TOF MS, electrospray ionization, positive and negative modes). Analytical TLC was performed on Machery-Nagel ready-to-use plates (PolyGram Alox N/UV_{254}). Detection was achieved by development with molybdatophosphoric acid solution (5% in EtOH). Column chromatography: Merck aluminum oxide 90 active neutral, 70–230 mesh. Elemental analyses were carried out by the Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie der Georg-August-Universität, Göttingen. Solvents were purified by standard procedures.

General Procedure for the Synthesis of Tertiary *sec*-Alkylamines 3: To a solution of the respective *N*,*N*-dialkylformamide **1** (5 mmol) in THF (40 mL) was added Me_3SiCl (543 mg, 5 mmol), Ti(O*i*Pr)$_4$ (48 mg, 0.17 mmol), and after stirring for 10 min, a solution of the respective Grignard reagent **2** was added at r. t. Stirring was continued at r. t. for 1 h, then 10% aq. NaOH (30 mL) was added. The mixture was filtered, and the filtrate was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography on aluminum oxide, eluting with hexane or hexane/*tert*-butyl methyl ether.

***N*-Benzhydryl-*N*,*N*-dimethylamine (3am):** From DMF (**1a**, 365 mg, 5.0 mmol) and phenylmagnesium bromide (**2m**, 11 mmol) the amine **3am** was obtained as a colorless solid (699 mg, 66%), m.p. 69 °C.[13]

***N*-(4,4′-Dimethylbenzhydryl)-*N*,*N*-dimethylamine (3an):** From DMF (**1a**, 365 mg, 5 mmol) and *p*-tolylmagnesium bromide (**2n**, 11 mmol) the amine **3an** was obtained as a colorless solid (478 mg, 40%), m.p. 40 °C.[14]

***N*-(4,4′-Dimethoxybenzhydryl)-*N*,*N*-dimethylamine (3ao):** From DMF (**1a**, 365 mg, 5 mmol) and 4-methoxyphenylmagnesium bromide (**2o**, 11 mmol) the amine **3ao** was obtained as a colorless solid (1070 mg, 80%), m.p. 83 °C.[15]

***N*-Benzhydrylpyrrolidine (3bm):** From *N*-formylpyrrolidine (**1b**, 496 mg, 5 mmol) and phenylmagnesium bromide (**2m**, 11 mmol) the amine **3bm** was obtained as a colorless solid (483 mg, 41%), m.p. 75 °C.[16]

***N*-(4,4′-Dimethylbenzhydryl)pyrrolidine (3bn):** From *N*-formylpyrrolidine (**1b**, 496 mg, 5 mmol) and *p*-tolylmagnesium bromide (**2n**, 11 mmol) the amine **3bn** was obtained as a colorless solid (390 mg, 29%), m.p. 73 °C. ^{1}H NMR ([D_6]DMSO): δ = 1.69 (m_c, 4 H), 2.22 (s, 6 H), 2.31 (m_c, 4 H), 4.11 (s, 1 H), 7.05 (d, $^3J_{H,H}$ = 7.9 Hz, 4 H), 7.29 (d, $^3J_{H,H}$ = 8.0 Hz, 4 H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 20.4 (CH_3), 23.0 (CH_2), 52.8 (CH_2), 74.5 (CH), 126.8 (CH), 128.7 (CH), 135.5 (C), 140.5 (C) ppm. MS (70 eV): *m*/*z* (%) = 265 (19) [M]$^+$, 195 (100) [M – C_4H_8N]$^+$, 174 (60) [M – C_7H_7]$^+$. $C_{19}H_{23}N$ (265.4): calcd. C 85.99, H 8.74, N 5.28; found C 86.00, H 8.70, N 5.54.

***N*-(4,4′-Dimethoxybenzhydryl)pyrrolidine (3bo):** From *N*-formylpyrrolidine (**1b**, 496 mg, 5 mmol) and 4-methoxyphenylmagnesium bromide (**2o**, 11 mmol) the amine **3bo** was obtained as a colorless solid (731 mg, 50%), m.p. 76 °C. ^{1}H NMR ([D_6]DMSO): δ = 1.66 (m_c, 4 H), 2.29 (m_c, 4 H), 3.67 (s, 6 H), 4.07 (s, 1 H), 6.08 (d, $^3J_{H,H}$ = 8.7 Hz, 4 H), 7.30 (d, $^3J_{H,H}$ = 8.7 Hz, 4 H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 23.0 (CH_2), 52.8 (CH_2), 54.8 (CH_3), 73.7 (CH), 113.5 (CH), 127.8 (CH), 136.8 (C), 157.7 (C) ppm. MS (70 eV): *m*/*z* (%) = 296 (1) [M – H]$^+$, 227 (100) [M – C_4H_8N]$^+$, 190 (4) [M – C_7H_7O]$^+$. $C_{19}H_{23}NO_2$ (297.4): calcd. C 76.74, H 7.80, N 4.71; found C 76.40, H 7.89, N 4.49.

***N*-(4,4′-Difluorobenzhydryl)pyrrolidine (3bp):** From *N*-formylpyrrolidine (**1b**, 496 mg, 5 mmol) and 4-fluorophenylmagnesium bromide (**2p**, 11 mmol) the amine **3 bp** was obtained as a yellow oil (624 mg, 46%). ^{1}H NMR ([D_6]DMSO): δ = 1.64 (m_c, 4 H), 2.27 (m_c, 4 H), 4.22 (s, 1 H), 7.01–7.08 (m, 4 H), 7.40–7.47 (m, 4 H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 23.0 (CH_2), 52.6 (CH_2), 73.1 (CH), 114.9 (d, $^2J_{C,F}$ = 21.1 Hz, CH), 128.6 (d, $^3J_{C,F}$ = 7.5 Hz, CH), 140.2 (C), 160.8 (d, $^1J_{C,F}$ = 243.0 Hz, 1 C) ppm. MS (70 eV): *m*/*z* (%) = 273 (35) [M]$^+$, 203 (100) [M – C_4H_8N]$^+$, 178 (78) [M – C_6H_4F]$^+$. $C_{17}H_{17}F_2N$ (273.3): calcd. C 74.70, H 6.27, N 5.12; found C 74.53, H 6.47, N 5.22.

***N*-(1-Ethylpropyl)pyrrolidine (3bq):** From *N*-formylpyrrolidine (**1b**, 496 mg, 5 mmol) and ethylmagnesium bromide (**2q**, 11 mmol) the amine **3bq** was obtained as a yellow oil (296 mg, 42%), b. p. 69–70 °C (19 mm).[17]

***N*-Benzhydrylpiperidine (3cm):** From *N*-formylpiperidine (**1c**, 565 mg, 5 mmol) and phenylmagnesium bromide (**2m**, 11 mmol) the amine **3 cm** was obtained as a colorless solid (954 mg, 76%), m.p. 74 °C.[18]

***N*-(4,4′-Dimethylbenzhydryl)piperidine (3cn):** From *N*-formylpiperidine (**1c**, 565 mg, 5 mmol) and *p*-tolylmagnesium bromide (**2n**, 11 mmol) the amine **3cn** was obtained as a colorless solid (625 mg, 45%), m.p. 66 °C. ^{1}H NMR ([D_6]DMSO): δ = 1.36 (m_c, 2 H), 1.45 (m_c, 4 H), 2.19 (s, 6 H), 2.21 (m_c, 4 H), 4.13 (s, 1 H), 7.03 (d, $^3J_{H,H}$ = 8.0 Hz, 4 H), 7.21 (d, $^3J_{H,H}$ = 8.1 Hz, 4 H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 20.4 (CH_3), 24.1 (CH_2), 25.6 (CH_2), 52.3 (CH_2), 74.9 (CH), 127.2 (CH), 128.7 (CH), 135.3 (C), 140.2 (C) ppm. MS (70 eV): *m*/*z* (%) = 279 (35) [M]$^+$, 195 (100) [M – $C_5H_{10}N$]$^+$, 188 (50) [M – C_7H_7]$^+$. $C_{20}H_{25}N$ (279.4): calcd. C 85.97, H 9.02, N 5.01; found C 86.09, H 9.07, N 5.16.

***N*-(4,4′-Dimethoxybenzhydryl)piperidine (3co):** From *N*-formylpiperidine (**1c**, 565 mg, 5 mmol) and 4-methoxyphenylmagnesium bromide (**2o**, 11 mmol) the amine **3co** was obtained as a yellow solid (804 mg, 52%), m.p. 86 °C. ^{1}H NMR ([D_6]DMSO): δ = 1.37 (m_c, 2 H), 1.48 (m_c, 4 H), 2.23 (m_c, 4 H), 3.69 (s, 6 H), 4.15 (s, 1 H), 6.83 (d, $^3J_{H,H}$ = 8.7 Hz, 4 H), 7.25 (d, $^3J_{H,H}$ = 8.7 Hz, 4 H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 24.1 (CH_2), 25.6 (CH_2), 52.3 (CH_2), 54.8 (CH_3), 74.0 (CH), 113.5 (CH), 128.3 (CH), 136.8 (C), 157.7 (C) ppm. MS (70 eV): *m*/*z* (%) = 311 (2) [M]$^+$, 227 (100) [M – $C_5H_{10}N$]$^+$. $C_{20}H_{25}NO_2$ (311.4): calcd. C 77.14, H 8.09, N 4.50; found C 77.13, H 7.94, N 4.48.

***N*-(4,4′-Difluorobenzhydryl)piperidine (3cp):** From *N*-formylpiperidine (**1c**, 565 mg, 5 mmol) and 4-fluorophenylmagnesium bromide (**2p**, 11 mmol) the amine **3cp** was obtained as a yellow oil (887 mg, 62%). ^{1}H NMR ([D_6]DMSO): δ = 1.39 (m_c, 2 H), 1.51 (m_c, 4 H), 2.24 (m_c, 4 H), 4.35 (s, 1 H), 7.08–7.14 (m, 4 H), 7.38–7.42 (m, 4 H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 24.0 (CH_2), 25.5 (CH_2), 52.1 (CH_2), 73.5 (CH), 114.9 (d, $^2J_{C,F}$ = 21.1 Hz, CH), 129.1 (d, $^3J_{C,F}$ = 7.5 Hz, CH), 138.7 (C), 160.8 (d, $^1J_{C,F}$ = 243.8 Hz, 1 C) ppm. MS (70 eV): *m*/*z* (%) = 287 (65) [M]$^+$, 203 (100) [M – $C_5H_{10}N$]$^+$, 192 (75) [M – C_6H_4F]$^+$. $C_{18}H_{19}F_2N$ (287.4): calcd. C 75.24, H 6.66; found C 75.38, H 6.34.

***N*-(1-Ethylpropyl)piperidine (3cq):** From *N*-formylpiperidine (**1c**, 565 mg, 5 mmol) and ethylmagnesium bromide (**2q**, 11 mmol) the amine **3cq** was obtained as a yellow oil (272 mg, 35%).[19]

***N*-Benzhydrylmorpholine (3dm):** From *N*-formylmorpholine (**1d**, 575 mg, 5 mmol) and phenylmagnesium bromide (**2n**, 11 mmol) the amine **3dm** was obtained as a colorless solid (548 mg, 43%), m.p. 70 °C.[20]

***N*-(4,4′-Dimethylbenzhydryl)morpholine (3dn):** From *N*-formylmorpholine (**1d**, 575 mg, 5 mmol) and *p*-tolylmagnesium bromide (**2n**, 11 mmol) the amine **3dn** was obtained as a yellow solid (630 mg, 45%), m.p. 63 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 2.22 (s, 6 H), 2.24 (t, $^3J_{H,H}$ = 4.5 Hz, 4 H), 3.57 (t, $^3J_{H,H}$ = 4.6 Hz, 4 H), 4.16 (s, 1 H), 7.07 (d, $^3J_{H,H}$ = 7.9 Hz, 4 H), 7.27 (d, $^3J_{H,H}$ = 8.0 Hz, 4 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 20.4 (CH$_3$), 52.1 (CH$_2$), 66.1 (CH$_2$), 74.8 (CH), 127.3 (CH), 128.8 (CH), 135.7 (C), 137.4 (C) ppm. MS (70 eV): *m*/*z* (%) = 281 (29) [M]$^+$, 195 (100) [M – C$_4$H$_8$NO]$^+$, 190 (10) [M – C$_7$H$_7$]$^+$. C$_{19}$H$_{23}$NO (281.4): calcd. C 81.10, H 8.24, N 4.98; found C 81.26, H 8.18, N 4.74.

***N*-(4,4′-Dimethoxybenzhydryl)morpholine (3do):** From *N*-formylmorpholine (**1d**, 575 mg, 5 mmol) and 4-methoxyphenylmagnesium bromide (**2o**, 11 mmol) the amine **3do** was obtained as a yellow oil (642 mg, 40%). ^{1}H NMR ([D$_6$]DMSO): δ = 2.25 (t, $^3J_{H,H}$ = 9.1 Hz, 4 H), 3.57 (m$_c$, 4 H), 3.69 (s, 6 H), 4.14 (s, 1 H), 6.84 (d, $^3J_{H,H}$ = 8.7 Hz, 4 H), 7.29 (d, $^3J_{H,H}$ = 8.7 Hz, 4 H) ppm. ^{13}C NMR ([D$_6$]-DMSO): δ = 52.1 (CH$_2$), 54.8 (CH$_3$), 66.1 (CH$_2$), 74.0 (CH), 113.6 (CH), 128.4 (CH), 134.5 (C), 157.9 (C) ppm. MS (70 eV): *m*/*z* (%) = 311 (1) [M]$^+$, 227 (100) [M – C$_4$H$_8$NO]$^+$, 206 (2) [M – C$_7$H$_7$O]$^+$.

***N*-(4,4′-Difluorobenzhydryl)morpholine (3dp):** From *N*-formylmorpholine (**1d**, 575 mg, 5 mmol) and 4-fluorophenylmagnesium bromide (**2p**, 11 mmol) the amine **3dp** was obtained as a colorless solid (588 mg, 41%), m.p. 75 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 2.22 (t, $^3J_{H,H}$ = 4.5 Hz, 4 H), 3.55 (t, $^3J_{H,H}$ = 4.5 Hz, 4 H), 4.29 (s, 1 H), 7.04–7.11 (m, 4 H), 7.38–7.43 (m, 4 H) ppm. ^{13}C NMR ([D$_6$]-DMSO): δ = 51.9 (CH$_2$), 66.1 (CH$_2$), 73.3 (CH), 115.1 (d, $^2J_{C,F}$ = 21.1 Hz, CH), 129.2 (d, $^3J_{C,F}$ = 8.3 Hz, CH), 138.1 (C), 160.9 (d, $^1J_{C,F}$ = 243.0 Hz, 1 C) ppm. MS (70 eV): *m*/*z* (%) = 289 (46) [M]$^+$, 203 (100) [M – C$_4$H$_8$NO]$^+$, 194 (10) [M – C$_6$H$_4$F]$^+$. C$_{17}$H$_{17}$F$_2$NO (289.3): calcd. C 70.57, H 5.92, F 13.13; found C 70.75, H 6.01, F 13.10.

General Procedure for the Synthesis of Tertiary *sec*-Alkylamines 4: To a solution of the respective *N*,*N*-dialkylformamide **1** (5 mmol) in THF (40 mL) was added Me$_3$SiCl (543 mg, 5 mmol) and Ti(O*i*Pr)$_4$ (48 mg, 0.17 mmol). After stirring for 10 min, solutions of MeMgCl and the respective second Grignard reagent were added simultanously at r.t. Stirring was continued for 1 h, then 10% aq. NaOH (30 mL) was added. The mixture was filtered, and the filtrate was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was distilled using a kugelrohr apparatus to furnish the product.

***N*-(1-Phenylethyl)-*N*,*N*-dimethylamine (4am):** From DMF (**1a**, 365 mg, 5 mmol), methylmagnesium chloride (5 mmol) and phenylmagnesium bromide (**2m**, 5 mmol) the amine **4am** was obtained as a yellow oil (440 mg, 60%).[21]

***N*-(1-Phenylethyl)piperidine (4cm):** From *N*-formylpiperidine (**1c**, 565 mg, 5 mmol), methylmagnesium chloride (5 mmol) and phenylmagnesium bromide (**2m**, 5 mmol) the amine **4 cm** was obtained as a yellow oil (433 mg, 46%).[22]

***N*-(1-Phenylethyl)morpholine (4dm):** From *N*-formylmorpholine (**1d**, 575 mg, 5 mmol), methylmagnesium chloride (5 mmol) and phenylmagnesium bromide (**2m**, 5 mmol) the amine **4dm** was obtained as a yellow oil (490 mg, 52%).[20]

***N*-[1-(4-Fluorphenyl)ethyl]piperidine (4cp):** From *N*-formylpiperidine (**1c**, 569 mg, 5 mmol), methylmagnesium chloride (5 mmol) and 4-fluorophenylmagnesium bromide (**2p**, 5 mmol) the amine **4cp** was obtained as a reddish oil (450 mg, 43%). ^{1}H NMR ([D$_6$]-DMSO): δ = 1.25 (d, $^3J_{H,H}$ = 6.8 Hz, 3 H), 1.33 (m$_c$, 2 H), 1.46 (m$_c$, 4 H), 2.29 (m$_c$, 4 H), 3.42 (q, $^3J_{H,H}$ = 6.8 Hz, 1 H), 7.07–7.37 (m, 4 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 18.4 (CH$_3$), 24.1 (CH$_2$), 25.7 (CH$_2$), 50.4 (CH$_2$), 62.9 (CH), 114.4 (d, $^2J_{C,F}$ = 20.4 Hz, CH), 128.9 (d, $^3J_{C,F}$ = 8.3 Hz, CH), 139.6 (C), 161.4 (d, $^1J_{C,F}$ = 152.4 Hz, 1 C) ppm. MS (70 eV): *m*/*z* (%) = 207 (7) [M]$^+$, 192 (100) [M – CH$_3$]$^+$, 123 (11) [M – C$_5$H$_{10}$N]$^+$, 112 (9) [M – C$_6$H$_4$F]$^+$.

***N*-(1-Methyl-2-phenyl)-*N*,*N*-dimethylamine (4ar):** From DMF (**1a**, 365 mg, 5 mmol), methylmagnesium chloride (5 mmol) and benzylmagnesium chloride (**2r**, 5 mmol) the amine **4ar** was obtained as a colorless oil (250 mg, 31%).[23]

Supporting Information (see also the footnote on the first page of this article): NMR spectra of tertiary *sec*-alkylamines.

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