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Synthesis of Trialkylamines with Extreme Steric Hindrance and Their Decay by a Hofmann-like Elimination Reaction

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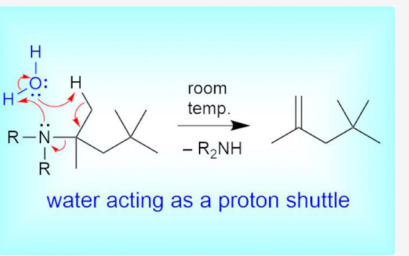
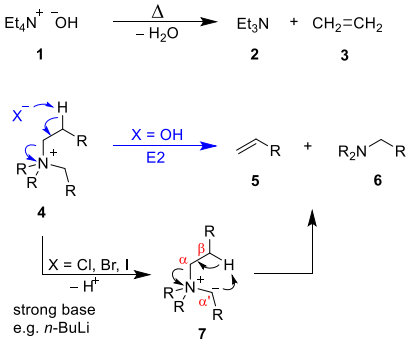
ABSTRACT: A number of amines with three bulky alkyl groups at the nitrogen, which surpass the steric crowding of triisopropylamine considerably, were prepared by using different synthetic methods. It turned out that treatment of *N*-chlorodialkylamines with organometallic compounds, for example, Grignard reagents, in the presence of a major excess of tetramethylenediamine offered the most effective access to the target compounds. The limits of this method were also tested. The trialkylamines underwent a dealkylation reaction, depending on the degree of steric stress, even at ambient temperature. Because olefins were formed in this transformation, it showed some similarity with the Hofmann elimination. However, the thermal decay of sterically overcrowded tertiary amines was not promoted by bases. Instead, this reaction was strongly accelerated by protic conditions and even by trace amounts of water. Reaction mechanisms, which were analyzed with the help of quantum chemical calculations, are suggested to explain the experimental results.



INTRODUCTION

The first report of the decay of a tetraalkylammonium salt, which resulted in the formation of a tertiary amine **2**, an olefin and water, dates back to 1851 (Scheme 1).[1] Such Hofmann elimination reactions were utilized for the analysis of natural products such as nitrogen bases and can also be used in organic synthesis.[2] This method to prepare alkenes includes regioselective generation of a terminal C=C bond and is presented in textbooks of organic chemistry as an E2 reaction.[3] However, other reaction mechanisms have also been discussed, for example, the E1cb two-step sequence, and alternatively, an α-elimination or the formation of an ylide intermediate.[4] In any case, a base is necessary to initiate the deprotonation of the substrate in the β-, α-, or α'-position. Performing the Hofmann elimination in the presence of reagents with different base strengths led to olefinic products with distinct stereochemistry, and this was explained through varying reaction mechanisms (e.g., E2 vs E1cb).[5] Whereas the classical transformation requires temperatures of 100−200 °C, treatment of quaternary ammonium salts with strong bases such as *n*-butyllithium enabled Hofmann elimination under significantly milder reaction conditions. Thus, a sequence via ylide intermediate **7** was suggested to rationalize the rapid formation of the olefin **5** from substrate **4** (Wittig modification, α',β mechanism).[6,7]

Scheme 1. First Hofmann Elimination Using Substrate 1 and Some Mechanisms of Such Reactions



Recently, we reported the synthesis of tertiary amines with three bulky alkyl groups, which established new records of steric distress.[8] These products exhibited restricted rotation about the C−N bond and thus surprising NMR spectra. Moreover, trialkylamines with a high degree of steric congestion such as **8** underwent Hofmann-like elimination when heated in toluene (Scheme 2). Hence, the secondary amine **9** and the olefin **10** were formed under mild reaction conditions in the absence of any additional base. Similarly, the 2-aminothiazole **11** underwent a cleavage reaction to produce **10** and **12** during attempts at isolation or on contact with silica gel at room temperature (rt).[9] In this report, the mechanism of such Hofmann-like elimination reactions, which differs

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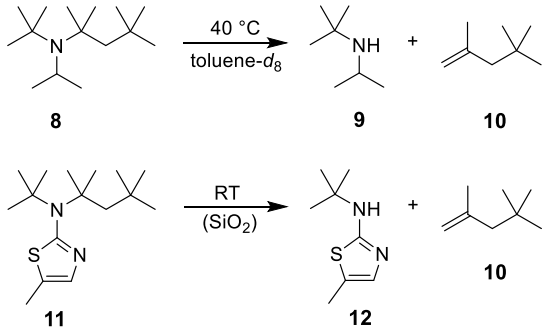
Scheme 2. Hofmann-like Elimination of Amines 8 and 11

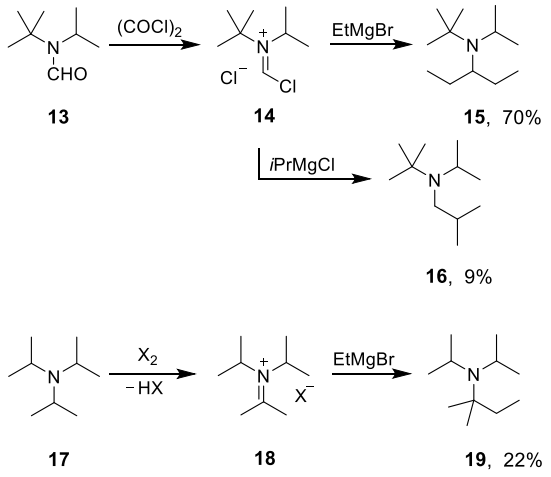


significantly from those of classical Hofmann eliminations, was studied experimentally and by using quantum chemical methods.

RESULTS AND DISCUSSION

Synthesis of Trialkylamines. We investigated different methods to prepare new amines, each bearing three bulky alkyl groups. First, we treated the Vilsmeier reagent **14**, which was easily available from formamide **13**,[8] with ethylmagnesium bromide and obtained the tertiary amine **15** in 70% yield based on **13** (Scheme 3). However, exposure of **14** to isopropyl-

Scheme 3. Synthesis of Trialkylamines via Iminium Salts

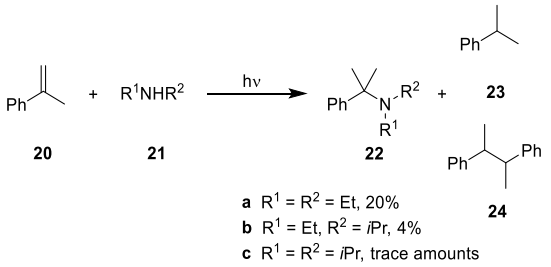


magnesium chloride did not lead to the desired 2,4-dimethylpent-3-ylamine because isobutylamine **16** was formed instead in low yield (9% based on **13**). Obviously, nucleophilic attack of the Grignard reagent at **14** was accompanied by β-hydride transfer of isopropylmagnesium chloride to the substrate. Another limitation resulted from the fact that dialkylformamides with bulkier groups, such as *N*,*N*-di-*tert*-butylformamide, did not produce iminium salts of type **14** as isolable precipitates. Direct treatment of the latter formamide with Grignard reagents, however, gave low yields of the desired trialkylamines only.[8] Furthermore, the reaction of di-*tert*-amylformamide with methyl Grignard reagents or methyllithium exclusively yielded the corresponding secondary amine via cleavage of the amide.

We also utilized the iminium salts **18**, which were prepared by oxidation of triisopropylamine (**17**) with the help of bromine or iodine. Subsequent exposure of **18** to ethylmagnesium bromide furnished the amine **19** in 22% yield based on **17**. The drawback of this simple method is due to the generation of the byproduct hydrogen halide, which transforms **17** into the corresponding ammonium salt. After addition of the Grignard reagent, the latter salt liberates **17**, which then has to be separated from **19**, giving a lower isolated yield of the desired amine. An additional limitation of this synthetic method resulted from the fact that halogen-induced oxidation of isopropylamines with greater steric hindrance than **17**, for example, *tert*-butyldiisopropylamine,[8] followed by treatment with Grignard reagents, did not lead to the desired trialkylamines.

An alternative method to prepare tertiary amines with a high degree of steric congestion is based on the photochemical hydroamination of styrene derivatives such as **20**, which was reported to furnish a 20% yield of **22a** when diethylamine (**21a**) was used as the reaction partner (Scheme 4).[10] The

Scheme 4. Synthesis of Trialkylamines by Photochemical Hydroamination



mechanism proposed for such transformations involves electron transfer, followed by regioselective proton transfer and carbon−nitrogen bond formation of the resulting radical pair. The generation of **22** is always accompanied by photochemical reduction of **20**, leading to **23** and **24** even though a great excess of **21a** is used. We performed the hydroamination of α-methylstyrene (**20**) by irradiation in the presence of a very large excess of the secondary amines **21b** or **21c** to get the products **22b** and **22c**, respectively. However, the yields were disappointing low, and isolation of the desired products proved to be laborious.

The reaction of *N*-chlorodialkylamines **25** with organometallic reagents, especially Grignard reagents in the presence of a major excess of tetramethylethylenediamine (TMEDA), is one of the most potent methods to prepare tertiary amines with three bulky alkyl groups,[8,11] particularly as the starting compounds are easily available by chlorination of the corresponding secondary amines using *N*-chlorosuccinimide (NCS). When we utilized this method for the synthesis of the trialkylamines **22b,c**, the yields were significantly higher than those which were achieved in the photochemical hydroamination of α-methylstyrene (**20**). Most transformations, summarized in Scheme 5, were performed with the help of Grignard reagents; *n*-butyllithium was used in the case of **27a**, isobutyllithium was used for **27b**, and *sec*-butyllithium was used for **26d** and **27d**.[12] The amine **26a** was prepared with the aid of methyllithium in 37% yield, while the reagent methylmagnesium bromide led to a similar yield and methylmagnesium chloride or methylmagnesium iodide gave lower yields of **26a**.[13] When the yields of **22b** and **22c** are compared with each other or those of **26a−e**, **27a−e**, **30a,b**, or **30c−e** are analyzed, it is obvious that primary organometallic compounds afforded the best yields, whereas tertiary organo-

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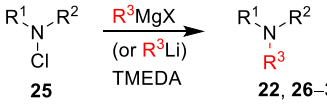
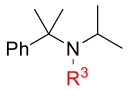
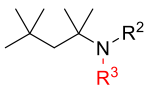
Scheme 5. Synthesis of Trialkylamines from *N*-Chlorodialkylamines 25

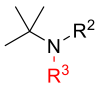




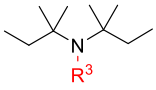
22b R^3 = Et, 49%
22c R^3 = *i*Pr, 38%



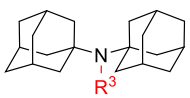
26a R^2 = *t*-Bu, R^3 = Me, 37%
26b R^2 = *t*-Bu, R^3 = Et, 43%
26c R^2 = *t*-Bu, R^3 = cyclopentyl, 4%
26d R^2 = *t*-Bu, R^3 = *s*-Bu, 8% (NMR)
26e R^2 = *t*-Bu, R^3 = Cy, 6% (NMR)
26f R^2 = 1-adamantyl, R^3 = *i*Pr, 4% (NMR)



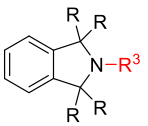
27a R^2 = *t*-Bu, R^3 = *n*-Bu, 68%
27b R^2 = *t*-Bu, R^3 = *i*-Bu, 62%
27c R^2 = *t*-Bu, R^3 = CH_2*t*-Bu, 33%
27d R^2 = *t*-Bu, R^3 = *s*-Bu, 27%
27e R^2 = *t*-amyl, R^3 = *i*Pr, 26%
27f R^2 = Cy, R^3 = Cy, 22%
27g R^2 = *i*Pr, R^3 = *i*Pr, 46%



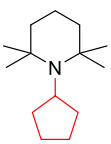
28a R^3 = cyclopentyl, 25%
28b R^3 = Cy, 22%
28c R^3 = *i*Pr, 19%



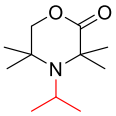
29a R^3 = CH_2*t*-Bu, 36%
29b R^3 = cyclopentyl, 26%
29c R^3 = *i*Pr, 30%
29d R^3 = *exo*-2-norbornyl, 16%



30a R = Me, R^3 = *i*Pr, 26%
30b R = Me, R^3 = *t*-Bu, 5.5%
30c R = Et, R^3 = Et, 64%
30d R = Et, R^3 = *i*Pr, 22%
30e R = Et, R^3 = *t*-Bu, ca. 3%



31, 22%



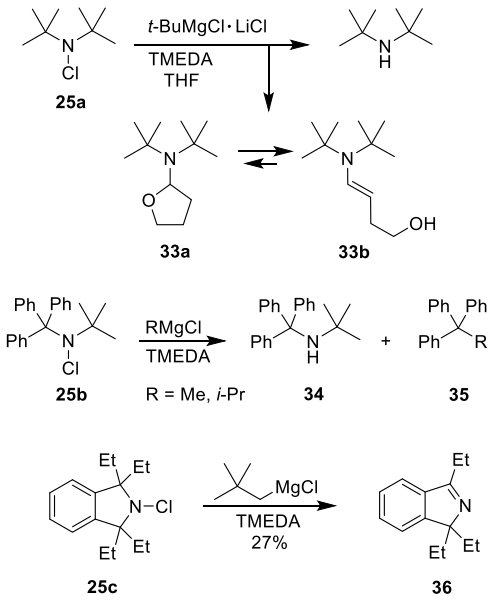
32, 40%

metallic reagents produced significantly lower yields than secondary reagents. Decreasing yields can be correlated with increasing steric congestion in the resulting trialkylamines; however, there is an extra effect in the case of tertiary organometallic compounds. Thus, treatment of *N*-chlorodicyclohexylamine with *tert*-butylmagnesium chloride did not lead to the desired product **27f**, while **27f** is formed in 22% yield from *N*-*tert*-butyl-*N*-chlorocyclohexylamine and cyclohexylmagnesium chloride. We expected a low yield in the synthesis of the extremely sterically hindered amine **30e**. Surprisingly, generation of **30e** from *tert*-butylmagnesium chloride and the corresponding *N*-chloroamine **25** was accompanied by the creation of **30c**,[14] which could not be separated from the desired product.

The formation of secondary amines by reduction of the *N*-chlorodialkylamines **25** was always observed, when such substrates were treated with organometallic reagents to prepare trialkylamines. In the case of low yields of the desired tertiary amines and especially with tertiary organometallic compounds, the main reaction leads to the unwanted secondary amines. Nevertheless, amines with three bulky alkyl groups such as **32** can be synthesized in moderate yield, although the product includes a lactone unit. On the other hand, *tert*-octylamines **26d–f** (*tert*-octyl = 1,1,3,3-tetramethylbutyl) were accessible with low yields only. These yields were determined by ^{1}H NMR spectroscopy because isolation of the tertiary amines was always accompanied by a cleavage reaction with formation of the olefin **10** and the corresponding secondary amine. Thus, the substances **26d–f** are unstable and show properties similar to those of amine **8**.

When we treated the substrate **25a** with *tert*-butyllithium to prepare tri-*tert*-butylamine, the limits of this synthetic method were exceeded (Scheme 6). Instead of the desired product, we

Scheme 6. Limits of the Synthesis of Tertiary Amines from Sterically Demanding *N*-Chlorodialkylamines 25



obtained di-*tert*-butylamine nearly exclusively; however, a small amount (ca. 1% yield) of the surprising trialkylamine **27a** was also isolated. Possibly, buyable *tert*-butyllithium included a small impurity of *n*-butyllithium, which was responsible for the formation of **27a**. The reaction of **25a** with *tert*-butylmagnesium chloride, which was activated by exposure to lithium chloride,[15] led in the presence of TMEDA and tetrahydrofuran (THF) to a small yield of the equilibrating products **33a** and **33b**, but the desired tri-*tert*-butylamine was not formed. Treatment of **25a** with cyclopropyllithium was also in vain although the desired product, di-*tert*-butylcyclopropylamine, was previously prepared by another method.[16] In the case of the starting compound **25b**, which was quantitatively available from the corresponding secondary amine **34** and trichloroisocyanuric acid (TCCA), the two very bulky alkyl groups prevented any generation of trialkylamines; and even if **25b** was reacted with secondary or primary Grignard reagents, the formation of the dechlorination product **34** and the hydrocarbons **35** was exclusively observed. When the substrate **25c** was treated with neopentylmagnesium chloride, the surprising imine **36** was obtained instead of the desired tertiary amine. Finally, we also tested the arylation of *N*-chloro-*tert*-butylisopropylamine with the help of 2,6-dimethylphenylmag-

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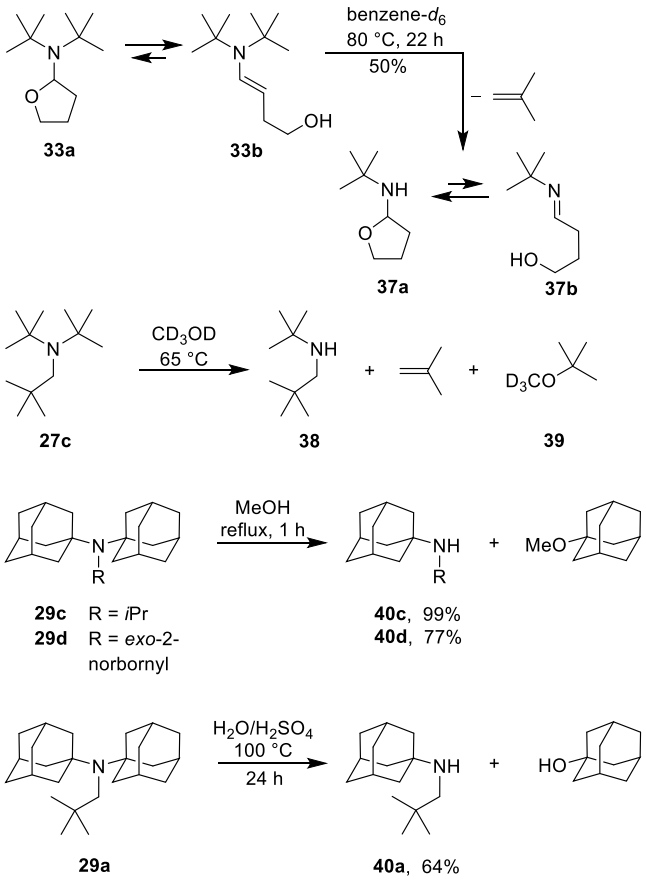
nesium bromide. This experiment did not lead to the tertiary aniline derivative because of clearly excessive steric hindrance.[17]

Dealkylation of Tertiary Amines. We investigated the decay of unstable *tert*-octylamines **8** and **26f** by heating solutions in toluene-d_8 at 40 °C. Under these conditions, **26f** showed a half-life $t_{1/2}$ of ca. 60 h (^{1}H NMR), whereas decomposition of **8** led to $t_{1/2}$ of 30 h. In both cases, the olefin **10** was formed, according to Hofmann's rule, besides the corresponding secondary amines. When the rates of the reaction **8** → **9** + **10** were measured in the temperature range of 20−60 °C, we determined E_a = (19.5 ± 1.3) kcal/mol, ln(A) = 19.8 ± 2.1, $\Delta H^{\ddagger}$ = (18.9 ± 1.3) kcal/mol, $\Delta S^{\ddagger}$ = (−20.9 ± 4.2) cal/mol K, and $\Delta G^{\ddagger}_{313}$ = (25.4 ± 1.6) kcal/mol. It turned out that the elimination of an olefin was strongly accelerated if traces of water were present in the toluene solution of the tertiary amine. When a small amount of H_2O or alternatively an equivalent amount of D_2O were dissolved in the solvent toluene-d_8, a kinetic isotope effect with k_H/k_D = 1.9 was measured for the Hofmann-like elimination **8** → **9** + **10**.[12] Thus, the cleavage of the hydrogen−oxygen bond of water seems to be involved in the elimination reaction. On the other hand, addition of *n*-butyllithium to a solution of **8** in toluene-d_8 stopped the formation of **9** and **10** at 40 °C. Obviously, any traces of moisture and protic conditions were completely precluded by the organometallic reagent. Thus, the stabilizing properties of *n*-butyllithium in the thermolysis of **8** are in marked contrast to the classical Hofmann elimination of quaternary ammonium salts, which is sharply accelerated by the same reagent (Scheme 1). We also studied the thermal decay of the tertiary amine **26b** in toluene-d_8 at 100 °C, leading to **10** and *tert*-butylethylamine. With a half-life of $t_{1/2}$ = 1−2 days, this transformation proved to be significantly slower than the analogous reactions of **8** or **26f**. The elimination process of **26b** was not enhanced in the presence of additional TMEDA, but even decelerated by addition of the base 1,4-diazabicyclo[2.2. 2]octane. On the other hand, traces of water, dissolved in toluene-d_8, or addition of 1 equiv of trichloroacetic acid caused strongly accelerated dealkylation of **26b**.

After analyzing the thermal decay of several other sterically hindered trialkylamines, it turned out that primary or secondary alkyl groups were never split off because liberation of tertiary alkyl groups was favored to generate an olefin and the corresponding secondary amine. The tendency to undergo this Hofmann-like elimination reaction roughly correlates with the degree of steric congestion around the amine nitrogen atom. Whereas heating of substrate **27e** in anhydrous toluene-d_8 at 100 °C led to a half-life of $t_{1/2}$ = 9 days, the decay of the less sterically stressed amines **22c** and **27c** was slower under the same conditions because a consumption of only ca. 12−13% and formation of **20** or isobutene besides the corresponding secondary amines was detected after 25 days. Other trialkylamines, for example, **27g**, are nearly stable at 100 °C in toluene-d_8 (60−140 days). Tertiary *tert*-octylamines **26** create a special case because **10** is always liberated selectively in the thermal decay, and the formation of other olefins, for instance, isobutene was not observed. Moreover, these Hofmann-like elimination reactions occurred more rapidly than expected, possibly because additional intrinsic strain within the 1,1,3,3-tetramethylbutyl group is also released when **10** is generated. Hence, substrates such as **8** or **26d−f** show a lower stability and a greater reactivity to form the secondary amines by thermal decay than the trialkylamine **28c**, although this compound includes a higher degree of steric congestion around the nitrogen atom than amine **8**. The latter assumption is based on comparing the analogous secondary amines and the fact that the nucleophilicity of di-*tert*-amylamine in the presence of the electrophile allenyl isothiocyanate is lower than that of *tert*-butyl-*tert*-octylamine.[9]

The tertiary amine **33a** liberated isobutene under relatively mild conditions to generate an equilibrating mixture of the known[18] secondary amine **37a** and the imine **37b** (Scheme 7).

Scheme 7. Decay of Trialkylamines under Protic Conditions



Presumably, the primary alcohol **33b** and its protic properties are responsible for the ease of the reaction. Because of the steric stress in **33a**, the equilibrium of the tertiary amine is strongly shifted to acyclic **33b**, and **33a** could be detected at low temperature only, with **33a**/**33b** = 1:2 (^{1}H NMR, −50 °C). On the other hand, steric effects are less dominant in the case of the secondary amine **37a**; thus, we obtained the product with **37a**/**37b** = 4:1. Whereas the thermal decay of **27c** in toluene-d_8 at 100 °C proved to be very slow (see above), the same substrate was consumed in CD_3OD at 65 °C with a half-life of $t_{1/2}$ = 11.3 h. Besides the expected products **38** and isobutene, we detected the ether **39** with 57% yield (^{1}H NMR). Obviously, the Hofmann-like elimination was accompanied by an S_N1-type displacement reaction of **27c** because it is evident that **39** was not formed by addition of CD_3OD at isobutene. When the tertiary amine includes 1-adamantyl units as the only tertiary alkyl groups, thermal decay by liberation of an olefin was not observed, and S_N1 products were exclusively generated under protic conditions. Thus, the trialkylamines **29c,d** rapidly led to the corresponding secondary amines **40**

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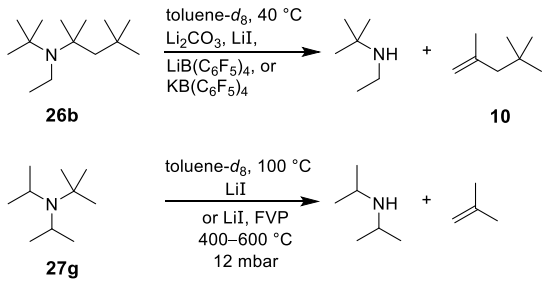
and 1-methoxyadamantane after heating with methanol. Treatment of **29a** with dilute sulfuric acid (8%) analogously afforded **40a** and 1-adamantanol.

Because protic reaction conditions turned out to effectively facilitate dealkylation of sterically stressed amines, the question arose whether alkali cations could also act as catalysts in such transformations. Whereas addition of *n*-butyllithium, in which the lithium is strongly coordinated, to a solution of **8** in toluene-d_8 stopped the Hofmann-like elimination at 40 °C (see above), exposure of such a solution to lithium iodide achieved instantaneous decay of **8** to yield **9** and **10**. We studied similar reactions of the less reactive substrate **26b** at 40 °C in order to classify the catalytic properties of different alkali salts (Scheme 8).[12] Substoichiometric amounts (20 mol %) of the weakly

Scheme 8. Dealkylation of Trialkylamines Catalyzed by Alkali Salts



coordinated salts potassium tetrakis(pentafluorophenyl)borate and especially lithium tetrakis(pentafluorophenyl)borate proved to be significantly more effective than lithium iodide, while a suspension of lithium carbonate was nearly ineffective. When the trialkylamine **27g**, which presents only a low degree of steric congestion, was treated with robust lithium iodide in toluene-d_8 at 100 °C, a very slow dealkylation reaction with the formation of isobutene and diisopropylamine was detected. In the presence of chelating 1,2-dimethoxyethane, the latter catalytic activity of lithium iodide was quenched. Finally, we tested flash vacuum pyrolysis (FVP) using a tube with glass or quartz Raschig rings, which were coated with lithium iodide. Even at high temperatures, however, the consumption of **27g** and the generation of diisopropylamine were incomplete.

Quantum Chemical Calculations. The experimental findings show that highly congested amines undergo facile elimination. Thus, for instance, amine **8** undergoes rapid elimination upon heating in toluene, while other less hindered amines are more resistant. The impossibility so far of isolating tri-*tert*-butylamine is attributed to an especially facile elimination. We sought to enhance the understanding of the relationship between strain and ease of elimination using electronic structure calculations.

First, we desired to quantify steric distress, so as to illustrate its correlation with the empirically observed ease of elimination. Such quantification can be achieved conceptually through the use of hypothetical reactions of the form shown below in Scheme 9. Such reactions are isodesmic, conserving the number of C−H, N−H, and C−N bonds, but remove the steric interactions between the three alkyl groups.

Table 1 lists strain energies computed in this manner for several amines having progressively greater congestion. Indeed, the strain in **8** is considerable (17.6 kcal/mol), but that in tri-*tert*-butylamine is still far greater (37.2 kcal/mol). On the other hand, most of this strain is released when even just one of the

Scheme 9. Quantification of Steric Strain in Amines via Group Separation Reactions

Table 1. Calculated Steric Strain of Amines $R^1R^2R^3N$

R^1	R^2	R^3	strain energy[a] (kcal/mol)	$\sum A^b$ (deg)
t-Bu	*t*-Oct	H	2.9	341.5
t-Bu	*t*-Bu	H	3.0	346.6
t-Bu	*t*-Oct[c]	*i*Pr	17.6	354.5
t-Bu	*t*-Bu	*t*-Bu	37.2	353.4

[a]Strain energy defined as $-\Delta H$ (0 K) for the group separation reaction in Scheme 9. [b]Sum of CNC bond angles in the optimized structure. [c]*t*-Oct = *tert*-octyl = 1,1,3,3-tetramethylbutyl.

bulky groups is replaced by hydrogen; large strain energies require that all three substituents be bulky. Thus, for instance, all but 3.0 kcal/mol of the 37.2 kcal/mol of strain in tri-*tert*-butylamine is eliminated once just one of the *tert*-butyl groups is removed. Similarly, all but 2.9 kcal/mol of the strain in **8** is relieved if just the isopropyl group is removed. This fact helps explain the ease of elimination. An elimination reaction only removes one of the three bulky alkyl groups from an amine such as **8** or tri-*tert*-butylamine, but that is sufficient to relieve the vast majority of the strain. If removing just one alkyl group released only a proportionate amount of the total strain, there would not be so much of a driving force for the elimination reaction.

Another reasonable measure of strain in amines is the sum of the CNC bond angles about the nitrogen atom. This sum correlates with planarity, varying from 360° for a perfectly planar nitrogen to 328.4° for a perfectly "tetrahedral" geometry to still less for an even more highly pyramidalized case. The bond angles yield a fairly similar story to the group separation energies: tri-*tert*-butylamine and **8** are much more strained than the disubstituted amines.

Calculations also yield some insights into the likely mechanism of elimination. One mechanism that might be considered for these elimination reactions, which apparently do not require added base, is the cyclic, unimolecular process shown in Scheme 10. Table 2 shows calculated barrier heights

Scheme 10. Unimolecular Elimination Mechanism

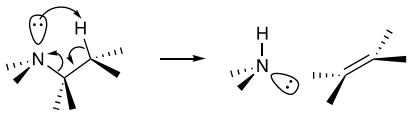


Table 2. Calculated Reaction Barriers for Elimination Reactions of Amines $R^1R^2R^3N$ via Mechanisms in Schemes 10 and 11 (kcal/mol)

R^1	R^2	R^3	w/o H_2O[a]	w/H_2O[b]
t-Bu	H	H	68.9	55.0
t-Bu	*t*-Bu	H	63.9	49.7
t-Bu	*t*-Oct[c]	*i*Pr	50.3	39.4
t-Bu	*t*-Bu	*t*-Bu	43.1	35.4

[a]Calculated barrier for the mechanism in Scheme 10. [b]Calculated barrier for the mechanism in Scheme 11. [c]*t*-Oct = *tert*-octyl = 1,1,3,3-tetramethylbutyl.

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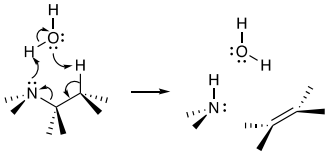
for this mechanism. Indeed, the barrier decreases substantially as the steric strain of the amine increases, from 68.9 kcal/mol for *tert*-butylamine, to 63.9 kcal/mol for di-*tert*-butylamine, to 50.3 kcal/mol for **8**, and finally to 43.1 kcal/mol for tri-*tert*-butylamine. The trend is consistent with experiment. However, the absolute barriers are much too high to account for the experimental rates of reaction, which require barriers of no more than about 25 kcal/mol for the most hindered amines. Furthermore, the completely intramolecular reaction mechanism is excluded based on the observed isotope effect, even though the deuterium isotope effect is likely quite difficult to interpret in greater detail.

A slight variation on the mechanism is to consider the involvement of a single water molecule acting as a proton shuttle, as shown in Scheme 11, allowing a more favorable transition-state geometry. The corresponding barriers (Table 2) are indeed lower by 8−14 kcal/mol. They again show the trend of decreasing barrier and therefore greater ease of elimination, with increasing steric distress. However, the absolute barriers are still too high to account for the experimental observations, which require barriers no higher than about 25 kcal/mol for highly hindered amines. This could well be because a more complete description of solvent participation is required than is possible to achieve with a continuum model.

Scheme 11. Water-Assisted Elimination Mechanism



Another possibility, however, is that the reaction is intermolecular rather than intramolecular. Without stating that this is literally the mechanism, one can say that the steps outlined in Scheme 12 are necessary to accomplish the reaction: protonation of the tertiary amine nitrogen, departure of the secondary amine leaving group, and deprotonation of the carbon adjacent to the nitrogen. The steps do not necessarily occur in the order shown, and some or all steps could be simultaneous. Dimethylamine is used as an example proton shuttle.

Scheme 12. Steps Necessary for an Elimination Reaction of a Tertiary Amine

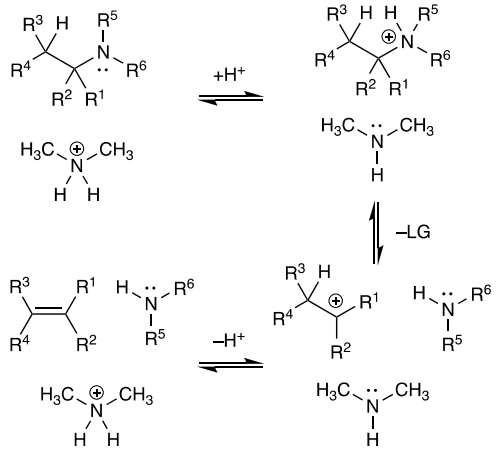


Table 3 shows the calculated energies of these constituent processes. First, it is well to note that the elimination reaction is quite endothermic for ethyldimethylamine and for *tert*-butyldimethylamine but highly exothermic (by 22 kcal/mol) for tri-*tert*-butylamine. The extreme favorability of the reaction can be accounted for by the reduction in steric strain in going from tri- to di-*tert*-butylamine. This is in some sense by itself enough to account for the facile elimination reaction of tri-*tert*-butylamine.

However, Table 3 also shows that tri-*tert*-butylamine is considerably more easily protonated than less congested tertiary amines. For instance, it is 8 kcal/mol more basic than *tert*-butyldimethylamine. Leaving group departure also gets easier. Upon going from ethyldimethylamine to *tert*-butyldimethylamine, leaving group departure becomes 27 kcal/mol more favorable because the resultant tertiary carbocation is far more stable than the ethyl cation. Upon going to tri-*tert*-butylamine, leaving group departure becomes yet 29 kcal/mol more favorable this time presumably as a result of the tremendous strain that is relieved. The change agrees rather well with the 34 kcal/mol estimated difference in strain energies between tri-*tert*-butylamine and di-*tert*-butylamine (Table 1).

It was also possible in some cases to find transition structures for an intermolecular E2 process, in which ammonia acted as the base on the protonated tertiary amines ("E2 Bar." in Table 3). The barrier declines 4 kcal/mol on going from ethyldimethylamine to *tert*-butyldimethylamine. In the case of tri-*tert*-butylamine, and amine **8**, the reaction is so exothermic that no transition structure could be located.

Taken together, the trends observed in Table 3 suggest that the elimination reaction of tri-*tert*-butylamine should be highly facile, much more so than that of less sterically hindered amines, particularly if a proton source is available. The tendency of the highly congested amines to undergo elimination results in very large part from the relief of extreme steric distress. In addition, however, the tendency of tertiary alkyl groups to yield highly stabilized tertiary carbocations, and eventually alkene products, perhaps also plays a role in facilitating the reaction. From this perspective, tri-1-adamantylamine might prove more kinetically stable than other similarly congested amines, such as tri-*tert*-butylamine and **8** because of the lack of either a stable carbocation intermediate or alkene product.

CONCLUSIONS

In summary, we attempted to determine how much steric stress trialkylamines can tolerate. To this end, we tested different methods to prepare these target compounds. However, the synthetic access is not the only limiting factor because sterically overcrowded tertiary amines are susceptible to a rapid dealkylation reaction with formation of an olefin and a secondary amine. Consequently, amines with three bulky alkyl groups are unstable, especially under protic conditions, as demonstrated by experiments and also with the help of quantum chemical calculations. Hence, it is still unclear whether tri-*tert*-butylamine will be isolable at ambient temperature even if a synthetic pathway to this compound is available.

Currently, we are trying to investigate the molecular structure of the sterically overcrowded amines by using

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Table 3. Calculated Energies of the Steps of an Elimination Process for Tertiary Amines as Outlined in Scheme 12 (kcal/mol)

R^{A}[a]	R^{5}	R^{6}	$+H^{+}$	$-LG$[b]	$+H^{+}-LG$[c]	$-H^{+}$	RXN[d]	E2 Bar.
Et	Me	Me	−4.6	+76.7	+72.1	−54.6	+17.5	+32.5
t-Bu	Me	Me	−7.0	+49.7	+42.7	−28.5	+14.2	+28.7
t-Bu	*t*-Bu	Me	−11.1	+41.7	+30.6	−28.5	+2.1	N/A
t-Oct[e]	*t*-Bu	*i*Pr	−13.1	+27.9	+14.8	−23.6	−8.8	N/A
t-Bu	*t*-Bu	*t*-Bu	−15.1	+21.2	+6.1	−28.5	−22.4	N/A

[a]R^{A} is the group $-(CR^{1}R^{2}-CHR^{3}R^{4})$ in Scheme 12. [b]The carbocation left is ethyl for the first row, the *tert*-octyl for the 4th row, and *tert*-butyl for the other rows. [c]Sum of first two steps. [d]Sum of all three steps. [e]*t*-Oct = *tert*-octyl = 1,1,3,3-tetramethylbutyl.

single-crystal X-ray diffraction and temperature-dependent high-resolution NMR spectroscopy. Moreover, we are attempting to prepare amines with even more steric congestion, for example, open-chain tri-*tert*-alkylamines, by oxidative ring opening of unsaturated 2,2,6,6-tetramethylpiperidines and 2,2,5,5-tetramethylpyrrolidines at low temperatures.

EXPERIMENTAL SECTION

General. All reactions dealing with air- or moisture-sensitive compounds were carried out in a dry reaction vessel under a positive pressure of nitrogen. Air- and moisture-sensitive liquids and solutions were transferred via a syringe. All reactions were carried out with freshly distilled, dry solvents. Anhydrous solvents were distilled immediately before use. AgOTf was obtained commercially from abcr (Germany). *t*-BuMgCl, MeMgCl, MeMgBr, *i*PrMgCl, LiCl, NCS, and TMEDA were obtained commercially from Acros Organics (Belgium). *i*BuLi, *n*-BuLi, *sec*-BuLi, MeLi, *i*PrMgBr, *i*PrMgBr·LiCl, CyMgCl, and 2-*exo*-bromonorbonane were obtained commercially from Sigma-Aldrich (Germany). α-Methylstyrene (**20**) and 1-bromoadamantane were obtained from Acros Organics (Belgium), and **21a** and **21b** were obtained from Merck KGaA (Germany). Cumylamine was bought from Fluorochem (UK). Diisopropylamine (**21c**) was purchased from Dr. Grüssing GmbH (Germany). 2,2,6,6-Tetramethylpiperidine was obtained commercially from Merck KGaA (Germany). *tert*-Octylamine was obtained from TCI (Japan). The Grignard-reagents 2-*exo*-norbornylMgBr, EtMgBr, neopentylMgBr, cyclopentylMgBr, and *t*-BuMgBr were prepared from the corresponding alkyl bromide and magnesium turnings following a general literature procedure and used immediately after preparation.[19,20] Compounds **8**,[8] **9**,[21] **11**,[9] **12**,[9] **13**,[8] **17**,[22] **25a**,[8,23] **26b**,[8] **27e**,[8] **27g**,[8] **28c**,[8] **29c-d**,[8] di-*tert*-butylamine,[24] 1,1,3,3-tetramethylisoindoline,[25] 1,1,3,3-tetraethyl-isoindoline,[25] di-*tert*-amyl-amine,[26,27] *tert*-butyl-*tert*-octylamine,[24b] di-1-adamantylamine,[28] 3,3,5,5-tetramethylmorpholin-2-one,[29] *tert*-butylcyclohexylamine,[29] 2-ethyl-1,1,3,3-tetraethylisoindoline (**30c**),[14] 2-isopropyl-1,1,3,3-tetraethylisoindoline (**30d**),[14] and *N*-*tert*-butyl-*N*-tritylamine (**34**)[30] were prepared according to reported procedures. The NMR data of amine **40c** were confirmed by the literature.[29]

NMR spectra were recorded with a UNITY INOVA 400 FT spectrometer (Varian Inc., Palo Alto, CA, USA) operating at 400 MHz for ^{1}H NMR and 100.6 MHz for ^{13}C NMR; ASCEND 600 FT spectrometer (Bruker Corp., Billerica, MA, USA) operating at 600 MHz for ^{1}H NMR and 150.9 MHz for ^{13}C NMR. ^{1}H NMR and ^{13}C NMR signals were referenced with the help of the solvent signals and recalculated relative to TMS. Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, br = broad), coupling constant in hertz (Hz), and the number of hydrogen atoms. NMR spectra were measured at 25 °C unless noted otherwise. In all cases of ^{13}C NMR spectra, DEPT135 experiments were also performed. Assignments of NMR signals were further supported by correlation spectroscopy, heteronuclear single quantum correlation, and heteronuclear multiple bond correlation 2D-NMR methods and also by comparison of the data of homologous compounds in several cases. Signal assignment was omitted if it was unclear. Mass spectra were obtained from a micrOTOF QII spectrometer (Bruker Corp., Billerica, MA, USA), utilizing an electrospray-ionization technique (source: Apollo II ESI) from a 15T solariX FT-ICR-MS (Bruker) or from a timsTOF spectrometer (Bruker). Quantitative elementary analyses were performed on a vario Micro cube (Elementar Analysensysteme GmbH, Langenselbold, HE, Germany). Melting points (mp) were measured by BOETIUS-method on a heating apparatus from VEB Analytik Dresden PHMK 74/0032. Reaction monitoring was realized via analytical gas chromatography (GC) using a gas chromatograph 5890 Series II [Hewlett Packard Inc., Palo Alto, CA, USA; column: HP-5MS (cross-linked 5% Ph Me silicone) 30 m × 0.25 mm × 0.25 μm]. For the separation of complex mixtures, a preparative gas chromatograph GC-8A (Shimadzu Corp., Kyoto, Japan) was used with a Carbowax-column (KOH, 1 or 3 m, inj.-temp.: 70 °C, col.-temp.: 60 °C, carrier gas: helium 5.0, 30 mL/min). For the photosynthesis, a 150 W high-pressure Heraeus TQ 150 quartz Hg lamp with a filter >320 nm was used. The thermolysis and methanolysis of amines in solution were performed in NMR tubes, which were heated in a heating block. The coated Raschig rings for FVP were prepared by entering the Raschig rings in a solution of 1 g LiI in 30 mL acetone, removing the solvent in vacuum and drying at 10^{-2} Torr and 80 °C. The FVP was performed at 400 °C, 12 mbar, and a bath temperature of 50 °C. Starting from 210.7 mg (1.34 mmol) of diisopropyl-*tert*-butylamine (**27g**), the FVP yielded, for example, 150.5 mg of a mixture of 72% diisopropyl-*tert*-butylamine, 25% diisopropylamine, and 3% isobutene.

N-(1-Adamantyl)-tert-octylamine. Silver trifluoromethanesulfonate (0.66 g, 2.58 mmol) and 1-bromoadamantane (0.55 g, 2.58 mmol) were mixed in abs. dichloromethane (DCM) at 0 °C and stirred overnight in the dark. Then potassium carbonate (1.78 g, 12.9 mmol) and *tert*-octylamine (0.5 g, 3.87 mmol) were added and stirred for 4 h at 0 °C. At 10 °C, the mixture was quenched with saturated aqueous sodium bicarbonate and extracted with DCM. The organic phase was dried and concentrated in vacuum. For purification, the product was acidified with aqueous HCl and washed with Et_2O. The aqueous phase was basified with NaOH, extracted with DCM again, and dried over K_2CO_3. The product was obtained after removing the solvent as a colorless liquid with a yield of 0.48 g (1.82 mmol, 47%). ^{1}H NMR (600 MHz, C_6D_6): δ 1.97 (br s, 3H, CH), 1.74−1.75 (m, 6H, CH_2(ad)), 1.56−1.61 (m, 6H, CH_2(ad)), 1.39 (s, 2H, CH_2), 1.26 (s, 6H, $C(CH_3)_2$), 1.11 (s, 9H, *t*-Bu). The NH signal was not observed. $^{13}C\{^{1}H\}$ NMR (151 MHz, C_6D_6): δ 59.5 (s, $N-C(CH_3)_2$), 56.3 (s, NC(ad)), 52.3 (t, CH_2), 46.8 (t, CH_2(ad)), 37.1 (t, CH_2(ad)), 32.9 (q, $(CH_3)_2$), 32.4 (q, *t*-Bu), 32.2 (s, *t*-Bu), 30.5 (d, CH). HRMS *m*/*z*: calcd for $C_{18}H_{34}N$ $[M + H]^{+}$, 264.2686; found, 264.2688.

N-Isopropylcumylamine.[31] Cumylamine (2.0 g, 14.8 mmol) and diisopropyl sulfate (4.2 g, 23.0 mmol) were heated to 110 °C and stirred for 3 h. After cooling to rt, NaOH (20 mL, 25%) was added and stirred for about 1.5 h until everything was dissolved. After extraction with Et_2O, drying over $MgSO_4$, and removal of the solvent, 2.15 g of a yellow oil remained, which was purified by flash chromatography (first CH_2Cl_2, then Et_2O). After removal of the solvent of the Et_2O fraction, the product[31] was obtained with a yield of 1.32 g (7.4 mmol, 50%) as a slightly yellowish liquid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45−7.50 (m, 2H, Ph), 7.29−7.35 (m, 2H, Ph), 7.19−7.24 (m, 1H, Ph), 2.63 (sept, ^{3}J = 6.3 Hz, 1H, $C\underline{H}(CH_3)_2$), 1.49 (s, 6H, $CPh(C\underline{H}_3)_2$), 0.93 (d, ^{3}J = 6.3 Hz, 6H, $CH(C\underline{H}_3)_2$). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$): δ 148.5 (s, Ph), 127.9 (d, Ph),

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126.2 (d, Ph), 125.9 (d, Ph), 56.2 ($\underline{C}Ph(CH_3)_2$), 44.1 (d, $\underline{C}H(CH_3)_2$), 30.2 (q, $CPh(\underline{C}H_3)_2$), 25.7 (q, $CH(\underline{C}H_3)_2$).

N-Chlorodialkylamines were prepared from the corresponding secondary amines analogously to reported procedures.[32,33]

N-Isopropyl-N-chlorocumylamine. *N*-Isopropylcumylamine (2.13 g, 12.0 mmol) in CH_2Cl_2 (15 mL) was mixed with NCS (1.95 g, 14.6 mmol) in portions and stirred at 25 °C for 4 h and then poured onto 50 mL of ice/water. After phase separation, extraction three times with *n*-pentane, washing the organic extracts five times with water, drying over $MgSO_4$, and removal of the solvent in vacuum, 2.39 g (11.3 mmol, 94%) of the product remained as a yellow liquid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.52−7.55 (m, 2H, Ph), 7.31−7.35 (m, 2H, Ph), 7.23−7.27 (m, 1H, Ph), 3.11 (sept, ^3J = 6.2 Hz, 1H, $C\underline{H}(CH_3)_2$), 1.57 (s, 6H, $CPh(C\underline{H}_3)_2$), 1.07 (d, ^3J = 6.2 Hz, 6H, $CH(C\underline{H}_3)_2$). $^{13}C\{^1H\}$ NMR (150.9 MHz, $CDCl_3$): δ 147.2 (s, Ph), 128.2 (d, Ph), 126.9 (d, Ph), 126.2 (d, Ph), 67.5 (s, $\underline{C}Ph(CH_3)_2$), 53.8 (d, $\underline{C}H(CH_3)_2$), 27.1 (q, $CPh(\underline{C}H_3)_2$), 21.6 (q, $CH(\underline{C}H_3)_2$). HRMS *m*/*z*: calcd for $C_{11}H_{19}ClNNa$ $[M + Na]^+$, 234.1020; found, 234.1019.

N-(1-Adamantyl)-N-chloro-tert-octylamine. Similar to procedures of the literature,[32,33] 1-adamantyl-*tert*-octylamine (250 mg, 1 mmol) was used to generate the product, obtained as a viscous oil with a yield of 280 mg (0.94 mmol, 94%). ^{1}H NMR (600 MHz, C_6D_6): δ 2.10 (m, 6H, CH_2), 1.94 (br s, 3H, CH), 1.78 (s, 2H, CH_2), 1.47−1.51 (m, 6H, CH_2), 1.41 (s, 6H, $C(CH_3)_2$), 1.12 (s, 9H, C-*t*-Bu). $^{13}C\{^1H\}$ NMR (150.9 MHz, C_6D_6): δ 69.9 (s, N−C), 66.8 (s, N−C(ad)), 54.9 (t, CH_2), 43.2 (t, CH_2(ad)), 36.7 (t, CH_2(ad)), 32.1 (q, *t*-Bu), 32.0 (s, *t*-Bu), 31.8 (q, $C(\underline{C}H_3)_2$), 30.9 (d, CH). HRMS *m*/*z*: calcd for $C_{18}H_{33}NCl$ $[M + H]^+$, 298.2296; found, 298.2296.

N-tert-Butyl-N-chlorocyclohexylamine. The desired compound was prepared by the same procedure using *tert*-butylcyclohexylamine[29] (1.5 g, 9.6 mmol). The product was obtained as a yellowish oil with a yield of 1.6 g (8.4 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.00−3.07 (m, 1H, CH), 1.55−1.82 (m, 7H, CH_2), 1.25 (s, 9H, *t*-Bu), 1,19−1.28 (m, 2H, CH_2), 1,04−1.13 (m, 1H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 62.4 (s, *t*-Bu), 62.0 (d, CH), 31.9 (t, CH_2), 28.5 (q, *t*-Bu), 26.0 (t, CH_2), 25.6 (t, CH_2). HRMS *m*/*z*: calcd for $C_{10}H_{20}ClNNa$ $[M + Na]^+$, 212.1176; found, 212.1177.

4-Chloro-3,3,5,5-tetramethylmorpholin-2-one. Analogously to instruction above, 3,3,5,5-tetramethylmorpholin-2-one (1 g, 6.37 mmol) was used to synthesize the product as a greenish solid with a yield of 0.99 g (5.17 mmol, 81%). mp 38−45 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.07 (s, 2H, CH_2), 1.56 (s, 6H, 3-Me), 1.24 (s, 6H, 5-Me). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 172.0 (s, C═O), 75.2 (t, CH_2), 67.5 (s, C-3), 58.9 (s, C-5), 27.0 (q, 3-Me), 21.8 (q, 5-Me). Anal. Calcd for $C_8H_{14}NO_2Cl$: C, 50.13; H, 7.36; N, 7.31. Found: C, 49.69; H, 7.17; N, 7.22.

2-Chloro-1,1,3,3-tetramethylisoindoline. The target compound was prepared in the same way by using 1,1,3,3-tetramethylisoindoline (2.0 g, 11.4 mmol)[25] and *N*-chlorosuccinimide (1.6 g, 12.0 mmol). After extraction, 2-chloro-1,1,3,3-tetramethylisoindoline was obtained as pure low melting colorless solid with a yield of 2.1 g (10.0 mmol, 88%). It could be used directly without further purification. mp 35−36 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25−7.27 (m, 2H, CH), 7.13−7.15 (m, 2H, CH), 1.45 (s, 12H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_6D_6): δ 144.7 (s, C), 127.3 (d, CH), 121.4 (d, CH), 69.0 (s, $C(CH_3)_2$), 26.8 (q, CH_3). HRMS *m*/*z*: calcd for $C_{12}H_{18}N$ $[M - Cl + 2H]^+$, 176.1434; found, 176.1495.

*N-Chloro-N-tert-butyltritylamine (**25b**).* *N-tert*-Butyltrityl-amine (1 g, 2.4 mmol)[30] was dissolved in DCM (20 mL) and cooled to 0 °C. TCCA (3.2 mmol, 0.72 g) was added and stirred for 3 h. Then, pentane (20 mL) was added and the organic phase was washed with water and then dried with potassium carbonate. After removing the solvent, the product was obtained as a yellowish tough wax with a yield of 0.84 g (2.4 mmol, 99%). ^{1}H NMR (400 MHz, C_6D_6): δ 7.82−7.83 (m, 6H, *o*-H), 7.03−7.07 (m, 6H, *m*-H), 6.91−6.94 (m, 3H, *p*-H), 1.04 (s, 9H, *t*-Bu). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_6D_6): δ 145.3 (s, Ph), 130.4 (d, *o*-C), 127.3 (d, *m*-C), 126.5 (d, *p*-C), 81.4 (s, N−$\underline{C}(Ph)_3$), 66.5 (s, *t*-Bu), 30.2 (q, *t*-Bu). HRMS *m*/*z*: calcd for $C_{23}H_{24}NClNa$ $[M + Na]^+$, 372.1489; found, 372.1489.

*2-Chloro-1,1,3,3-tetraethylisoindoline (**25c**).* The desired compound was prepared in the same way by using 1,1,3,3-tetraethylisoindoline (4.0 g, 17.3 mmol)[25] and NCS (2.4 g, 18.0 mmol). After extraction, 2-chloro-1,1,3,3-tetraethylisoindoline was obtained as a pure low melting colorless solid with a yield of 4.2 g (16.3 mmol, 91%). It could be used directly without further purification. mp 42−43 °C. ^{1}H NMR (400 MHz, C_6D_6): δ 7.03−7.05 (m, 2H, CH), 6.83−6.85 (m, 2H, CH), 1.95−2.05 (m, 4H, $C\underline{H}_2CH_3$), 1.72−1.81 (m, 4H, $C\underline{H}_2CH_3$), 0.81 (t, ^3J = 6 Hz, 12H, $CH_2C\underline{H}_3$). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_6D_6): δ 142.1 (s, C), 126.3 (d, CH), 123.2 (d, CH), 74.0 (s, $\underline{C}(CH_2CH_3)_2$), 29.5 (t, $\underline{C}H_2CH_3$), 9.0 (q, $CH_2\underline{C}H_3$). Anal. Calcd for $C_{16}H_{24}ClN$: C, 72.29; H, 9.10; N, 5.27. Found: C, 72.14; H, 9.22; N, 5.19.

Preparation of Tertiary Amines. *Method A (Electrophilic Amination).* TMEDA (12 mmol) and the respective organometallic alkylation reagent (6 mmol) were dissolved in Et_2O or THF (10 mL) at −78 °C and stirred for 1 h. The corresponding chloroamine (2 mmol) was dissolved in Et_2O/THF (5 mL) and slowly dropped in. The reaction mixture was stirred for further 2 h and warmed to rt afterwards. Then, the reaction mixture was put on ice/water (100 mL) and extracted with Et_2O (50 mL). The organic phase was washed with water (30 mL) and dried over K_2CO_3. The solvent was removed under vacuum, and the residue was purified chromatographically over basic alumina (Et_2O/hexane). The tertiary amines usually lead to chromatographic R_f values of approximately 0.9. In some cases, the undesired secondary amine was separated by recondensation at 10^{-3} mbar.

*N-tert-Butyl-N-isopropylpentan-3-amine (**15**).* *N-tert*-Butyl-*N*-(chloromethylene)-isopropyliminium chloride (**14**, 6.9 mmol; in situ generated, see the synthesis of **16** from **13**) was suspended in a 100 mL three-necked flask under a nitrogen atmosphere in THF (20 mL) and cooled to −78 °C. EtMgBr was slowly added (11.6 mL, 11.8 g, 34.9 mmol, 3 M in Et_2O) within 10 min via a septum. The cooling bath was removed, and the mixture was stirred at rt for 60 min. The reaction mixture was then hydrolyzed in ice/water (500 mL). The pH of the solution was adjusted to 1 by using conc. HCl (60 mL), and the solution was then washed with diethyl ether (300.0 mL). The aqueous phase was made strongly alkaline with NaOH pellets (38.6 g, 0.9 mol) and extracted with diethyl ether. The combined ether phases were dried for 1 h over $MgSO_4$. The obtained organic phase was distilled to remove the solvent (25 cm Vigreux column; oil bath up to 140 °C). A recondensation was carried out (6.8×10^{-3} mbar). Finally, any remaining diethyl ether was completely removed with the help of a rotary evaporator (20 mbar). The amine **15** was obtained as a colorless, clear liquid with a characteristic smell with a yield of 0.9 g (4.9 mmol, 70%). The pure compound **15** (0.3 g, 1.6 mmol) was placed in a flask, mixed with a saturated ethanolic solution of picric acid (10 mL), and stirred for 30 min. The resulting crystals were aspirated sharply over a frit, washed with EtOH, and then recrystallized from EtOH. The picrate of **15** was obtained as fine yellow crystals (mp 136−138 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.23 (sept, ^3J = 6.9 Hz, 1H, $-C\underline{H}(CH_3)_2$), 2.45 (quint, ^3J = 7.0 Hz, 1H, $C\underline{H}(CH_2CH_3)_2$), 1.46 (qd, ^3J = 7.4 Hz, ^3J = 7.0 Hz, 4H, $CH(C\underline{H}_2CH_3)_2$), 1.15 (s, 9H, $C(C\underline{H}_3)_3$), 1.07 (d, ^3J = 6.9 Hz, 6H, $CH(C\underline{H}_3)_2$), 0.88 (t, ^3J = 7.4 Hz, 6H, $CH(CH_2C\underline{H}_3)_2$). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 60.1 (d, $\underline{C}H(CH_2CH_3)_2$), 56.0 (s, $\underline{C}(CH_3)_3$), 46.8 (d, $\underline{C}H(CH_3)_2$), 31.4 (q, $C(\underline{C}H_3)_3$), 28.6 (t, $CH(\underline{C}H_2CH_3)_2$), 24.8 (q, $CH(\underline{C}H_3)_2$), 12.8 (q, $CH(CH_2\underline{C}H_3)_2$). Anal. Calcd for $C_{18}H_{30}N_4O_7$ (picrate): C, 52.16; H, 7.30; N, 13.52. Found: C, 52.33; H, 7.32; N, 13.33.

*N-tert-Butyl-N-isobutylisopropylamine (**16**).* *N-tert*-Butyl-*N*-isopropylformamide (**13**, 1.0 g, 6.9 mmol)[34] was dissolved in toluene (20 mL) and cooled to −78 °C. Oxalyl chloride (0.9 mL, 1.3 g, 10.5 mmol) was slowly dripped in via a septum. Then, the reaction mixture was stirred for 30 min at −78 °C and another 60 min at rt. Diethyl ether (60 mL) was added under exclusion of moisture, so the iminium salt precipitated, and it was washed with Et_2O afterward. The salt was dissolved in THF (10 mL) and added to a suspension of isopropylmagnesium chloride (20 mL, 40 mmol, 2 M in THF), TMEDA (12.5 mL, 83 mmol), and THF (20 mL) cooled to −60 °C.

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After stirring overnight at rt, the mixture was added to 100 mL ice/water and mixed with diethyl ether (50 mL), and the organic phase was then washed with water (30 mL) and dried over K_2CO_3. The solvent was removed in vacuum at 100 mbar, and the product was recondensed at 0 °C and 5 mbar. It was obtained as a colorless liquid with a yield of 110 mg (0.64 mmol, 9%). ^{1}H NMR (400 MHz, C_7D_8): δ 3.14 (sept, 1H, ^3J = 6.7 Hz, N−CH), 2.22 (d, ^3J = 7.4 Hz, 2H, CH_2), 1.61 (m, 1H, C<u>H</u>−CH_2), 1.00 (s, 9H, *t*-Bu), 0.97 (d, ^3J = 6.7 Hz, 6H, *i*Pr), 0.90 (d, ^3J = 6.6 Hz, 6H, *i*Bu). ^{13}C{^{1}H} NMR (100.6 MHz, C_7D_8): δ 55.5 (s, *t*-Bu), 51.2 (t, CH_2), 46.9 (d, N−CH), 30.3 (q, *t*-Bu), 28.8 (q, *i*Pr), 23.0 (d, <u>C</u>H−CH_2), 20.9 (q, *i*Bu). HRMS *m*/*z*: calcd for $C_{11}H_{26}N$ [M + H]$^+$, 172.2065; found, 172.2058.

*N-tert-Amyl-diisopropylamine (**19**).* Triisopropylamine (**17**) (0.5 g, 3.49 mmol) was dissolved in hexane (2 mL), and a saturated solution of iodine (2 g, 15.7 mmol) in hexane was added dropwise. After complete addition, stirring was continued for 2 h at rt. The supernatant solution was then decanted, and the residue was washed 3 or 4 times with hexane so that the solvent was only slightly purple. The brown residue was dissolved in THF (15 mL). Then, EtMgBr (15 mL, 3 M in Et_2O) was rapidly added while cooling with ice/water and stirring for a further 2 h after removal of the cooling bath. The reaction mixture was carefully added to ice/water, adjusted to pH 1 with conc. HCl, and washed 3 times with Et_2O. Then, the mixture was basified to pH 14 with conc. NaOH under cooling and extracted three times with Et_2O. After drying over $MgSO_4$, the solvent was distilled off over a column. The bath temperature was increased up to 130 °C. When nothing more passed over, the residue was recondensed and further purified by prep. GC. The product was isolated as a colorless liquid with a yield of 67 mg (0.39 mmol, 22% based on the maximum amount of **18**, which can be generated from **17**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.20 (sept, ^3J = 6.9 Hz, 2H, C<u>H</u>$(CH_3)_2$), 1.38 (q, ^3J = 7.4 Hz, 2H, C<u>H</u>$_2$$CH_3$), 1.11 (s, 6H, NC$(C\underline{H}_3)_2$), 1.10 (d, ^3J = 6.9 Hz, 12H, CH$(C\underline{H}_3)_2$), 0.81 (t, ^3J = 7.4 Hz, 3H, $CH_2C\underline{H}_3$). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 58.5 (s, N<u>C</u>$(CH_3)_2$), 45.8 (d, <u>C</u>H$(CH_3)_2$), 35.5 (t, <u>C</u>H$_2$$CH_3$), 27.7 (q, NC$(\underline{C}H_3)_2$), 24.7 (q, CH$(\underline{C}H_3)_2$), 9.0 (q, $CH_2\underline{C}H_3$). HRMS *m*/*z*: calcd for $C_{11}H_{26}N$ [M + H]$^+$, 172.2060; found: 172.2062.

*N-Ethyl-N-isopropylcumylamine (**22b**). Photochemical Method.* A solution of *N*-ethylisopropylamine (3.32 g, 38.11 mmol) and α-methylstyrene (150 mg, 1.27 mmol) in hexane (200 mL) was irradiated under cooling with ice/water. The light source was a 150 W high-pressure Heraeus TQ 150 quartz Hg lamp with a filter >320 nm and a glass irradiation vessel. Nitrogen was bubbled in before the irradiation was started and continued for 28 h. During this time, α-methylstyrene was added six times (150 mg, 1.27 mmol, every 4 h, total amount: 1.050 g, 8.88 mmol) to the photolysis solution. After this time, the photolysis solution was filtered to remove any insoluble products, and the solvent and volatile reaction products were evaporated in vacuum (1 mbar). The procedure above was performed twice to obtain sufficient materials to be used as a standard. The residue was purified via column chromatography (silica gel) using hexane/CH_2Cl_2 (10:1 to 0:1 gradient) and then EtOAc as the eluent. The last eluting fraction was identified as the product with an impurity of cumyl alcohol. A further column chromatography (basic alumina) using hexane/CH_2Cl_2 (5:2) gave 81 mg (0.39 mmol, 4%) of the product as a colorless liquid.

Method A (Electrophilic Amination). A solution of *N*-isopropyl-*N*-chlorocumylamine (0.45 g, 2.13 mmol) in Et_2O (10 mL), TMEDA (5.2 g, 4 mL, 44.8 mmol), and EtMgBr (4 mL, 8 mmol, 2 M in Et_2O) were used to generate **22b**. The product was purified by flash chromatography on a silica gel with Et_2O/*n*-pentane (1:1 to 1:0 gradient), R_f = 0.89 for pure Et_2O. This generated 213 mg (1.04 mmol, 49%) of the product as a pale yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (dd, J = 8.3 Hz, J = 1.1 Hz, 2H, *o*-H−C_6H_4), 7.30 (t, J = 7.7 Hz, 2H, *m*-H−C_6H_4), 7.19 (t, J = 7.3 Hz, 1H, *p*-H−C_6H_4), 2.84 (sept, ^3J = 6.6 Hz, 1H, C<u>H</u>$(CH_3)_2$), 2.67 (q, ^3J = 7.1 Hz, 2H, C<u>H</u>$_2$$CH_3$), 1.38 (s, 6H, C$(C\underline{H}_3)_2$Ph), 1.09 (t, ^3J = 7.1 Hz, 3H, $CH_2C\underline{H}_3$), 0.94 (d, ^3J = 6.6 Hz, 6H, CH$(C\underline{H}_3)_2$). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 151.4 (s, C-1), 127.7 (d, C-3, C-5), 126.3 (d, C-2, C-6), 125.7 (d, C-4), 62.0 (s, <u>C</u>$(CH_3)_2$Ph), 47.9 (d, <u>C</u>H$(CH_3)_2$), 35.6 (t, <u>C</u>H$_2$$CH_3$), 27.3 (q, C$(\underline{C}H_3)_2$Ph), 22.4 (q, CH$(\underline{C}H_3)_2$), 20.4 (q, $CH_2\underline{C}H_3$). HRMS *m*/*z*: calcd for $C_{14}H_{24}N$ [M + H]$^+$, 206.1903; found, 206.1901.

*N,N-Diisopropylcumylamine (**22c**). Method A.* *N*-Isopropyl-*N*-chlorocumylamine (0.45 g 2.13 mmol) in Et_2O (10 mL), TMEDA (5.2 g, 4 mL, 44.8 mmol), and isopropylmagnesium chloride (3.5 mL, 7 mmol, 2 M in THF) were used. After removing the solvent, a yellowish oil remained, which was purified by flash chromatography on a silica gel with Et_2O/*n*-pentane (1:1), R_f = 0.89. The product was obtained with a yield of 0.18 g (0.82 mmol, 38%) as a slightly yellowish oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.53−7.56 (m, 2H, Ph), 7.26−7.29 (m, 2H, Ph), 7.14−7.18 (m, 1H, Ph), 3.00 (sept, ^3J = 6.9 Hz, 2H, C<u>H</u>$(CH_3)_2$), 1.52 (s, CPh$(C\underline{H}_3)_2$, 6H), 1.13 (d, ^3J = 6.9 Hz, 12H, CH$(C\underline{H}_3)_2$). ^{13}C{^{1}H} NMR (150.9 MHz, $CDCl_3$): δ 153.3 (s, Ph), 127.5 (d, Ph), 126.2 (d, Ph), 125.5 (d, Ph), 62.9 (<u>C</u>Ph$(CH_3)_2$), 47.3 (d, <u>C</u>H$(CH_3)_2$), 29.3 (q, CPh$(\underline{C}H_3)_2$), 24.1 (q, CH$(\underline{C}H_3)_2$). HRMS *m*/*z*: calcd for $C_{15}H_{26}N$ [M + H]$^+$, 220.2060; found, 220.2062.

*N-tert-Butyl-N-methyl-tert-octylamine (**26a**).*[12] *Method A.* *N-tert*-Butyl-*N*-chloro-*tert*-octylamine (0.2 g, 0.91 mmol),[7] dissolved in Et_2O (10 mL), and TMEDA (1.08 g, 1.4 mL, 9.28 mmol) with methyllithium (0.6 mL, 1.8 mmol, 3 M in 1,2-dimethoxyethane) were used. The product **26a** was obtained as a colorless liquid with a yield of 66 mg (0.33 mmol, 37%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H, CH_3−N), 1.43 (s, 2H, CH_2−C−N), 1.25 (s, 6H, $(CH_3)_2$−C−N), 1.21 (s, 9H, N-*t*-Bu), 1.01 (s, 9H, C-*t*-Bu). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 61.0 (s, $(CH_3)_2$−<u>C</u>−N), 56.6 (s, N-*t*-Bu), 54.2 (t, CH_2), 33.9 (q, CH_3−N), 32.1 (s, <u>C</u>-*t*-Bu), 31.8 (q, N-*t*-Bu), 31.1 (q, C-*t*-Bu), 30.4 (q, $(\underline{C}H_3)_2$−C−N). HRMS *m*/*z*: calcd for $C_{13}H_{30}N$ [M + H]$^+$, 200.2378; found, 200.2369.

*N-tert-Butyl-N-cyclopentyl-tert-octylamine (**26c**). Method A.* With *N-tert*-butyl-*N*-chloro-*tert*-octylamine (420 mg, 1.95 mmol),[8] TMEDA (1.2 g, 1.6 mL, 10.3 mmol), and cyclopentylMgBr (1.33 mL, 4 mmol, 3 M in Et_2O), the product was obtained as a colorless liquid with a yield of 20 mg (0.078 mmol, 4%). The ^{1}H NMR spectrum indicated a purity of 90%; the decay products *N-tert*-butylcyclopentylamine and **10** were present with 9% and 1%, respectively. ^{1}H NMR (400 MHz, C_7D_8): δ 3.48 (quint, 1H, N−CH), 1.58−1.83 (m, 8H, $(-CH_2-)_4$), 1.39 (s, 2H, C<u>H</u>$_2$-*t*-Bu), 1.34 (s, 6H, CMe_2), 1.28 (s, 9H, N-*t*-Bu), 1.02 (s, 9H, C-*t*-Bu). ^{13}C{^{1}H} NMR (100.6 MHz, C_7D_8, 213 K): δ 62.7 (s, CMe_2), 61.6 (s, CMe_2), 61.0 (d, CH), 60.2 (d, CH), 58.9 (s, N-*t*-Bu), 57.1 (s, N-*t*-Bu), 55.0 (t, CH_2), 53.0 (t, CH_2), 34.0 (q, CMe_2), 33.0 (t, CH_2), 32.7 (q, CMe_2), 32.5 (q, N-*t*-Bu), 32.3 (q, N-*t*-Bu), 32.1 (q, C-*t*-Bu), 31.89 (s, C-*t*-Bu), 31.88 (s, C-*t*-Bu), 31.8 (q, C-*t*-Bu), 27.0 (t, CH_2), 24.9 (t, CH_2), 24.6 (t, CH_2). HRMS *m*/*z*: calcd for $C_{17}H_{36}N$ [M + H]$^+$, 254.2848; found, 254.2863.

*N-sec-Butyl-N-tert-butyl-tert-octylamine (**26d**). Method A.* According to the same procedure, *N-tert*-butyl-*N*-chloro-*tert*-octylamine (420 mg, 1.95 mmol),[8] TMEDA (1.2 g, 1.6 mL, 10.3 mmol), and *sec*-BuLi (3.1 mL, 4 mmol, 1.3 M in cyclohexane/hexane) gave 35 mg (0.15 mmol, 8% NMR yield) of the product as a colorless liquid, but still slightly contaminated by the decomposition products. ^{1}H NMR (400 MHz, C_7D_8): δ 2.95−3.05 (m, 2H, N−CH), 1.90 (d, ^2J = 14.7 Hz, 1H, CH_2), 1.85 (d, ^2J = 14.7 Hz, 1H, CH_2), 1.50−1.72 (m, 4H, CH−C<u>H</u>$_2$), 1.32 (s, 6H, CMe2), 1.31 (s, 6H, CMe_2), 1.27 (d, 1H, Me−C<u>H</u>, second signal overlapped), 1.26 (s, 9H, N-*t*-Bu), 1.25 (s, 9H, N-*t*-Bu), 1.00 (s, 9H, C-*t*-Bu), 0.99 (s, 9H, C-*t*-Bu), 0.902 (t, ^3J = 7.6 Hz, 2H, CH_2−<u>Me</u>), 0.898 (t, ^3J = 7.6 Hz, 2H, CH_2−<u>Me</u>). Because of fast decomposition, we were unable to get a complete ^{13}C{^{1}H} NMR spectrum or HRMS for characterization.

*N-tert-Butyl-N-cyclohexyl-tert-octylamine (**26e**). Method A.* *N-tert*-Butyl-*N*-chloro-*tert*-octylamine (550 mg, 2.5 mmol),[8] TMEDA (1.5 g, 2.0 mL, 13.2 mmol), and CyMgCl (2.5 mL, 5 mmol, 2 M in Et_2O) were used. The product **26e** was obtained with a yield of 39 mg (0.15 mmol, 6% NMR yield) as a colorless liquid. ^{1}H NMR (400 MHz, C_7D_8): δ 2.80−2.89 (m, 2H, N−CH), 1.42 (s, 6H, CMe_2), 1.34 (s, 6H, CMe_2), 1.33 (s, 9H, *t*-Bu), 1.27 (s, 9H, *t*-Bu), 1.25 (s, 9H, *t*-Bu), 1.18 (s, 9H, *t*-Bu). Because of fast decomposition and low yield, we were unable to get complete NMR spectra or HRMS for characterization.

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*N-(1-Adamantyl)-N-isopropyl-tert-octylamine (**26f**). Method A.* With *N*-(1-adamantyl)-*N*-chloro-*tert*-octylamine (140 mg, 0.86 mmol), TMEDA (1.4 g, 1.8 mL, 11.3 mmol), and *i*PrMgCl (1.4 mL, 2.8 mmol, 2 M in THF), the product **26f** was obtained as a colorless liquid with a yield of 9 mg (0.03 mmol, 4% NMR yield). ^{1}H NMR (600 MHz, C_7D_8): δ 3.56 (sept, ^3J = 7.2 Hz, 1H, N−CH), 3.50* (sept, ^3J = 7.2 Hz, 1H, N−CH), 2.14 (m, 1H, CH_2(ad)), 1.98−2.01 (m, 8H, CH, CH_2(ad)), 1.95 (s, 2H, CH_2), 1.63* (s, 2H, CH_2), 1.56 (m, 6H, CH_2 (ad, overlapped)), 1.46 (s, 6H, $C(CH_3)_2$), 1.40* (s, 6H, $C(CH_3)_2$), 1.36* (d, ^3J = 7.2 Hz, 6H, *i*Pr), 1.33 (d, ^3J = 7.2 Hz, 6H, *i*Pr), 1.04* (s, 9H, *t*-Bu), 1.02 (s, 9H, *t*-Bu). $^{13}C\{^1H\}$ NMR (151 MHz, C_7D_8): δ 64.6 (s, N−C), (* marks the minor rotamer), 62.7 (s, N−C), 62.6* (s, N−C), 60.4* (s, N−C), 56.4* (t, CH_2), 55.4 (t, CH_2), 48.7* (d, N−CH), 46.5 (d, N−CH), 45.1* (t, CH_2(ad)), 44.5 (t, CH_2(ad)), 37.3 (t, CH_2(ad)), 37.2* (t, CH_2(ad)), 35.9 (t, CH_2), 33.3* (t, CH_2), 32.6 (q, *t*-Bu), 32.5* (q, *t*-Bu), 32.0* (s, *t*-Bu), 31.8 (s, *t*-Bu), 31.2 (d, CH(ad)), 31.0 (d, CH (ad)), 27.8* (q, *i*Pr), 27.3 (q, *i*Pr). HRMS *m*/*z*: calcd for $C_{21}H_{40}N$ $[M + H]^+$, 306.3161; found, 306.3169.

*N,N-Di-tert-butyl-n-butylamine (**27a**). Method A.* A mixture of *n*-BuLi (10 mL, 25 mmol, 2.5 M in *n*-hexane), TMEDA (19.3 g, 15 mL, 166 mmol), and *N*,*N*-di-*tert*-butylchloroamine (1.0 g, 6.11 mmol)[8,23] was used. The product was purified by prep. GC. After that, **27a** was obtained with a yield of 0.77 g (4.15 mmol, 68%) as a colorless liquid. ^{1}H NMR (400 MHz, C_7D_8): δ 0.93 (t, ^3J = 7.3 Hz, 3H, CH_3−CH_2), 1.18 (s, 18H, $C(CH_3)_3$, overlapped), 1.18−1.25 (m, 2H, CH_3CH_2, overlapped), 1.45−1.53 (m, 2H, CH_2), 2.43−2.47 (m, 2H, N−CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_7H_8): δ 14.5 (q, CH_3CH_2), 20.9 (t, CH_2), 32.0 (q, $C(CH_3)_3$), 39.3 (t, CH_2), 47.5 (t, CH_2), 57.4 (s, $C(CH_3)_3$). HRMS *m*/*z*: calcd for $C_{12}H_{28}N$ $[M + H]^+$, 186.2216; found, 186.2217.

*N,N-Di-tert-butyl-isobutylamine (**27b**). Method A.* A solution of *i*-BuLi (13 mL, 22 mmol, 1.7 M in *n*-heptane), TMEDA (19.3 g, 15 mL, 166 mmol), and *N*,*N*-di-*tert*-butylchloroamine (1.0 g, 6.11 mmol)[8,23] were used for the reaction. The product was purified by prep. GC. This gave **27b** with a yield of 0.70 g (3.78 mmol, 62%) as a colorless liquid. ^{1}H NMR (400 MHz, C_7D_8): δ 2.27 (d, ^3J = 7.4 Hz, 2 H, CH_2), 1.64−1.75 (m, 1H, CH), 1.15 (s, 18H, $C(CH_3)_3$), 0.91 (d, ^3J = 6.7 Hz, 6H, $(CH_3)_2CH$). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_7D_8): δ 57.2 (s, $C(CH_3)_3$), 54.8 (t, CH_2), 32.2 (q, $C(CH_3)_3$), 31.5 (d, $(CH_3)_2CH$), 20.8 (q, $(CH_3)_2CH$). HRMS *m*/*z*: calcd for $C_{12}H_{28}N$ $[M + H]^+$, 186.2216; found, 186.2218.

*N,N-Di-tert-butyl-neopentylamine (**27c**). Method A.* According to the general protocol using neopentylmagnesium bromide (9 mmol in 10 mL Et_2O), *N*,*N*-di-*tert*-butylchloroamine (0.5 g, 3 mmol)[8,23] was converted into product **27c** as a yellowish liquid with a yield of 200 mg (1 mmol, 33%). ^{1}H NMR (600 MHz, C_6D_6): δ 2.53 (s, 2H, CH_2), 1.18 (s, 18H, *t*-Bu), 1.03 (s, 9H, neopentyl). $^{13}C\{^1H\}$ NMR (150.9 MHz, C_6D_6): δ 56.9 (s, *t*-Bu), 56.7 (t, CH_2), 33.0 (q, *t*-Bu), 31.08 (q, neopentyl), 31.07 (s, neopentyl). HRMS *m*/*z*: calcd for $C_{13}H_{30}N$ $[M + H]^+$, 200.2378; found, 200.2373.

*N,N-Di-tert-butyl-sec-butylamine (**27d**). Method A.* Using *sec*-BuLi [20 mL, 26 mmol, 1.3 M in cyclohexane/hexane (92:8)], TMEDA (19.3 g, 166 mmol), and *N*,*N*-di-*tert*-butylchloroamine (1.0 g, 6.11 mmol)[8,23] in 15 mL pentane, the product was isolated with 0.30 g yield (1.62 mmol, 27%) as a colorless liquid. ^{1}H NMR (400 MHz, C_7D_8): δ 2.95−3.04 (m, 1H, CH_3CH), 1.59−1.70 (m, 1H, CH_2), 1.47−1.59 (m, 1H, CH_2), 1.29 (s, 9H, $C(CH_3)_3$), 1.23 (d, ^3J = 6.9 Hz, 3H, CH_3CH), 1.21 (s, 9H, $C(CH_3)_3$), 0.91 (t, ^3J = 7.5 Hz, 3H, CH_3CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_7D_8): δ 58.4 (s, $C(CH_3)_3$), 57.1 (s, $C(CH_3)_3$), 55.4 (d, CH_3CH), 34.7 (q, $C(CH_3)_3$), 34.3 (t, CH_2), 32.9 (q, $C(CH_3)_3$), 22.5 (q, CH_3CH), 13.2 (q, CH_3CH_2). HRMS *m*/*z*: calcd for $C_{12}H_{28}N$ $[M + H]^+$, 186.2216; found, 186.2214.

*N-tert-Butyl-N,N-dicyclohexylamine (**27f**). Method A.* Analogously to the common procedure, *N*-*tert*-butyl-*N*-chlorocyclohexylamine (2.6 mmol, 0.5 g), TMEDA (4.6 g, 6.0 mL, 40 mmol), and cyclohexylmagnesium chloride (8 mmol, 4 mL, 2 M in Et_2O) were used to obtain the product **27f** as a yellowish liquid with a yield of 137 mg (57 mmol, 22%). ^{1}H NMR (400 MHz, C_6D_6): δ 2.72−2.79 (tt, ^3J = 11.9 Hz, 2.9 Hz, 2H, CH), 1.74−1.76 (m, 8H, CH_2), 1.50−1.59 (m, 6H, CH_2), 1.20 (s, 9H, *t*-Bu), 1.18−1.29 (m, 4H, CH_2), 1.00−1.08 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_6D_6): δ 57.7 (d, CH), 55.9 (s, *t*-Bu), 36.3 (t, CH_2), 31.6 (q, *t*-Bu), 27.9 (t, CH_2), 26.6 (t, CH_2). HRMS *m*/*z*: calcd for $C_{16}H_{32}N$ $[M + H]^+$, 238.2535; found, 238.2541.

*N,N-Di-(tert-amyl)-cyclopentylamine (**28a**). Method A.* The reaction was carried out following the typical procedure using *N*-chloro-*N*,*N*-di-*tert*-amylamine (0.50 g, 2.62 mmol),[8] cyclopentylmagnesium bromide (7.85 mL, 3.93 mmol, 0.5 M in diethyl ether), and TMEDA (5.00 g, 43.1 mmol). The crude product was subjected to a vacuum recondensation using a liquid nitrogen trap. The desired product **28a** was collected at 50 °C and 1 mbar as a pure colorless oil with a yield of 0.15 g (0.665 mmol, 25%). ^{1}H NMR (400 MHz, C_6D_6): δ 3.44 (quint, ^3J = 9.6 Hz, 1H, CH), 1.35−1.84 (m, 12H), 1.22 (br s, 12H, $C(CH_3)_2$), 0.96 (t, ^3J = 7.6 Hz, 6H, CH_2CH_3). $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6): δ 60.2 (br s, NC), 59.6 (s, NC), 59.3 (d, CH), 37.1 (bt, CH_2), 32.8 (t, CH_2), 32.7 (q, CH_3), 29.8 (bq, CH_3), 24.0 (t, CH_2), 23.9 (t, CH_2), 9.4 (q, CH_2CH_3), 9.2 (q, CH_2CH_3). HRMS *m*/*z*: calcd for $C_{15}H_{32}N$ $[M + H]^+$, 226.2535; found, 226.2509.

*N,N-Di-(tert-amyl)-cyclohexylamine (**28b**). Method A.* The reaction was carried out by using *N*-chloro-*N*,*N*-di-*tert*-amylamine (0.50 g, 2.62 mmol),[8] TMEDA (5.0 g, 43.1 mmol), and cyclohexylmagnesium chloride (1.96 mL, 2 M in THF, 3.93 mmol). The crude product was subjected to a vacuum recondensation using a liquid nitrogen trap, and the desired product **28b** was collected at 50 °C and 1 mbar as a pure colorless oil with a yield of 0.14 g (0.58 mmol, 22% yield). ^{1}H NMR (400 MHz, C_6D_6): δ 2.78 (tt, ^3J = 11.6 Hz, ^3J = 2.8 Hz, 1H, CH), 1.53−1.86 (m, 10H), 1.48 (q, ^3J = 7.6 Hz, 2H, CH_2CH_3), 1.29 (s, 6H, $C(CH_3)_2$), 1.20−1.23 (m, 2H, CH_2), 1.19 (s, 6H, $C(CH_3)_2$), 0.95 (t, ^3J = 7.6 Hz, 6H, CH_2CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_6D_6): δ 61.4 (s, $C(CH_3)_2$), 59.6 (s, $C(CH_3)_2$), 59.4 (d, CH), 37.4 (t, CH_2), 37.1 (t, CH_2), 36.8 (t, CH_2), 31.6 (t, CH_2), 28.8 (q, $C(CH_3)_2$), 28.5 (q, $C(CH_3)_2$), 26.6 (t, CH_2), 9.7 (q, CH_2CH_3), 9.4 (q, CH_2CH_3). HRMS *m*/*z*: calcd for $C_{16}H_{34}N$ $[M + H]^+$, 240.2691; found, 240.2668.

*N,N-Di-(adamantan-1-yl)-neopentylamine (**29a**). Method A.* The reaction was performed using *N*-chloro-*N*,*N*-di-adamantan-1-ylamine (0.32 g, 1.00 mmol),[8] neopentylmagnesium chloride (1.50 mL, 1.50 mmol, 1 M in diethyl ether), and TMEDA (3.00 g, 26.20 mmol). The crude product was dissolved in MeOH (20 mL) and heated at 50 °C, and the product was filtered off while hot. The desired product **29a** was collected as a pure white solid with a yield of 0.12 g (0.36 mmol, 36%). mp 123−125 °C. ^{1}H NMR (400 MHz, C_6D_6): δ 2.75 (s, 2H, $CH_2C(CH_3)_3$), 1.98−2.07 (m, 18H), 1.56−1.63 (m, 12H), 1.10 (s, 9H, $C(CH_3)_3$). $^{13}C\{^1H\}$ NMR (100 MHz, C_6D_6): δ 58.2 (s, C), 51.8 (t, $CH_2C(CH_3)_3$), 44.4 (t, CH_2), 36.8 (t, CH_2), 31.1 (s, $CH_2C(CH_3)_3$), 30.8 (q, $CH_2C(CH_3)_3$), 30.7 (d, CH). Anal. Calcd for $C_{25}H_{41}N$: C, 84.44; H, 11.62; N, 3.94. Found: C, 84.12; H, 11.53; N, 3.87.

*N,N-Di-(adamantan-1-yl)-cyclopentylamine (**29b**). Method A.* The reaction was carried out using *N*-chloro-*N*,*N*-di-adamantan-1-ylamine (0.32 g, 1.00 mmol),[8] TMEDA (3.00 g, 26.20 mmol), and cyclopentylmagnesium bromide (3.0 mL, 1.50 mmol, 0.50 M in diethyl ether). The crude product was added to MeOH (30 mL) and heated at 50 °C, and the product was filtered off while hot. The desired product **29b** was collected as a pure white solid with a yield of 0.09 g (0.25 mmol, 26%). mp 124−125 °C. ^{1}H NMR (400 MHz, C_6D_6): δ 3.52 (quint, ^3J = 9.6 Hz, 1H, CH), 2.16 (br s, 6H), 2.01 (br s, 6H), 1.97 (br s, 8H), 1.40−1.72 (m, 18H). $^{13}C\{^1H\}$ NMR (100.6 MHz, C_6D_6): δ 61.1 (s, C), 59.7 (s, C), 58.5 (d, CH), 44.9 (t, CH_2), 44.7 (t, CH_2), 36.9 (t, CH_2), 36.8 (t, CH_2), 34.1 (t, CH_2), 30.9 (d, CH), 30.6 (d, CH), 24.0 (t, CH_2). HRMS *m*/*z*: calcd for $C_{25}H_{40}N$ $[M + H]^+$, 354.3161; found, 354.3135.

*2-Isopropyl-1,1,3,3-tetramethylisoindoline (**30a**). Method A.* By using 2-chloro-1,1,3,3-tetramethylisoindoline (0.5 g, 2.4 mmol), TMEDA (5.0 g, 43.1 mmol), and isopropylmagnesium chloride (2.4 mL, 4.8 mmol, 2 M in THF), a crude product was obtained, which was subjected to column chromatography with basic aluminium oxide

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as the stationary phase and *n*-hexane as the mobile phase. The least polar fraction was collected, and the solvent was removed under vacuum to obtain the desired product **30a** as a white solid with a yield of 0.16 g (0.62 mmol, 26% yield). Further purification was performed by recrystallization from methanol. mp 41−42 °C. ^{1}H NMR (400 MHz, C_6D_6): δ 7.12−7.14 (m, 2H, C$\underline{H}$), 6.97−6.98 (m, 2H, C$\underline{H}$), 3.36 (sept, ^3J = 6 Hz, 1H, C$\underline{H}(CH_3)_2$), 1.41 (s, 12H, C($C\underline{H}_3$)$_2$), 1.26 (d, ^3J = 6 Hz, 6H, CH($C\underline{H}_3$)$_2$). ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 147.5 (s, C), 125.7 (d, $\underline{C}H$), 120.0 (d, $\underline{C}H$), 64.4 (s, $\underline{C}(CH_3)_2$), 43.8 (d, $\underline{C}H(CH_3)_2$), 30.1 (q, C($\underline{C}H_3$)$_2$), 24.1 (q, CH($\underline{C}H_3$)$_2$). HRMS *m*/*z*: calcd for $C_{15}H_{24}N$ [M + H]$^+$, 218.1903; found, 218.1904.

*2-(tert-Butyl)-1,1,3,3-tetramethylisoindoline (**30b**). Method A.* The reaction was carried out using 2-chloro-1,1,3,3-tetramethylisoindoline (0.5 g, 2.4 mmol), TMEDA (5.0 g, 43.1 mmol), and *tert*-butylmagnesium chloride (2.8 mL, 4.8 mmol, 1.7 M in diethyl ether). The crude product was subjected to column chromatography using basic aluminum oxide as the stationary phase and *n*-hexane as the mobile phase. The least polar fraction was collected, and the solvent was removed under vacuum to obtain the desired product **30b** as a pure white solid with a yield of 30.0 mg (0.13 mmol, 5.5%). Further purification could be done by washing with methanol. mp 70−72 °C. ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 7.17−7.20 (m, 2H, CH), 7.10−7.13 (m, 2H, CH), 1.59 (s, 12H, C($C\underline{H}_3$)$_2$), 1.47 (s, 9H, C($C\underline{H}_3$)$_3$). ^{13}C{^{1}H} NMR (100.6 MHz, $(CD_3)_2CO$): δ 148.5 (s, CH$\underline{C}$), 126.5 (d, CH), 121.0 (d, CH), 66.9 (s, $\underline{C}(CH_3)_2$), 54.8 (s, $\underline{C}(CH_3)_3$), 33.6 (q, C($\underline{C}H_3$)$_2$), 33.4 (q, C($\underline{C}H_3$)$_3$). HRMS *m*/*z*: calcd for $C_{16}H_{26}N$ [M + H]$^+$, 232.2065; found, 232.2062.

*2-(tert-Butyl)-1,1,3,3-tetraethylisoindoline (**30e**). Method A.* The reaction was carried out using 2-chloro-1,1,3,3-tetraethylisoindoline (0.6 g, 2.4 mmol), TMEDA (5.0 g, 43.1 mmol), and *tert*-butylmagnesium chloride (2.8 mL, 4.8 mmol, 1.7 M in diethyl ether). The crude product was subjected to thick-layer chromatography using basic aluminum oxide as the stationary phase and *n*-hexane as the mobile phase. The least polar fraction was collected. The solvent was removed under vacuum to get a 1:1.2 mixture of the desired product **30e** with a yield of 20.0 mg (0.07 mmol, 3%) and 1,1,2,3,3-pentaethylisoindoline (**30c**) as an inseparable side product. ^{1}H NMR (400 MHz, C_6D_6): δ 7.09−7.11 (m, 2H, CH), 6.87−6.89 (m, 2H, CH), 1.98 (q, ^3J = 6 Hz, 8H, C$\underline{H}_2$CH$_3$), 1.41 (s, 9H, C($C\underline{H}_3$)$_3$), 0.84 (t, ^3J = 6 Hz, 12H, CH$_2$C$\underline{H}_3$). ^{13}C{^{1}H} NMR (100.6 MHz, C_6D_6): δ 145.9 (s, C), 126.5 (d, CH), 121.8 (d, CH), 75.1 (s, C), 55.6 (s, C), 36.2 (t, CH$_2$), 33.9 (q, (CH$_3$)$_3$), 10.5 (q, CH$_2$$\underline{C}H_3$). HRMS *m*/*z*: calcd for $C_{20}H_{34}N$ [M + H]$^+$, 288.2691; found, 288.2688.

*N-Cyclopentyl-2,2,6,6-tetramethylpiperidine (**31**). Method A.* By using cyclopentylMgCl (3 mL, 6 mmol, 2 M in Et_2O), TMEDA (3.4 g, 4.5 mL, 30 mmol), and *N*-chloro-2,2,6,6-tetramethylpiperidine (0.5 g, 2.85 mmol),[23,35] the product was obtained as a colorless liquid with a yield of 133 mg (0.63 mmol, 22%). ^{1}H NMR (600 MHz, C_6D_6): δ 3.31 (tt, ^3J = 11.4 Hz, 7.7 Hz, 1H, N−CH), 1.68−1.81 (m, 4H, CH$_2$), 1.54−1.61 (m, 2H, CH$_2$), 1.47−1.51 (m, 2H, CH$_2$), 1.41−1.43 (m, 6H, CH$_2$), 1.18 (s, 12H, N−C(CH$_3$)$_2$). ^{13}C{^{1}H} NMR (151 MHz, C_6D_6): δ 59.9 (d, N−CH), 54.9 (s, N−C), 44.0 (t, CH$_2$), 33.9 (t, CH$_2$), 29.8 (q, CH$_3$), 23.2 (t, CH$_2$), 18.1 (t, CH$_2$). HRMS *m*/*z*: calcd for $C_{14}H_{28}N$ [M + H]$^+$, 210.2216; found, 210.2219.

*4-Isopropyl-3,3,5,5-tetramethylmorpholin-2-one (**32**). Method A.* According to the general procedure, 4-chloro-3,3,5,5-tetramethylmorpholin-2-one (0.2 g, 1 mmol), TMEDA (1.7 g, 2.3 mL, 15 mmol), and *i*PrMgCl (1.5 mL, 3 mmol, 2 M in THF) were used to obtain the product **32** as a colorless liquid with a yield of 79 mg (0.4 mmol, 40%). IR ($CHCl_3$) $\tilde{\nu}_{max}$: 1723 cm^{-1} (C═O). ^{1}H NMR (400 MHz, C_6D_6): δ 3.50 (s, 2H, CH$_2$), 2.83 (sept, ^3J = 7.1 Hz, 1H, *i*Pr), 1.35 (s, 6H, 3-Me), 0.92 (d, ^3J = 7.1 Hz, 6H, *i*Pr), 0.83 (s, 6H, 5-Me). ^{13}C{^{1}H} NMR (100.6 MHz, C_6D_6): δ 174.2 (s, C═O), 79.8 (t, CH$_2$), 61.6 (s, C-3), 52.4 (s, C-5), 46.8 (d, *i*Pr), 27.7 (q, 3-Me), 25.0 (q, *i*Pr), 23.9 (q, 5-Me). HRMS *m*/*z*: calcd for $C_{11}H_{22}NO_2$ [M + H]$^+$, 200.1651; found, 200.1651.

*(E)-4-(Di-tert-butylamino)but-3-en-1-ol (**33b**).* Anhydrous LiCl (300 mg, 7 mmol) was mixed with THF (5 mL), and a *t*-BuMgCl solution (4.1 mL, 7 mmol, 1.7 M in Et_2O) was added. This solution was stirred for 3 days at rt and then cooled to −70 °C, and TMEDA (1.6 g, 2.1 mL, 14 mmol) was added. After 2 h, *N*-chloro-*N*,*N*-di-*tert*-butylamine (0.57 g, 3.5 mmol)[8,23] was added slowly at the same temperature. The reaction mixture was slowly warmed to 0 °C after about 2 h and then recondensed at 10^{-2} mbar and 0 °C. The volatiles were removed at 4 mbar and 0 °C. The product **33b** was obtained as a colorless liquid with a yield of 14 mg (0.055 mmol, 1.6% NMR yield). ^{1}H NMR (400 MHz, C_6D_6): δ 5.70 (dt, ^3J = 13.2 Hz, ^4J = 1.1 Hz, 1H, N−C$\underline{H}$═), 5.24 (dt, ^3J = 13.3 Hz, ^3J = 7.4 Hz, 1H, CH═C$\underline{H}$−CH$_2$), 3.38 (t, ^3J = 6.4 Hz, 2H, C$\underline{H}_2$−OH), 2.05−2.11 (m, 2H, ═CHC$\underline{H}_2$), 1.19 (s, 18H, *t*-Bu). ^{13}C{^{1}H} NMR (100.6 MHz, C_6D_6): δ 137.2 (d, N−CH═), 125.7 (d, ═$\underline{C}$H−CH$_2$), 62.2 (t, $\underline{C}$H$_2$−OH), 55.5 (s, *t*-Bu), 33.4 (t, ═C−$\underline{C}$H$_2$), 31.6 (q, *t*-Bu). HRMS *m*/*z*: calcd for $C_{12}H_{27}NO$ [M + 2H]$^+$, 201.2093; found, 201.2089.

*1,1,3-Triethyl-1H-isoindol (**36**). Method A.* TMEDA (0.7 g, 0.9 mL, 6 mmol) was dissolved in Et_2O (10 mL), and neopentylmagnesium bromide (3 mL, 3 mmol, 1 M in Et_2O) was slowly added at 0 °C. After 1 h, 2-chloro-1,1,3,3-tetraethylisoindoline (**25c**, 300 mg, 1.1 mmol) was dropped in. The product was isolated with the help of a thin-layer chromatography plate of silica (Et_2O/pentane = 1:1) and obtained as a yellowish liquid with a yield of 60 mg (0.3 mmol, 27%). ^{1}H NMR (600 MHz, C_6D_6): δ 7,06−7.15 (m, 4H, aryl), 2.64 (q, ^3J = 7.5 Hz, 2H, 3-Et), 2.14 (dq, ^2J = 13.5 Hz, ^3J = 7.4 Hz, 2H, 1-Et), 1.84 (dq, ^2J = 13.5, Hz ^3J = 7.4 Hz, 2H, 1-Et), 1.34 (t, ^3J = 7.5 Hz, 3H, 3-Et), 0.58 (t, ^3J = 7.4 Hz, 6H, 1-Et). ^{13}C{^{1}H} NMR (150.9 MHz, C_6D_6): δ 172.2 (s, N═C), 156.6 (s, aryl), 140.4 (s, aryl), 127.9 (d, aryl (superimposed by C_6D_6)), 127.0 (d, aryl), 121.6 (d, aryl), 120.7 (d, aryl), 81.0 (s, C-1), 31.0 (t, 1-Et), 23.8 (t, 3-Et), 11.5 (q, 3-Et), 8.3 (q, 1-Et). HRMS *m*/*z*: calcd for $C_{14}H_{20}N$ [M + H]$^+$, 202.1596; found, 202.1589.

*N-(1-Adamantyl)-neopentylamine (**40a**).* *N*,*N*-Di-1-adamantyl-neopentylamine (**29a**, 5.0 mg, 14 mmol) was dissolved in dilute H_2SO_4 (10 mL, 8%$_{aq}$) and heated at 100 °C for 24 h. Then, the solution was neutralized with a NaOH solution and extracted with pentane. The organic phase was dried with potassium carbonate, and after removal of the solvent, product **40a** was isolated as a white solid with a yield of 2.0 mg (9 mmol, 64%). mp 206−210 °C. ^{1}H NMR (600 MHz, C_6D_6): δ 2.29 (s, 2H, N−CH$_2$), 1.98 (br s, 3H, CH), 1.54−1.61 (m, 12H, ad), 0.98 (s, 9H, *t*-Bu). ^{13}C{^{1}H} NMR (150.9 MHz, C_6D_6): δ 52.3 (t, N−CH$_2$), 43.1 (s, N−C(overlapped)), 43.1 (t, ad(overlapped)), 37.1 (t, ad), 31.3 (s, *t*-Bu), 30.1 (d, ad), 27.8 (q, *t*-Bu). HRMS *m*/*z*: calcd for $C_{15}H_{28}N$ [M + H]$^+$, 222.2222; found, 222.2218.

*N-(Bicyclo[2.2.1]heptan-exo-2-yl)adamantan-1-amine (**40d**).* *N*,*N*-Di-(adamantan-1-yl)-*N*-(*exo*-bicyclo[2.2.1]heptan-2-yl)-amine (**29d**, 0.20 g, 0.53 mmol)[8] was refluxed in MeOH for 1 h. The solvent was evaporated under vacuum. The crude product was purified via thick layer chromatography by using basic aluminum oxide as the stationary phase and *n*-hexane as the mobile phase. The desired product **40d** was collected as a white solid with a yield of 0.10 g (0.41 mmol, 77%). mp 162−164 °C. ^{1}H NMR (400 MHz, C_6D_6): δ 2.72 (dd, ^3J = 8 Hz, ^3J = 4 Hz, 1H), 2.15 (br s, 1H), 1.95−2.02 (m, 4H), 1.54−1.66 (m, 14H), 1.37−1.45 (m, 2H), 0.99−1.12 (m, 4H), NH signal was not found. ^{13}C{^{1}H} NMR (100 MHz, C_6D_6): δ 53.5, 50.6, 45.2, 44.3, 44.0, 36.8, 35.7, 35.1, 29.8, 28.6, 26.9. HRMS *m*/*z*: calcd for $C_{17}H_{28}N$ [M + H]$^+$, 246.2222; found, 246.2219.

Computational Details. All calculations were carried out using either G09[36] or G16.[37] Geometry optimizations were carried out at B3LYP/6-31G(d), followed by frequency calculations and then single-point energy calculations at B2PLYPD/6-311+G(2df,2p).[38] Energies reported in Tables 1−3 represent B2PLYPD/6-311+G(2df,2p), plus a zero-point energy correction at B3LYP/6-31G(d). This combination has been found previously to give energies in good accord with the highest-quality composite procedures such as CBS-QB3 and G-4.[39] Qualitatively similar results were also obtained via M062X/6-31G(2df,p) and wB97XD/def2TZVP optimizations. The values in Table 3 additionally include a correction for solvation in toluene, using the default continuum-based model in Gaussian 16 [scrf = (solvent = toluene)].[40]

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For the elimination processes explored in Table 3, the step of leaving group departure presents multiple possibilities in some cases. The most energetically favorable route was always chosen. For ethyldimethylamine, that means loss of dimethylamine leaving behind the ethyl cation. For most of the other cases, it means departure of a secondary amine such that *tert*-butyl cation is left behind. In the case of amine **8**, the most favorable route was found to be loss of *tert*-butylisopropylamine leaving behind the "*tert*-octyl" cation, in accord with the experimental finding that 2,4,4-trimethyl-1-pentene is the observed alkene product.

For each compound studied, the lowest energy conformation was used for analysis. For simpler structures, all conformations were generated systematically, the geometries were optimized, and the energies were computed at B3LYP/6-31G(d) in order to determine the lowest energy conformation. For the larger structures, the GMMX[41] conformational search engine that is integrated into GaussView 6[42] was used to identify low-energy conformations. Parameters used were MM3 force field, 20 kcal/mol energy window, 10,000 search steps, and "both" as method (varying Cartesian coordinates as well as bond rotation). All rotatable bonds were selected manually. For each molecule, the initially generated set of structures was first subjected to HF/STO-3G optimization, followed by removal of duplicate structures, followed by refinement at B3LYP/6-31G(d).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c01790.

NMR spectra, kinetic data, and computational details (PDF)

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The authors declare no competing financial interest.

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