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Approaches to primary tert-alkyl amines as building blocks

Christina Tzitzoglaki[‡], Antonios Drakopoulos[‡], Athina Konstantinidi, Ioannis Stylianakis, and Antonios Kolocouris *

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, National and Kapodistrian University of Athens, Panepistimioupolis-Zografou, 15771 Athens, Greece
E-mail: ankol@pharm.uoa.gr

In memory of Professor George B. Foscolos

1 Abstract

Primary *tert*-alkyl amines represent analogues of amantadine, a fragment commonly linked to pharmacophoric groups to enhance biological activity. The preparation of primary *tert*-alkyl amines is considered to be a difficult problem. Four synthetic procedures, which have been previously reported for the synthesis of amines with primary (RCH_2NH_2) or secondary ($RR'CHNH_2$) alkyl and/or aryl groups, were tested for the synthesis of primary *tert*-alkyl amines ($RR'R''CNH_2$) in aliphatic series including adamantane adducts. These procedures included the formation and reduction of *tert*-alkyl azides, the Ritter reaction in standard and modified conditions, the addition of organometallic reagents to *N-tert*-butyl sulfinyl ketimines and one-pot reactions between nitriles and organometallic reagents in the presence of a Lewis acid, $Ti(iPrO)_4$ or $CeCl_3$. These synthetic routes are unexplored for primary *tert*-alkyl amines and their unexpected results should be included in organic chemistry literature. The reaction conditions and substrate limitations were studied for each procedure, with the first procedure being the more general and applicable also for compounds bearing bulky adducts.

Keywords: Primary tert-alkyl amine, tert-alkyl azide reduction, Ritter reaction, N-tert-butanesulfinyl imine reduction, organometallic addition to 1-adamantanecarbonitrile, $Ti(iPrO)_4$

2 Introduction

Remarkably simple aminoadamantane structures hit targets like viroporins to combat Influenza virus A and the NMDA receptor for symptomatic relief in Parkinson Disease and Alzheimer Disease.[1] Adamantane is a lipophilic symmetrical hydrocarbon cage which is often used -itself or modified- as a fragment in drug molecule design and optimization. Amantadine and several simple analogues represent such building blocks which can be favorably modified and linked with known pharmacophoric groups, resulting in enhanced biological activity. Examples are molecules: (a) with glucocerebrosidase activity potentially useful for atherosclerosis;[2] (b) K^+ channel activity and hypoglycemic properties;[3] (c) affinity for opioid receptor;[4] (d) affinity for σ-receptor[5] which is involved in psychotic disorders; (e) affinity for soluble epoxide hydrolase[6] which is deemed valuable for various diseases; (f) dipeptidyl peptidase IV inhibitory potency[7] for the treatment of type 2 diabetes mellitus, (g) influenza A amantadine resistance[8] etc (Figure S1).

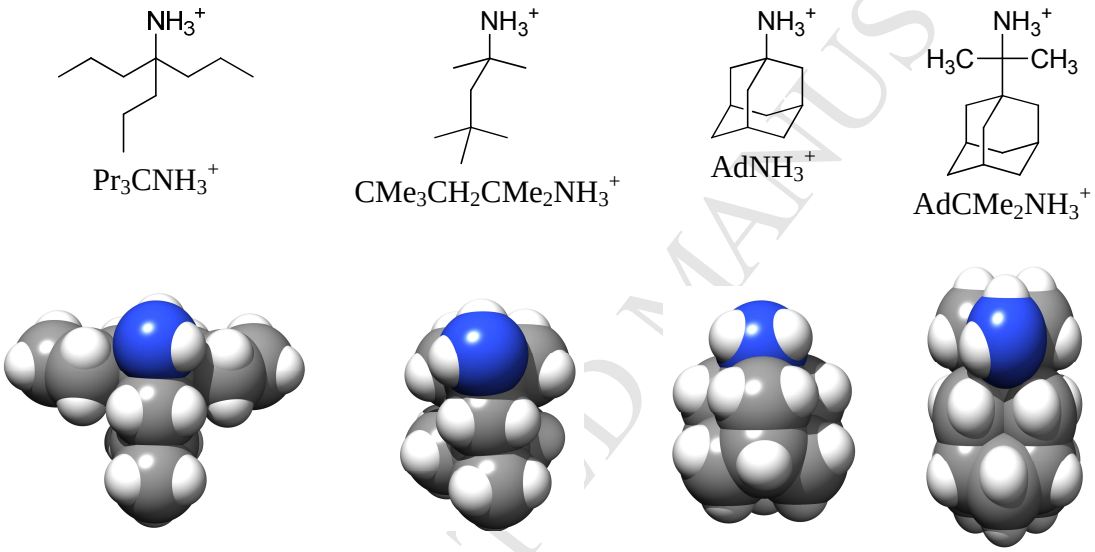


Figure 1. Top: $Pr_3CNH_3^+$ and $CMe_3CH_2CMe_2NH_3^+$ are open cage analogues of amantadine ($AdNH_3^+$). Compounds $AdNH_3^+$ and $AdCMe_2NH_3^+$ are potent influenza A wild-type M2 protein inhibitors. Bottom: van der Waals spheres representation of Pr_3CNH_2 , $CMe_3CH_2CMe_2NH_2$, $AdNH_2$ and $AdCMe_2NH_2$.

Although amantadine has been long marketed as an antiviral drug for influenza A, it was only after 2008 that high resolution structures from x-ray and ssNMR experiments showed that the primary binding site of amantadine is the lumen of the four-helix bundle of tetrameric M2 (M2TM: amino acids 22-46) that forms the proton transport path.[9] We are interested in the preparation of primary *tert*-alkyl amines in aliphatic series, including common alkyl chain and adamantane substituents. These compounds may be used as lipophilic amine building blocks for the development of drug molecules acting against wild type and mutant M2 protein of amantadine-resistant influenza A virus strains[8] or addressing other biological targets. For example, it was reported that 1,1,3,3-tetramethylbutylamine ($CMe_3CH_2CMe_2NH_2$)[10] and 2-(1-adamantyl)-2-propanamine ($AdCMe_2NH_2$)[11] block the M2 channel with an efficiency comparable to amantadine (Figure 1).

The preparation of primary *tert*-alkyl amines or α,α,α-trisubstituted primary amines is considered to be a difficult problem.[12] If one of the substituents of the desired primary *tert*-alkyl amine is itself a bulky *tert*-alkyl

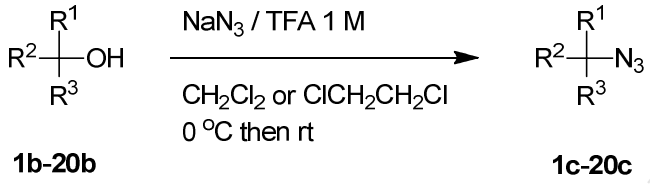
group or adamantyl group, steric crowding is expected to increase the difficulty of the preparation. When the starting material is a *tert*-alkyl alcohol, a general and widely used route is the Ritter reaction,[13] providing the primary *tert*-alkyl amine in two steps. This procedure has some considerable disadvantages, such as the drastic conditions and moderate overall yields. Therefore, several procedures have been widely applied to convert primary and secondary alcohols to the corresponding azides -based on the S_N2 mechanism- which then can be reduced to the corresponding amines.[14-16] However, only limited examples of robust procedures have been published on the conversion of *tert*-alkyl alcohols[16-20] to the corresponding amines, and some of them used elaborate reactants.[16,20] Furthermore, while several reagents have been developed for the reduction of primary and secondary azides to the corresponding amines, when a *tert*-alkyl azide is the substrate its reduction is considered to be inconvenient.[12]. In this work, we present our efforts towards the synthesis of primary *tert*-alkyl amines, including adamantyl as one of the alkyl groups, and we compare the various aforementioned procedures.

3 Results and Discussion

Tert-alkyl azide reduction (Procedure A)

***Tert*-alkyl azide formation.** Procedure A may start with a ketone or other suitable starting material, e.g. an acid chloride. The *tert*-alkyl alcohol was obtained by the reaction of the starting material with a suitable organometallic reagent. Subsequently, it was converted to the *tert*-alkyl azide which was then subjected to a reduction, affording the primary *tert*-alkyl amine. The conversion of tertiary adamantanols to the corresponding azides was routinely performed in our lab using a mixture of $CHCl_3/H_2SO_4$ 57 % and sodium azide in good yields.[21] These reaction conditions were applied to linear *tert*-alkyl alcohols, like BuEt(*n*-Pr)COH (**1b**), obtained from 3-heptanone (**1a**) and PrMgBr. A mixture of the azide $BuEtPrCN_3$ (**1c**) and the precursor alcohol **1a** was obtained in 60:40 ratio, based on the integration of ^{13}C NMR signals (Table S1, entry 1). The reaction proceeds via the formation of a carbonium ion which is trapped by the azide anion. It seems that the 2-alkyl-2-adamantyl carbonium intermediates from tertiary 2-alkyl-2-adamantanols are more stable, and thus form more efficiently compared to those formed by *tert*-alkyl alcohols.[22] A more efficient formation of the aforementioned linear azide was not achieved after increasing the sulfuric acid concentration to 70 % (Table S1, entry 2); instead a ketone product was also formed along with the azide. This ketone may be formed through a Schmidt rearrangement mechanism which produces an imine that can be hydrolyzed to a ketone -as has been previously reported for the *tert*-butyl substrate.[23] The *tert*-alkyl alcohol **1b** was treated with $CHCl_3$/TFA 0.5M/NaN_3 mixture, and the reaction product was a mixture of the azide **1c** and the precursor alcohol **1b** in a 70:30 ratio -according to the ^{13}C NMR spectrum. An increase in TFA concentration to 1 M was tested but the same mixture was afforded (Table S1, entries 3, 4), while further increase of the TFA concentration to 5M caused a decomposition of the substrate. Changing the solvent from $CHCl_3$ to CH_2Cl_2 or $ClCH_2CH_2Cl$, i.e. from $CHCl_3$/TFA 1 M/NaN_3 to CH_2Cl_2 or $ClCH_2CH_2Cl$/TFA 1 M/NaN_3, resulted in the azide as the only product (Table S1, entry 5; Table 1, entry 1).

Table 1. Conversion of *tert*-alkyl alcohols to *tert*-alkyl azides using a NaN_3/TFA in CH_2Cl_2 or $ClCH_2CH_2Cl$ (Procedure A).[a]



1b-20b **1c-20c**

Entry	Ketone + organometallic reagent	Alcohol R^1,R^2,R^3	Isolated Yield	Azide R^1,R^2,R^3	Isolated Yield
1	3-heptanone (**1a**) + PrMgBr	Bu,Et,Pr, **1b**	80%	Bu,Et,Pr, **1c**[b]	87%
2	4-heptanone (**2a**) + PrMgBr	Pr,Pr,Pr, **2b**	78%	Pr,Pr,Pr,, **2c**[b]	78%
3	5-nonanone (**3a**) + BuMgBr	Bu,Bu,Bu, **3b**	80%	Bu,Bu,Bu, **3c**[b]	82%
4	4-heptanone (**2a**) + BuMgBr	Bu,Pr,Pr, **4b**	71%	Bu,Pr,Pr, **4c**[b]	71%
5	4-heptanone (**2a**) + iBuLi	iBu,Pr,Pr, **5b**	80%	iBu,Pr,Pr, **5c**[b]	86%
6	5-nonanone (**3a**) + PrMgBr	Bu,Bu,Pr, **6b**	70%	Bu,Bu,Pr, **6c**[b]	75%
7	2,6-dimethyl-heptan-4-one (**4a**) + BuLi	iBu,iBu,Bu, **7b**	80%	iBu,iBu,Bu, **7c**[c]	76%
8	2-adamantanone (**5a**) + MeMgBr	2Ad, Me, **8b**	88%	2- Ad, Me, **8c**[b]	88%
9	2-adamantanone (**5a**) + EtLi	2Ad, Et, **9b**	80%	2- Ad, Et, **9c**[b]	80%
10	2-adamantanone (**5a**) + $CH_2CH=CH_2MgBr$ then PtO_2/H_2	2Ad, Pr, **10b**	89%	2- Ad, Pr, **10c**[b]	66%
11	2-adamantanone (**5a**) + BuLi	2Ad, Bu, **11b**	76%	2- Ad, Bu, **11c**[b]	76%
12	2-adamantanone (**5a**) + PhLi	2Ad, Ph, **12b**	95%	2- Ad, Ph, **12c**[b]	95%
13	2-adamantanone (**5a**) + BnMgBr	2Ad, Bn, **13b**	50%	2- Ad, Bn, **13c**[b]	50%
14	2-adamantanone (**5a**) + pMeOBn	2Ad, MeOBn, **14b**	53%	2- Ad, MeOBn, **14c**	53%
15	1AdCOCl (**6a**) + MeMgBr	1Ad, Me, Me, **15b**	80%	1Ad,Me,Me, **15c**[b]	80%
16	1AdCOCl (**6a**) + EtLi	1Ad, Et, Et, **16b**	77%	1Ad, Et, Et, **16c**[b]	77%
17	1AdCOCl (**6a**) + AllylMgBr	1Ad, Allyl, Allyl, **17b**	44%	1Ad, Allyl, Allyl, **17c**[b]	44%
18	1AdCOCl (**6a**) + $CH_2CH=CH_2MgBr$ then PtO_2/H_2	1Ad, Pr, Pr, **18b**	59%	1Ad, Pr, Pr, **18c**[b]	37%
19	1AdCOCl (**6a**) + $BrMg(CH_2)_4MgBr$	C_5H_{11}, 1Ad, **19b**	90%	C_5H_{11}, 1Ad, **19c**[b]	90%
20	2-cyclohexanone (**7a**) + 1-AdLi	C_6H_{13}, 1Ad, **20b**	65%	Cy, 1-Ad, **20c**[b]	65%

[a]Completion of reaction was checked by ^{13}C NMR peaks integration; [b]CH_2Cl_2 used; [c]$ClCH_2CH_2Cl$ used

The aforementioned reaction conditions were then tested against *tert*-alkyl alcohols **2b-20b** for the preparation of azides **2d-20d** (Table 1, entries 2-20). Alcohols **1b-4b, 6b** were obtained from the reaction between the ketones **1a-3a** respectively and the suitable Grignard reagent (Table 1, entries 1-4,6). The

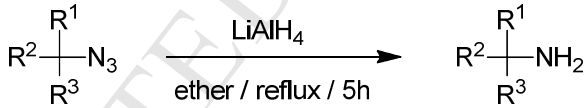
iBuPr$_2$COH (**5b**) was obtained from the addition of isobutyl lithium to 4-heptanone (**2a**). Similarly iBuBu$_2$COH (**7b**) (Table 1, entry 7) was afforded through addition of isobutyl lithium to 5-nonanone (**3a**). Starting from alcohols **1b-7b** and using the conditions shown in Table 1, i.e. CH_2Cl_2 or $ClCH_2CH_2Cl$/TFA 1 M/NaN_3, correspondingly, the azides **1c-7c** were afforded in yields 71-87% (Table 1). In the adamantane series, tertiary alcohols **8b**, **9b**, **11b**, **12b** were obtained by treating 2-adamantanone **5a** with an oganolithium (R=Et,Bu) or an organomagnesium reagent (R=Me,Ph,PhCH$_2$,pMeOPhCH$_2$), as depicted in Figure S1. For the synthesis of the propyl derivative **10b**, 2-adamantanone reacted with vinyl magnesium bromide and the produced allyl alcohol was hydrogenated under PtO_2. Compound **15b** was prepared from the reaction between 1-adamantane carbonyl chloride (**6a**) (the corresponding ethyl ester was also successfully trialed) and CH_3MgI, as expected.[11] Alcohol **16b** was prepared in high yield from the reaction between 1-adamantane carbonyl chloride (**6a**) and EtLi. The reaction of allylmagnesium bromide with **6a** afforded diallyl alcohol **17b**, which was subsequently hydrogenated under PtO_2 catalyst to afford alcohol **18b** (Figure S2). Starting from alcohols **8b-18b** and using the above conditions the azides **8c-18c** were afforded in yields 37-88% (Table 1). A trial to prepare the cyclopentenol precursor of cyclopentanol **19b** through cyclization of **17b** using first generation Grubbs catalyst was unsuccessful. Diallyl azide **17c** was prepared from **17b** with a 44% yield. Compounds **19b**, **20b** were synthesized according to the procedure included in reference 30. According to the reaction conditions presented in Table 1, changing the solvent from $CHCl_3$ to CH_2Cl_2 or $ClCH_2CH_2Cl$ increased considerably the *tert*-alkyl azide yield. The *tert*-alkyl azide formation proceeds through an ion pair intermediate, i.e. the *tert*-alkyl carbocation/TFA anion, generated by the *tert*-alkyl alcohol treatment with TFA. This is more favored in dichloromethane compared to chloroform due to the higher dielectric constant of CH_2Cl_2 (ε = 8.93) or $ClCH_2CH_2Cl$ (ε = 10.4), compared to $CHCl_3$ (ε = 4.81). The former can stabilize the carbonium ion and thus facilitate its formation, according also to DFT calculations included in the Supplementary material (Table S3, S4). When ether was used as a solvent (ε = 4.33), the starting alcohol was afforded. Protic solvents have also high dielectric constants, but *tert*-alkyl azides are formed in low yields in protic solvents due to the competitive solvolysis reaction.[24]

***Tert*-alkyl azide reduction.** It was tested if primary *tert*-alkyl amines **1d-7d** could be formed conventionally from primary *tert*-alkyl azides **1c-7c** through a $LiAlH_4$ reduction[21,25,26] or a catalytic hydrogenation, for example using Pd/C.[27] In general, these methods were considered to be high yielding[25,26] without a systematic investigation regarding the structure of the *tert*-alkyl substrate; e.g. in one case it was reported that the reduction took a different route, yielding a triazene.[28] On the other hand, the reduction of *tert*-alkyl azides to *tert*-alkyl amines has been reported to be an inconvenient transformation, albeit without further explanations and citations.[12] The reduction of the *tert*-alkyl azides **1c-20c** using $LiAlH_4$ in refluxing ether for 5 h yielded the primary *tert*-alkyl amines **1d-20d** in good (Table 2, entries 1,2,5,15,17,19,20) to moderate yields (Table 2, entries 3,4,6,7,16,18). The antiviral bulky aminoadamantanes **8d-13d, 15d-20d**[11,29,30] were also afforded (Table 2, entries 8-20, Figures S1-S4), with the notable exception of **17d** where decomposition took place. The yields of compounds **15d**, **16d**, **18d** were improved (Figure S2), compared to previous results.[11] The reaction was performed using 4 equivalents of $LiAlH_4$ in a slurry with a concentration of 1 g $LiAlH_4$/80 mL dry ether under reflux. The resulting amines were isolated through standard hydrolysis conditions and filtration of the reaction mixture. The ethereal solution was extracted with hydrochloride solution 6%, the acidic solution was made alkaline with solid sodium carbonate and the mixture was extracted with ether to afford amines **1d-20d**. The purity was higher than 95%, according to the relative integration of amine signals with impurities signals detected in ^{13}C NMR spectra. The amines were further purified through formation of crystalline ammonium salts with fumaric acid and recrystallization using ethanol/ether. A probable competitive reaction lowering the

yield of the amine is the formation of an imine which can be formed through an intramolecular Schmidt rearrangement via a nitrene intermediate.[31] When refluxing THF was used, lower yields were obtained. The yield was not improved when the refluxing ethereal conditions were changed to ambient temperature. The $LiAlH_4$ reaction of diallyl azide **17c** did not afford the diallylamine but led to decomposition.

It is noteworthy that a critical reduction in yield was observed when transitioning from Pr_3 to Bu_3 substrate (Table 2, see entries 2,3,10,11), due to the formation of unsaturated products and extensive decomposition. To investigate further the effect of the structure of the *tert*-alkyl group to the yield of the reduction of the azido group, the alcohols **5b**, **6b** and the corresponding azides **5c**, **6c** including the combination of $BuPr_2$ and Bu_2Pr substitution on the tertiary carbon were synthesized (Table 2, entries 5,6). As depicted in Table 2, the yield for the $BuPr_2$ substrate in amine **5d** (Table 2, entry 5) was 58% and in close proximity to the 60% yield obtained with Pr_3 substrate in amine **2d** (Table 2, entry 2). The yield was reduced progressively from 35% in the Bu_2Pr substrate of amine **6d** (Table 2, entry 6), to 20% in the Bu_3 or iBu_2Bu substrates of amines **3d**, **7d** respectively (Table 2, entries 3,7). Also, changing the tri-alkyl group from Pr_3 to $iBuPr_2$ reduced significantly the yield to 14% in amine **4d** (Table 2, entry 4). Although the yields included in Table 2 were not optimized, the procedure was general for all the substrates applied, except entry 17. While in all cases refluxing ether seems to be an optimal choice for $LiAlH_4$ reduction of the *tert*-alkyl azides, these conditions did not work well in one case (Table 2, entry 14). It was observed that between Bn and pMeOBn substrate (Table 2, entries 13 and 14), refluxing ether conditions led to complete reduction for Bn substrate (Table2, entry 13), but for pMeOBn the reduction yield was only 18% and most of the azide **14c** was isolated unreacted (Table 2, entry 14). Refluxing THF was applied for effective reduction of the azide **14c**. The p-methoxy group in amine **16d** was deprotected to the p-hydroxy group using BF_3 in dry ether at -80 ºC to afford the aminoderivative **21** (Figure S5).

Table 2. Reaction of *tert*-alkyl azides with $LiAlH_4$ in refluxing dry ether (Procedure A).[a]



1c-20c **1d-20d**

Entry	Azide R^1,R^2,R^3	Amine product R^1,R^2,R^3	Isolated Yield
1	Bu,Et,Pr, **1c**	Bu,Et,Pr, **1d**	67%
2	Pr,Pr,Pr, **2c**	Pr,Pr,Pr, **2d**	60%
3	Bu,Bu,Bu, **3c**	Bu,Bu,Bu, **3d**	20%
4	iBu,Pr,Pr, **4c**	iBu,Pr,Pr, **4d**	14%
5	Bu,Pr,Pr, **5c**	Bu,Pr,Pr, **5d**	58%
6	Bu,Bu,Pr, **6c**	Bu,Bu,Pr, **6d**	35%
7	iBu,iBu,Bu, **7c**	iBu,iBu,Bu, **7d**	20%
8	2Ad, Me, **8c**[b]	2Ad, Me, **8d**	77%
9	2Ad, Et, **9c**	2Ad, Et, **9d**	71%
10	2Ad, Pr, **10c**	2Ad, Pr, **10d**	74%
11	2Ad, Bu, **11c**	2Ad, Bu, **11d**	23%
12	2Ad, Ph, **12c**	2Ad, Ph, **12d**	55%

13	2Ad, Bn, **13c**	2Ad, Bn, **13d**	45%
14	2Ad, MeOBn, **14c**	2Ad, MeOBn, **14d**	18%, 48%[a]
15	1Ad, Me, Me, **15c**	1Ad, Me, Me, **15d**	73%
16	1Ad, Et, Et, **16c**	1Ad, Et, Et, **16d**	23%
17	1Ad, Allyl, Allyl, **17c**	1Ad, Allyl, Allyl, **17d**	-[b]
18	1Ad, Pr, Pr, **18c**	1Ad, Pr, Pr, **18d**	14%
19	C_5H_{11}, 1Ad, **19c**	C_5H_{11}, 1Ad, **19d**	56%[c]
20	C_6H_{13}, 1Ad, **20c**	C_6H_{13}, 1Ad, **20d**	48%[c]

[a]Completion of reaction was observed by NMR; [b]decomposition; [c]prepared as depicted in Figures S3, S4

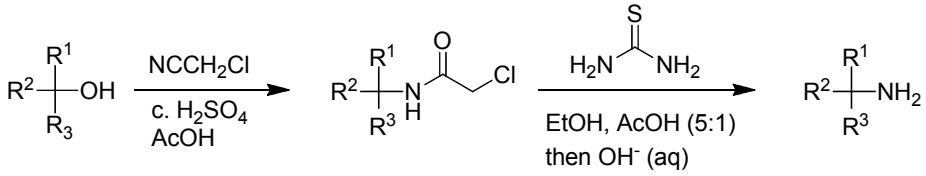
A few other reagents were tested for reduction of the tert-alkyl azido group; however, no significant improvement was achieved in yield compared to the $LiAlH_4$ reduction. Some representative trials include the catalytic hydrogenation with Pd/C (10%)[27] for 18 h using different solvents (AcOEt, MeOH, MeOH/NH_3(g), MeOH/$CHCl_3$) or different pressure conditions (50 psi or 1 Atm). For example, for the $BuEtPrCN_3$ (**1c**) the highest yield achieved with catalytic hydrogenation was 57% for $EtPrBuC\text{-}NH_2$ (**1d**); while Bu_3CN_3 (**3c**) afforded $Bu_3C\text{-}NH_2$ (**3d**) in 11% yield. The catalytic hydrogenation of compound **17c** led to a complex mixture of products. The yields were also low or poor when reduction of $EtPrBuCN_3$ (**1c**) was attempted with: (a) $FeCl_3/NaI$[32] (10%); (b) Me_3SiCl/NaI[33] (4%); (c) by applying Staudinger reaction conditions and hydrolysis of the phosphazene in THF/H_2O under reflux[19,34] (13%); (d) $NaBH_4/CuSO_4\cdot 5H_2O$[35] (23%). When Pr_3CN_3 (**2c**) was used in combination with $(EtO)_3P$/benzene/TosOH/EtOH[19,34,36] or with $SnCl_2$/PhSH/Et_3N[37] the yields of the obtained amine **2d** were 35% and 33% respectively. When Bu_3CN_3 (**3c**) was used as the substrate, the same reagents afforded $Bu_3C\text{-}NH_2$ (**3d**) in yields 18% and 8%. The conclusion drawn from the trials described is that the weak spot of procedure A, which is responsible for the serious decrease of the overall yield, is the reduction step of the *tert*-alkyl azide to the corresponding primary *tert*-alkyl amine, particularly when the alkyl chain length is increasing. Other possibly more efficient procedures were then investigated, especially for the synthesis of crowded amines like Bu_3CN_3 (**3d**) which was produced in low yield with procedure A.

Ritter reaction (Procedure B)

Common Ritter reaction. The Ritter reaction[12] was tested using common[12,38] (KCN, c.H_2SO_4, heat; see Table S2, entries 1,2) or slightly modified conditions (urea, c.H_2SO_4, heat; see Table S2, entry 3). The results showed that these common Ritter reaction conditions proved, at best equally effective, compared to procedure A, for the preparation of the $BuEtPrCNH_2$ (**1d**) in 47% yield (see Table S2, entry 1), and significantly worse for the preparation of Bu_3CNH_2 (**3d**) in 4-5% (yield see Table S2, entry 3).

Modified Ritter reaction. A modified Ritter reaction scheme was tested, which was suggested as a general scheme for the synthesis of primary *tert*-alkyl amines.[39] This methodology is reported to employ the formation of *N-tert*-alkyl chloroacetamides after reaction of *tert*-alkyl alcohols with chloroacetonitrile. The chloroacetyl group can be subsequently cleaved smoothly with thiourea, leading to the formation of the respective amine (Table 3).

Table 3. Modified Ritter reaction through chloroacetamides which are hydrolyzed with thiourea for the preparation of primary *tert*-alkyl amines (Procedure B).



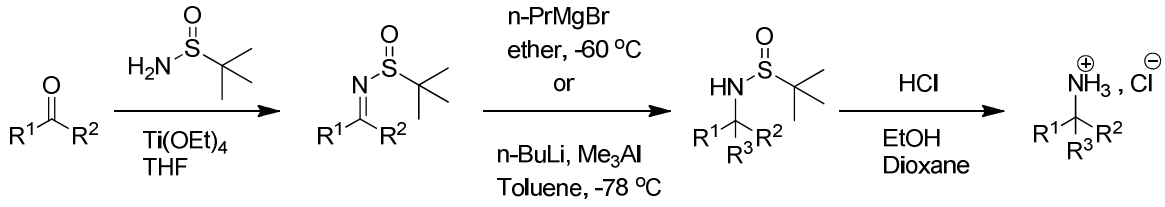
Entry	Alcohol R^1,R^2,R^3	Chloroacetamide R^1,R^2,R^3	Isolated Yield	Amine R^1,R^2,R^3	Isolated Yield
1	Pr,Pr,Pr, **2b**	Pr,Pr,Pr, **22**	48%	Pr,Pr,Pr, **2d**	80%
2	Bu,Bu,Bu, **3b**	Bu,Bu,Bu, **23**	51%	Bu,Bu,Bu, **3d**	61%

Using this procedure, $Pr_3C\text{-}NH_2$ (**2d**) and $Bu_3C\text{-}NH_2$ (**3d**) were successfully obtained from the corresponding *tert*-alkyl alcohols **2b** and **3b** through intermediate chloroacetamides **22** and **23**. In the latter case, the yield of the chloroacetyl group cleavage step was lower. However, as the alkyl group size was increasing, the efficiency of Ritter-like procedures for the synthesis of primary *tert*-alkyl amines was reduced; possibly due to a retro-Ritter reaction.[40] Especially, when the common Ritter reaction conditions were applied, the yield was reduced dramatically (Table S2, entries 2,3). After work-up of the reaction mixture in the second step and the isolation of amines **2d** or **3d** through extraction with an aqueous hydrochloric acid solution, the organic layer contained an unsaturated product, possibly formed through a retro-Ritter reaction. The modified Ritter reaction scheme included as a second step a more efficient chloroacetyl group cleavage, affording the primary *tert*-alkyl amine in yields 80% and 60% for substrates Pr_3C and Bu_3C respectively. The azide reduction had moderate to low yields, 60% and 20% respectively, for the same substrates. However, in the first step the *tert*-alkyl azides **2c**, **3c** are formed in higher yields compared to the *tert*-alkyl chloroacetamides **22** and **23.** Procedure B, while providing amine **11d** through chloroacetamide **24** successfully, was not productive when applied for the synthesis of amines **15d** or **18d**. The relevant trials afforded chloroacetamides **25, 26** in low to moderate yield, due to the formation of an alkene by-product, and the cleavage of the chloroacetyl group with thiourea gave correspondingly the *tert*-alkyl amines **15d**, **18d** only in traces (Figure S5).

Addition of organometallic reagents to *N-tert*-butylsulfinyl imines (Procedure C)

The procedure consisting of the addition of organomagnesium or organolithium reagents to the *N-tert*-butylsulfinyl imines[41,42] **28** and **29** and deprotection of *N-tert*-butylsulfinamides **30** and **31**,[41,42] proved successful for the synthesis of the *tert*-alkyl amines **2d** and **3d** (Table 4). However, more elaborate conditions and more expensive reagents (e.g. *tert*-butanesulfinamide) were needed, compared to the previous procedures. For the preparation of $Bu_3C\text{-}NH_2$ (**3d**), the addition of BuLi/$AlMe_3$ to imine **28** was applied, which proved to be more efficient compared to BuMgBr or BuLi.[41,42]

Table 4. Synthesis of primary *tert*-alkyl amines by the addition of organometallic reagents to *N-tert*-butylsulfinyl imines (Procedure C).



Entry	Ketone R^1,R^2	*N*-*t*Bu-sulfinylimine R^1,R^2	Isolated Yield	*t*Bu-sulfinamide[a] R^1,R^2,R^3	Amine R^1,R^2,R^3	Isolated[b] Yield
1	Pr,Pr, **2a**	Pr,Pr, **28**	70%	Pr,Pr,Pr, **30**	Pr,Pr,Pr, **2d**	40%
2	Bu,Bu, **3a**	Bu,Bu, **29**	77%	Bu,Bu,Bu, **31**	Bu,Bu,Bu, **3d**	25%

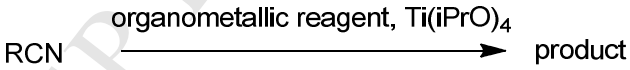
[a]yield not determined; [b]from the *N*-*tert*-butylsulfinyl imine

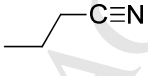
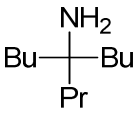
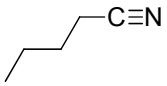
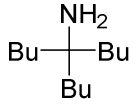
Starting from the same commercially available ketone, procedure A applied the sequence ketone → *tert*-alkyl alcohol → *tert*-alkyl azide → *tert*-alkyl amine; procedure B using the modified Ritter reaction applied the sequence ketone → *tert*-alkyl alcohol → *tert*-alkyl chloroacetamide → *tert*-alkyl amine; procedure C applied the sequence ketone → *tert*-butylsulfinyl imines → *tert*-butanesulfinamide → *tert*-alkyl amine. From 5-nonanone (**3a**) the synthesis of Bu_3CNH_2 (**3d**) was accomplished using the procedure A, B (modified Ritter) and C in 13%, 25%, and 19% yield respectively. Starting from 4-heptanone (**2a**), the synthesis of Pr_3CNH_2 (**2d**) was accomplished in 37%, 30%, 28% yield respectively. Procedure C, similarly to procedure B (modified Ritter), was also not productive in the adamantane series. The reaction of 1-adamantyl ethyl ketone **32** with *tert*-butanesulfinamide did not yield the corresponding *N*-*tert*-butylsulfinyl imine **33**. The formation of intermediates **27** and **33** suffers from steric hindrance, as suggested by Molecular Mechanics calculations (see Figure S5).

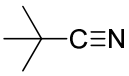
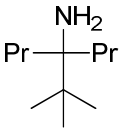
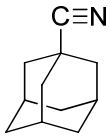
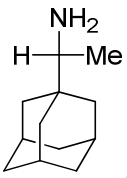
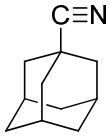
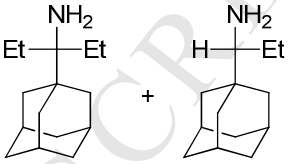
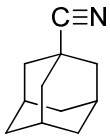
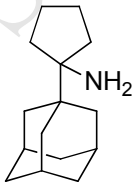
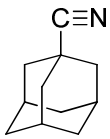
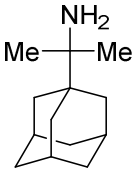
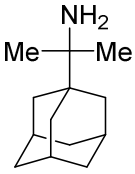
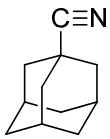
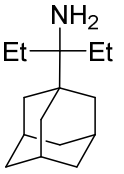
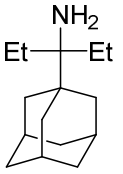
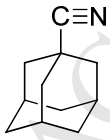
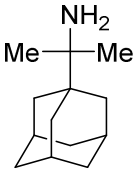
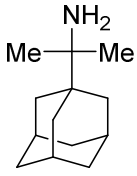
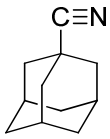
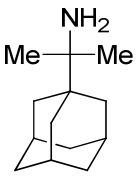
Addition of organometallic reagents to nitriles (Procedure D)

The one-pot synthesis of primary *tert*-alkyl amines through addition of organometallic reagents to nitriles in the presence of Lewis acid catalysts was investigated.[43-47] The synthesis of few *tert*-alkyl amines was first tested through a procedure following the Kulinkovich-de Meijere reaction conditions: addition of an excess of organometallic reagent (3-4 equivalents) to nitriles (1eq) mediated by $Ti(iPrO)_4$ (1 eq) in one-pot (Table 5).[12]

Table 5. One-pot synthesis of primary *tert*-alkyl amines by the addition of organometallic reagents to nitriles mediated by $Ti(iPrO)_4$ (Procedure D).



Entry	nitrile	reagents, protocol (1), (2)	Product: yield (1)	(2)
1	 **34**	BuMgBr ether,$Ti(iPrO)_4$[a]	 **6d**: 25%	Not tested
2	 **35**	BuMgBr ether,$Ti(iPrO)_4$[a]	 **3d**: 20%	Not tested

3	 **36**	PrMgBr ether, $Ti(iPrO)_4$[a]	 **38**: 20%	Not tested
4	 **37**	MeMgBr ether,$Ti(iPrO)_4$[a]	 **39**: 15%	Not tested
5	 **37**	EtMgBr ether, $Ti(iPrO)_4$[a]	 **16d**: 4% + **40**: 3%	Not tested
6	 **37**	$BrMg(CH_2)_4MgBr$ ether,$Ti(iPrO)_4$[b]	 **19d**: 10%	Not tested
7	 **37**	1. MeMgBr ether, $Ti(iPrO)_4$ 2. MeLi, ether[c]	 **15d**: 10%	 **15d**: 11%
8	 **37**	1. EtMgBr ether, $Ti(iPrO)_4$ 2. EtLi, ether[c]	 **16d**: 10%	 **16d**: 10%
9	 **37**	1. MeMgBr, $Ti(iPrO)_4$, ether 2. MeMgBr, ether[d]	 **15d**: 10%	 **15d**: 10%
10	 **37**	MeLi,$CeCl_3$, THF, -65 °C[e]	 **15d**: 12%	

(1) Kulinkovich-DeMeijere; (2) Kulinkovich-Szymoniak; [a]RMgBr(3eq)/$Ti(iPrO)_4$(1eq)/ether/24h/reflux; [b]$BrMg(CH_2)_4MgBr$(2eq)/$Ti(iPrO)_4$ (1eq)/ether/24h/reflux; [c]1.RMgBr(1eq)/$Ti(iPrO)_4$ (1eq)/ether/1h/rt 2.MeLi

(2eq) ether/24h/reflux. [d] MeMgBr (1eq)/Ti(iPrO)$_4$ (1eq)/ether/1h/rt 2. MeMgBr (2 eq)/ether/1h, rt. [e]MeLi (3 eq)/$CeCl_3$ (3 eq)/THF/4h/-65 ^oC.

One equivalent of the Grignard reagent reacted first with the nitrile, forming an imino derivative. Then Ti(iPrO)$_4$ was added to activate the imino functionality for the addition of a second equivalent of an organometallic reagent, which can be a different Grignard or an organolithium reagent (see Figure S6 for the detailed desciption of the original protocol).[12] Starting from the commercially available butanenitrile (**34**) and pentanenitrile (**35**), the preparation of $PrBu_2CNH_2$ (**6d**) and Bu_3CNH_2 (**3d**) was accomplished in 25% and 20% yield respectively (Table 5, entries 1, 2). In the original papers, the reaction was tested for nitriles up to secondary or benzonitrile.[10,45] We applied the Kulinkovich-de Meijere reaction to pivalonitrile (**36**). Treatment of nitrile **33** with propylmagnesium bromide (3 eq)/Ti(iPrO)$_4$ afforded the *t*-$BuPr_2CNH_2$ (**38**) in 20% yield (Table 5, entry 3). Following a work-up of the reaction mixture, the yield was determined for the reactions depicted in Table 5 after fumarate salt formation and recrystallization of the amine product, as previously. The Kulinkovich-de Meijere protocol was applied for the reaction of 1-adamantanecarbonitrile (**37**) and the simple Grignard reagents RMgBr (R=Me, Et) in the presence of Ti(iPrO)$_4$ for the synthesis of primary *tert*-alkyl adamantanamines **15d** and **16d** (Table 5, entries 4-9). The addition of ethylmagnesium bromide to 1-adamantanecarbonitrile (**37**) using the above conditions afforded a mixture of $AdEtCHNH_2$ (**40**) in 3% yield and $AdEt_2CNH_2$ **16d** in 4% yield; the ratio of **40** to **16d** was 60:40 according to the ^{13}C NMR spectrum (Table 5, entry 5). It was thought that a β-hydride addition from the second equivalent of the organometallic reagent to an imino group might explain the formation of the *sec*-alkyl amine **40** along with the *tert*-alkyl amine **16d**. However, it was striking that the application of MeMgBr afforded the secondary amine, that is, rimantadine $AdMeCHNH_2$ (**39**) in 15% yield (Table 5, entry 4); while unreacted AdMeC=NH imine was identified in the filtrate after filtration of the solid fumarare salt of the amine **39**. The application of an organolithium compound as the organometallic reagent in the second step was also tested using the Kulinkovich-de Meijere protocol (Figure S6). The desired *tert*-alkyl amines **15d**, **16d** were obtained in 10% yield (Table 5, entries 7, 8). In the fumarate salt, a small amount of the secondary amine **37** was again detected as a 10% contamination.

The organocerium reagent prepared from anhydrous cerium (III) chloride and methyl lithium was tested as candidate to a higher yield formation of *tert*-alkyl amine **16d**. This one-pot sequence was assumed to proceed through an activated imino functionality to give primary *tert*-alkylamines (Figure S7). The reaction of 3 equiv of $MeCeCl_2$ with 1-adamantanecarbonitrile (**32**) at -78 ºC and stirring the mixture at -65 ºC for 4 h was reported to afford **15d** in 75%.[46] We tested this procedure twice and the maximum yield obtained was 12% for **15d** (Table 5, entry 10).

The Kulinkovich-Szymoniak[43] reaction conditions were also tested for the preparation of **15d** and **16d**. In this protocol, the nitrile, Ti(iPrO)$_4$ and organometallic reagent were initially placed together in the reaction flask (see Figure S8 for the detailed desciption of the original protocol). Subsequently, an additional amount of organometallic reagent (the same as previously or different) is added. In our trials, we employed one equivalent of EtMgBr and then one equivalent of EtLi, or two equivalents of EtMgBr (Figure S8). This reaction sequence is based on the formation of a titatanocene compound including an electrophilic imine bond, which reacts with the second organometallic reagent (see Figure S8 for the detailed desciption of the original protocol). Using these conditions the pure amine **15d** or **16d** was isolated as crystalline fumarate in 10% yield (Table 5, entries 7,8). When the Kulinkovich-de Meijere protocol or the Kulinkovich-Szymoniak protocol was applied for the treatment of 1-adamantanecarbonitrile (**32**) with Ti(iPrO)$_4$/RMgBr and RLi, the *tert*-alkyl amine **15d** or **16d** was afforded in 10 to 11% yield (Table 5, entries 7,8). A recent report applied Ti(iPrO)$_4$ in combination with ethylmagnesium bromide under Kulinkovich-Szymoniak conditions was reported to afford **16d** in 52% yield.[47]

This result was not reproduced after several trials; the application of the Kulinkovich-Szymoniak protocol for the treatment of 1-adamantanecarbonitrile (**32**) with $Ti(iPrO)_4$, MeMgBr (1eq) and MeMgBr (2 eq) afforded the *tert*-alkyl amine **15d** in 8% yield (Table 5, entry 9). The Kulinkovich-de Meijere protocol with $Ti(iPrO)_4$ and MeMgBr (1eq) and MeMgBr (2 eq) afforded amine **15d** in 10% yield (Table 5, entry 9). The way that the organomagnesium reagent was added influenced the yield, in comparison to entry 4; applying the addition of the 3 equivalents in one step before addition of $Ti(iPrO)_4$ did not afford the desired amine **15d**. Trials using allylmagnesium bromide afforded a complex mixture of products either using Kulinkovich-de Meijere or Kulinkovich-Szymoniak. The reaction of adamantanacarbonitrile (**37**) with 1,4-bis(bromomagnesiobutane) afforded cyclopentanamine[21] **19d** in 10% yield (Table 5, entry 6). The overall yield using procedure A for the transformation of alcohol to amine **19d** starting from the commercially available 1-adamantanacarboxylic acid using treatment of 1-adamantanecarboxylate with 1,4-bis(bromomagnesiobutane) was ~ 32%.

4 Conclusions

Although elegant procedures have been developed for the preparation of primary *sec*-alkyl amines through the formation of carbon-carbon bonds in position alpha to the respective nitrogen (see for example reference 48), the synthesis of primary *tert*-alkyl amines, which are of great interest to the field of medicinal chemistry, is still not trivial. A systematic study of four standard procedures on the preparation of primary *tert*-alkyl amines was presented. Under procedure A, the *tert*-alkyl azides can be prepared from *tert*-alkyl alcohols using NaN_3 and dichloromethane or 1,2-dicholoroethane as optimal solvents, and the target amines are prepared by azides reduction with $LiAlH_4$, generally in refluxing ether. It was found that subtle changes of the size of the linear alkyl chain can influence the yield in the reduction step of this procedure. For example, a gradual reduction in yield from Pr_3C to Bu_3C substrate was observed. A modified Ritter reaction employing a *tert*-alkyl chloroacetamide intermediate (procedure B), the addition of organometallic reagents to *N*-*tert*-butyl sulfinyl ketimines (procedure C) or the one-pot reaction of nitriles with organometallic reagents in the presence of $Ti(iPrO)_4$ or $CeCl_3$ (procedure D) can be useful routes, but were not efficient when the substrate includes unique bulky adducts. The first protocol via azide reduction is rather general even for unique adamantane adducts.

5 Experimental Section

General. IR spectra were recorded on a Perkin-Elmer 833 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX 400 and AC 200 spectrometer at 400 and 50 MHz, respectively, using $CDCl_3$ as the solvent and TMS as the internal standard. Carbon multiplicities were established by the DEPT experiments. The 2D NMR techniques, HMQC and COSY, were used for the elucidation of the structures of intermediates and final products. Microanalyses were carried out by the Microanalyses lab of the National Center for Scientific Research, Demokritos, Athens, and the results obtained had a maximum deviation of ± 0.4% from the theoretical value. Compounds **9d-13d** were synthesized in reference 29 (see Figure S1); compounds **15d**, **16d** were synthesized in reference 11 but in this work were synthesized with improved yield (see Figure S2); compounds **19d**, **20d** were synthesized using the procedure described in reference 49 and in reference 30 as modification of the procedure applied in reference 48 (see Figures S3, S4). Caution should be kept when using NaN_3 or KCN in strong acid which can generate the toxic HCN or HN_3 respectively. When the adamantane ring is 2,2-disubstituted with A, B substituents one of the cyclohexane rings has the 2-substituent A in an axial position and another cyclohexane ring has the 2-substituent B in an axial position. Therefore 4,9-carbons of the

adamantane in one cyclohexane ring has protons 4ax,9ax and 4eq,9eq due to the 2-axial substituent A and 8,10-carbons of the adamantane in the other relevant cyclohexane ring has has protons 8ax,10ax and 8eq,10eq due to the 2-axial substituent B (Figure S9).

Procedure A

4-Ethyloctan-4-amine (BuEtPrCNH$_2$) 1d. 4-Ethyloctan-4-ol **1b** was obtained after treating a solution of 3-heptanone **1a** (1g, 8.77 mmol) in dry ether (30% solution w/v) with 1.2-molar excess of $CH_3CH_2CH_2MgBr$ (obtained from an 20% solution w/v solution of 1-bromopropane (2.1 g, 17.54 mmol) in dry ether and 1.3 equivalents of Mg (548 mg, 22.8 mmol)) under argon atmosphere and stirring the mixture overnight. After treating the mixture with saturated ammonium chloride following usual workup the corresponding tertiary alcohol **1b** was obtained. Yield 1.1 g, (80%); IR (Nujol) ν(OH) 3392 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.85 (t, J=7.1 Hz, 3H, $(CH_2)_3C\underline{H}_3$), 0.91 (t, J=7.1 Hz, 6H, $(CH_2)_2C\underline{H}_3$, $CH_2C\underline{H}_3$), 1.22-1.48 (m, 13H, $(C\underline{H}_2)_3CH_3$, $(C\underline{H}_2)_2CH_3$, $C\underline{H}_2CH_3$, OH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 7.9 ($(CH_2)_3\underline{C}H_3$), 14.3 ($(CH_2)_2\underline{C}H_3$), 14.9 ($CH_2\underline{C}H_3$), 16.9 ($(CH_2)_2\underline{C}H_2CH_3$), 23.5 ($CH_2\underline{C}H_2CH_3$), 25.8 ($CH_2\underline{C}H_2CH_2CH_3$), 31.7 ($\underline{C}H_2CH_3$), 38.6 ($\underline{C}H_2(CH_2)_2CH_3$), 41.4 ($\underline{C}H_2CH_2CH_3$), 74.3 ($\underline{C}OH$).

To a stirred mixture of sodium azide (488 mg, 7.50 mmol) and dry dichloromethane (15 mL), trifluoroacetic acid (2 mL, 25 mmol) was added at 0 °C. The resulting mixture was stirred for 10 min at 0 °C and a solution of the 4-ethyl-4-octanol **1b** (400 mg, 2.50 mmol) in 10 mL of dichloromethane was added dropwise. The mixture was stirred at 0-5 °C for 4 h and 24 h at ambient temperature. The mixture was made alkaline by adding NH_3 12 % (40 mL) and the organic phase was separated. The aqueous phase was extracted with dichloromethane and the combined organic phases were washed with water, brine and dried (Na_2SO_4). Solvent was evaporated in vacuo to afford 4-azido-4-ethyloctane, **1c**. Yield 398 mg, (87%); IR (Nujol) $\nu(N_3)$ 2093 cm^{-1}; ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 8.1 ($(CH_2)_3\underline{C}H_3$), 14.2 ($(CH_2)_2\underline{C}H_3$), 14.6 ($CH_2\underline{C}H_3$), 17.0($(CH_2)_2\underline{C}H_2CH_3$), 23.2 ($CH_2\underline{C}H_2CH_3$), 25.8 ($CH_2\underline{C}H_2CH_2CH_3$), 29.3 ($\underline{C}H_2CH_3$), 35.8 ($\underline{C}H_2(CH_2)_2CH_3$), 38.5 ($\underline{C}H_2CH_2CH_3$), 67.3 ($\underline{C}N_3$).

To a stirred suspension of $LiAlH_4$ (223 mg, 5.87 mmol) in dry ether (20 mL) was added dropwise at 0 °C a solution of the alkyl azide **1c** (269 mg, 1.47 mmol) in dry ether (15 mL). The mixture was refluxed for 5 h and then was treated with water, NaOH 10 % and water. The insoluble inorganic material was filtered-off, washed with ether and the filtrate was extracted with HCl 6%. The aqueous phase was made alkaline with solid sodium carbonate and was extracted with diclhoromethane or ether. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated in vacuo to afford the amine **1d**. Yield 150 mg, (65%); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 0.82 (t, J=7.1 Hz, 3H, $(CH_2)_3C\underline{H}_3$), 0.90 (t, J=7.1 Hz, 6H, $(CH_2)_2C\underline{H}_3$, $CH_2C\underline{H}_3$), 1.26-1.37 (m, 14H, $(C\underline{H}_2)_3CH_3$, $(C\underline{H}_2)_2CH_3$, $C\underline{H}_2CH_3$, NH_2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 7.9 ($(CH_2)_3\underline{C}H_3$), 14.3($(CH_2)_2\underline{C}H_3$), 15.0($CH_2\underline{C}H_3$), 16.8($(CH_2)_2\underline{C}H_2CH_3$), 23.6 ($CH_2\underline{C}H_2CH_3$), 25.9 ($CH_2\underline{C}H_2CH_2CH_3$), 32.6 ($\underline{C}H_2CH_3$), 39.6 ($\underline{C}H_2(CH_2)_2CH_3$), 42.4 ($\underline{C}H_2CH_2CH_3$), 53.6 ($\underline{C}NH_2$). MS (ES+) : $C_{10}H_{24}N^+$ ($M+H^+$) 158.2 Found: 158.2. Anal. ($C_{14}H_{27}NO_4$). Calcd. : C, 61.51; H, 9.96; N, 5.12. Found: C, 61.54; H, 10.16; N, 5.01.

4-Propylheptan-4-amine (Pr$_3$CNH$_2$) 2d. Tertiary alcohol **2b** was obtained after treating a solution of 4-heptanone **2a** (1g, 8.77 mmol) in dry diethyl ether (30% solution w/v) with 1.2-molar excess $CH_3CH_2CH_2MgBr$ (obtained from an 20% solution w/v solution of 1-bromopropane (2.1 g, 17.54 mmol) in dry ether and 1.3 equivalents of Mg (548 mg, 22.8 mmol)) under argon atmosphere and stirring the mixture overnight. After treating the mixture with saturated ammonium chloride following usual workup 4-propylheptan-4-ol **2b** was obtained. Yield 1.1 g, (78%); IR (Nujol) ν(OH) 3392 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 0.91 (t, J=7.1 Hz, 9H, 3x $CH_2CH_2C\underline{H}_3$), 1.15-1.41 (m, 12H, 3x$C\underline{H}_2CH_2CH_3$, 3x$CH_2C\underline{H}_2CH_3$), 2.10 (br s, OH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.9 ($\underline{C}H_3$), 17.0 ($CH_2\underline{C}H_2CH_3$), 42.0 ($CH_2\underline{C}H_2CH_3$), 74.7 ($\underline{C}OH$).

The 4-azido-4-propylheptane **2c** was prepared by treatment of the tertiary alcohol **2b** (400 mg, 2.50 mmol) with CH_2Cl_2 (15 mL)/NaN_3 (488 mg, 7.50 mmol)/TFA (2 mL, 25 mmol) according to the same procedure followed for 4-azido-4-ethyloctane **1c**. Yield 356 mg, (78%); IR (Nujol) $\nu(N_3)$ 2101 cm^{-1}; ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.4 ($3xCH_2CH_2\underline{C}H_3$), 16.9 ($3xCH_2\underline{C}H_2CH_3$), 38.9 ($3x\underline{C}H_2CH_2CH_3$), 66.8 ($\underline{C}N_3$).

The oily amine **2d** was prepared through $LiAlH_4$ (288 mg, 7.60 mmol) reduction of azide **2c** (350 mg, 1.90 mmol) in refluxing ether (20 mL) for 5h according to the same procedure followed for 4-ethyloctan-4-amine **1d**. 950 mg, Yield 50%; ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.88 (t, J=7.1 Hz, 9H), 1.27-1.45 (m, 12H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.9 ($\underline{C}H_3$), 16.8($CH_2\underline{C}H_2CH_3$), 42.9($CH_2\underline{C}H_2CH_3$), 53.4 ($\underline{C}NH_2$). MS (ES+) $C_{10}H_{24}N^+$ ($M+H^+$) 158.2 Found 158.2. Anal. ($C_{14}H_{27}NO_4$). Calcd. C, 61.51; H, 9.96; N, 5.12. Found: C, 61.66; H, 10.06; N, 5.13.

5-Butyl-nonan-5-amine (Bu_3CNH_2) 3d. 5-Butyl-nonan-5-ol, **3b** was obtained after treating a solution of 5-nonanone **3a** (1 g, 7.04 mmol) in dry diethyl ether (30% solution w/v) with 1.2-molar excess $CH_3CH_2CH_2CH_2MgBr$ (obtained from an 20% solution w/v solution of 1-bromobutane (1.9 g, 14.08 mmol) in dry ether and 1.3 equivalents of Mg (440 mg, 18.3 mmol) under argon atmosphere and stirring the mixture overnight. After treating the mixture with saturated ammonium chloride following usual workup the corresponding tertiary alcohol **3b** was obtained. Yield 1.1g, (80%); IR (Nujol) ν(OH) 3392 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 0.88 (t, J=7.1 Hz, 9H, $3xC\underline{H}_3CH_2CH_2CH_2$), 1.18-1.31 (m, 13H, $3xCH_3CH_2CH_2C\underline{H}_2$, 3x $CH_3CH_2\underline{CH}_2CH_2$, OH), 1.34-1.42 (m, 6H, 3x $CH_3\underline{CH}_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.2 ($3xCH_3$), 23.4 ($3xCH_3\underline{C}H_2CH_2CH_2$), 25.8 ($3xCH_3CH_2\underline{C}H_2CH_2$), 39.1 ($3xCH_3CH_2CH_2\underline{C}H_2$), 74.4 (COH).

The 5-azido-5-butylnonane **3c** was prepared by treatment of the tertiary alcohol **3b** (500 mg, 2.50 mmol) with CH_2Cl_2 (20 mL)/NaN_3 (489 mg, 7.50 mmol)/TFA (2 mL, 25 mmol) according to the same procedure followed for 4-azido-4-ethyloctane **1c**. Yield 460 mg, (82%); IR (Nujol) $\nu(N_3)$ 2095 cm^{-1}; ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.2 ($3xCH_3$), 23.2 ($3xCH_3\underline{C}H_2CH_2CH_2$), 25.9 ($3xCH_3CH_2\underline{C}H_2CH_2$), 36.4 ($3xCH_3CH_2CH_2\underline{C}H_2$), 66.9 ($CN_3$).

The oily amine **3d** was prepared through $LiAlH_4$ (270 mg, 7.11 mmol) reduction of azide **3c** (400 mg, 1.78 mmol) in refluxing ether (20 mL) for 5h according to the same procedure followed for 4-ethyloctan-4-amine **1d.** Yield 20%; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.89 (t, J=7.0 Hz, 9H, $3xCH_2CH_2CH_2C\underline{H}_3$), 1.15-1.30 (m, 18H, $3xC\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.3 ($3xCH_3$), 23.6 ($3xCH_3\underline{C}H_2CH_2CH_2$), 25.9 ($3xCH_3CH_2\underline{C}H_2CH_2$), 40.1 ($3xCH_3CH_2CH_2\underline{C}H_2$), 53.2 ($CNH_2$). MS(ES+) ($M+H^+$) $C_{13}H_{30}N^+$ 200.24 Found: 200.04. Anal. ($C_{17}H_{33}NO_4$) Calcd. C, 64.73; H, 10.54; N, 4.44. Found C, 64.54; H, 10.42; N, 4.63.

2-Methyl-4-propyl-heptan-4-amine (i-$BuPr_2CNH_2$) 4d. 2-methyl-4-propyl-heptan-4-ol **4b** was obtained after adding to i-butyllithium (14 mL, 21.9 mmol) reagent (1.6 M in hexanes) a solution of 4-heptanone **2a** (1g, 8.77 mmol) in dry ether (30% solution w/v) at 0 °C under argon atmosphere and stirring the mixture overnight, with lithium reagent being in a 2.5-molar excess. After treating the mixture with saturated ammonium chloride following usual workup the corresponding tertiary alcohol **4b** was obtained. Yield 1.2 g, (80%); IR (Nujol) ν(OH) 3422 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.86-0.89 (m, 6H, $2x(CH_2)_2C\underline{H}_3$) 0.92 (d, J=7.1 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.23-1.25 (m, 4H, $2xCH_2C\underline{H}_2CH_3$), 1.31 (d, J=6.9 Hz, 2H, $C\underline{H}_2CH(CH_3)_2$), 1.37-1.41 (m, 4H, $2xC\underline{H}_2CH_2CH_3$), 1.73 (sep, J=6.9 Hz, 1H, $CH_2C\underline{H}(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.78 ($2xCH_2CH_2\underline{C}H_3$), 17.01 ($2xCH_2\underline{C}H_2CH_3$), 23.8 ($CH_2\underline{C}H(CH_3)_2$), 24.9 ($CH_2CH(\underline{C}H_3)_2$), 42.23 ($2x\underline{C}H_2CH_2CH_3$), 48.13 ($\underline{C}H_2CH(CH_3)_2$), 75.22 (COH).

The 4-azido-2-methyl-4-propylheptane **4c** was prepared by treatment of the tertiary alcohol **4b** (500 mg, 2.90 mmol) with CH_2Cl_2 (25 mL)/NaN_3 (570 mg, 8.72 mmol) TFA (2.3 mL, 29 mmol) according to the same procedure followed for 4-azido-4-ethyloctane **1c**. Yield 490 mg, (86%); IR (Nujol) $\nu(N_3)$ 2101 cm^{-1}; ^{13}C NMR

($CDCl_3$, 50 MHz) δ (ppm) 14.6 ($2xCH_2CH_2\underline{C}H_3$), 17.1 ($2xCH_2\underline{C}H_2CH_3$), 23.9 ($CH_2\underline{C}H(CH_3)_2$), 24.4 ($CH_2CH(\underline{C}H_3)_2$), 39.1($2x\underline{C}H_2CH_2CH_3$), 45.1 ($\underline{C}H_2CH(CH_3)_2$), 67.0 ($CN_3$).

The oily amine **4d** was prepared through $LiAlH_4$ (309 mg, 8.12 mmol) reduction of azide **4c** (400 mg, 2.03 mmol) in refluxing ether (20 mL) for 5h according to the same procedure followed for 4-ethyloctan-4-amine **1d.** Yield 49 mg, (14%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.84-0.88 (m, 6H, $2x(CH_2)_2C\underline{H}_3$) 0.89 (d, J=7.1 Hz, 6H, $CH_2CH(C\underline{H}_3)_2$), 1.20-1.25 (m, 10H, $2xC\underline{H}_2C\underline{H}_2CH_3$, $C\underline{H}_2CH(CH_3)_2$); 1.62-1.71 (m, 1H, $CH_2C\underline{H}(CH_3)_2$) ; ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.86 ($2xCH_2CH_2\underline{C}H_3$), 16.93 ($2xCH_2\underline{C}H_2CH_3$), 23.8 ($CH_2\underline{C}H(CH_3)_2$), 25.4 ($CH_2CH(\underline{C}H_3)_2$), 43.36 ($2x\underline{C}H_2CH_2CH_3$), 49.15 ($\underline{C}H_2CH(CH_3)_2$), 54.17 ($CNH_2$). MS (ES+) $C_{11}H_{26}N^+$ ($M+H^+$) 172.2 Found 172.1. Anal. ($C_{15}H_{29}NO_4$) Calcd. C, 62.69; H, 10.17; N, 4.87. Found C, 62.34; H, 10.16; N, 4.61.

4-Propyl-octan-4-amine ($BuPr_2C$-NH_2) 5d. 4-Propyl-octan-4-ol **5b** was obtained after treating a solution of 4-heptanone **2a** (1g, 8.77 mmol) in dry diethyl ether (30% solution w/v) with 1.2-molar excess $CH_3CH_2CH_2CH_2MgBr$ (obtained from an 20% solution w/v solution of 1-bromobutane (2,4 g, 17.54 mmol) in dry ether and 1.3 equivalents of Mg (548 mg, 22.8 mmol)) under argon atmosphere and stirring the mixture overnight. After treating the mixture with saturated ammonium chloride following usual workup the corresponding tertiary alcohol **5b** was obtained. Yield 990 mg, (71 %); IR (Nujol) ν(N_3) 3392 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 0.85-0.91 (m, 9H, $C\underline{H}_3$), 1.21-1.31 (m, 9H, $2xCH_3CH_2C\underline{H}_2$, $CH_3CH_2C\underline{H}_2C\underline{H}_2$, OH), 1.34-1.42 (m, 6H, 2x $CH_3C\underline{H}_2CH_2$, $CH_3C\underline{H}_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.2 ($(CH_2)_3\underline{C}H_3$), 14.8 ($2x(CH_2)_2\underline{C}H_3$), 16.8 ($(CH_2)_2\underline{C}H_2CH_3$), 23.5 ($2xCH_2\underline{C}H_2CH_3$), 25.8 ($CH_2\underline{C}H_2CH_2CH_3$), 39.1 ($2x\underline{C}H_2CH_2CH_3$), 41.8 ($CH_3CH_2\underline{C}H_2COH$), 74.5 ($\underline{C}OH$).

The 4-azido-4-propyloctane **5c** was prepared was prepared by treatment of the tertiary alcohol **5b** (900 mg, 5.23 mmol) with CH_2Cl_2 (20 mL)/NaN_3 (1 g, 15.7 mmol)/TFA (4.1 mL, 52 mmol) according to the same procedure followed for 4-azido-4-ethyloctane **1c**. Yield 730 mg, (71%); IR (Nujol) ν(N_3) 2095 cm^{-1}; ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.2 ($(CH_2)_3\underline{C}H_3$), 14.6 ($2x(CH_2)_2\underline{C}H_3$), 17.0 ($(CH_2)_2\underline{C}H_2CH_3$), 23.2 ($2xCH_2\underline{C}H_2CH_3$), 25.9 ($CH_2\underline{C}H_2CH_2CH_3$), 36.4 ($2x\underline{C}H_2CH_2CH_3$), 39.0 ($CH_3CH_2\underline{C}H_2CN_3$), 66.9 ($\underline{C}N_3$).

The oily amine **5d** was prepared through $LiAlH_4$ (540 mg,14.2 mmol) reduction of azide **5c** (700 mg, 3.55 mmol) in refluxing ether (25 mL) for 5h according to the same procedure followed for 4-ethyloctan-4-amine **1d.** Yield 365 mg, (60%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.85-0.89 (m, 9H, $C\underline{H}_3$), 1.16-1.27 (m, 14H, $2xCH_3C\underline{H}_2C\underline{H}_2$, $CH_3C\underline{H}_2C\underline{H}_2C\underline{H}_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.0 ($(CH_2)_3\underline{C}H_3$), 14.8 ($2x(CH_2)_2\underline{C}H_3$), 16.7 ($(CH_2)_2\underline{C}H_2CH_3$), 23.4 ($2xCH_2\underline{C}H_2CH_3$), 25.7 ($CH_2\underline{C}H_2CH_2CH_3$), 39.9 ($2x\underline{C}H_2CH_2CH_3$), 42.8 ($CH_3CH_2\underline{C}H_2CNH_2$), 53.2 ($\underline{C}NH_2$). Anal. ($C_{15}H_{29}NO_4$) Calcd. C, 62.69; H, 10.17; N, 4.87. Found C, 62.66; H, 10.53; N, 4.89.

5-Propyl-nonan-5-amine (Bu_2PrCNH_2) 6d. 5-Propyl-nonan-5-ol **6b** was obtained after treating a solution of 5-nonanone **3a** (1 g, 7.04 mmol) in dry diethyl ether (30% solution w/v) with 1.2-molar excess $CH_3CH_2CH_2MgBr$ (obtained from 20% solution w/v solution of 1-bromopropane (1.9 g, 14.08 mmol) in dry ether and 1.3 equivalents of Mg (440 mg, 18.3 mmol) under argon atmosphere and stirring the mixture overnight. After treating the mixture with saturated ammonium chloride following usual workup the corresponding tertiary alcohol **6b** was obtained. Yield 915 mg, (70%); IR (Nujol) ν(OH) 3392 cm^{-1}; ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.2 ($2x\ \underline{C}H_3(CH_2)_3$), 14.8 ($\underline{C}H_3(CH_2)_2$), 16.8 ($2xCH_3\underline{C}H_2(CH_2)_2$), 23.5 ($2xCH_3CH_2\underline{C}H_2CH_2$), 25.8 ($CH_2\underline{C}H_2CH_3$), 39.2 ($2xCH_3(CH_2)_2\underline{C}H_2$), 41.8 ($\underline{C}H_2CH_2CH_3$), 74.5 ($\underline{C}OH$).

The 5-azido-5-propylnonane **6c** was prepared by treatment of the tertiary alcohol **6b** (500 mg, 2.69 mmol) with CH_2Cl_2 (20 mL)/NaN_3 (524 mg, 8.06 mmol)/TFA (2.2 mL, 27 mmol) according to the same procedure followed for 4-azido-4-ethyloctane **1c**. Yield 425 mg, (75%); IR (Nujol) ν(N_3) 2094 cm^{-1}; ^{13}C NMR ($CDCl_3$, 50

MHz) δ (ppm) 14.1 (2x $\underline{C}H_3(CH_2)_3$), 14.6 ($\underline{C}H_3(CH_2)_2$), 17.0 (2x$CH_3\underline{C}H_2(CH_2)_2$), 23.2 (2x$CH_3CH_2\underline{C}H_2CH_2$), 25.8 ($CH_2\underline{C}H_2CH_3$), 36.4 (2x$CH_3(CH_2)_2\underline{C}H_2$), 39.1 ($\underline{C}H_2CH_2CH_3$), 66.9 ($\underline{C}N_3$).

The oily amine **6d** was prepared through $LiAlH_4$ (289 mg, 7.60 mmol) reduction of azide **6c** (400 mg, 1.90 mmol) in refluxing ether (20 mL) for 5h according to the same procedure followed for 4-ethyloctan-4-amine **1c.** Yield 35%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, J=7.0 Hz, 9H, CH_3), 1.24-1.31 (m, 9H, CH_2), 1.34-1.40 (m, 6H, CH_2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.4 2x $\underline{C}H_3(CH_2)_3$), 15.1 ($\underline{C}H_3(CH_2)_2$), 16.9 (2x$CH_3\underline{C}H_2(CH_2)_2$), 23.7 (2x$CH_3CH_2\underline{C}H_2CH_2$), 25.9 ($CH_2\underline{C}H_2CH_3$), 40.4 (2x$CH_3(CH_2)_2\underline{C}H_2$), 42.9 ($\underline{C}H_2CH_2CH_3$), 53.4 ($CNH_2$). Anal. ($C_{16}H_{31}NO_4$) Calcd. C, 63.75; H, 10.37; N, 4.65. Found C, 63.84; H, 10.16; N, 5.01.

2-Methyl-4-isobutyl-octan-4-amine (i-Bu_2BuCNH_2) 7d. 2-Methyl-4-isobutyl-octan-4-ol **7b** was obtained after adding a solution of 2,6-dimethyl-heptan-4-one **4a** (1 g, 7.04 mmol) in dry diethyl ether (30% solution w/v) to n-butyllithium (1.6 M in hexanes), (13.5 mL, 21.1 mmol) at 0 °C under argon atmosphere and stirring the mixture overnight, with lithium reagent being in a 3.0 molar excess; After treating the mixture with saturated ammonium chloride following usual workup the corresponding tertiary alcohol **7b** was obtained. Yield 1.1 g, (80%); IR (Nujol) ν(OH) 3460 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.88 (t, J=7.0 Hz, 3H, $(CH_2)_2C\underline{H}_3$) 0.92-0.95 (m, 12H, 2x$CH_2CH(C\underline{H}_3)_2$), 1.19-1.35 (m, 10H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$, 2x$C\underline{H}_2CH(CH_3)_2$), 1.74 (sep, 2H, J=6.9 Hz, 2x$CH_2C\underline{H}(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.2 ($\underline{C}H_3(CH_2)_3$), 23.5 ($CH_3\underline{C}H_2(CH_2)_2$), 23.9 (2x$CH_2\underline{C}H(CH_3)_2$), 25.0 (2x$CH_2CH(\underline{C}H_3)_2$), 26.4 ($CH_2\underline{C}H_2CH_2CH_3$), 39.9 ($\underline{C}H_2(CH_2)_2CH_3$), 48.7 (2x$\underline{C}H_2CH(CH_3)_2$), 75.9 (COH).

The 4-azido-2-methyl-4-isobutyloctane **7c** was prepared by treatment of the tertiary alcohol **7b** (500 mg, 2.69 mmol) with CH_2Cl_2 (25 mL)/NaN_3 (525 mg, 8.07mmol)/TFA (2.2 mL, 26.9 mmol) according to the same procedure followed for 4-azido-4-ethyloctane **1c**. Yield 430 mg, (76%); IR (Nujol) ν(N_3) 2099 cm^{-1}; ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.2 ($\underline{C}H_3(CH_2)_3$), 24.0 ($CH_3\underline{C}H_2(CH_2)_{23}$), 24.2 (2x$CH_2\underline{C}H(CH_3)_2$), 24.6 (2x$CH_2CH(\underline{C}H_3)_2$), 26.3 ($CH_2\underline{C}H_2CH_2CH_3$), 36.4 ($\underline{C}H_2(CH_2)_2CH_3$), 45.5 (2x$\underline{C}H_2CH(CH_3)_2$), 67.1 ($CN_3$).

The oily amine **7d** was prepared through $LiAlH_4$ (288 mg, 7.58 mmol) reduction of azide **7c** (400 mg, 1.90 mmol) in refluxing ether (20 mL) for 5h according to the same procedure followed for 4-ethyloctan-4-amine **1d.** Yield 70 mg, (20%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.89 (t, J=7.0 Hz, 3H, $C\underline{H}_3(CH_2)_3$) 0.89-0.94 (m, 12H, 2x $CH_2CH(C\underline{H}_3)_2$), 1.25-1.32 (m, 10H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$, 2x$C\underline{H}_2CH(CH_3)_2$), 1.66-1.74 (m, 2H, 2x$CH_2C\underline{H}(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.3 ($\underline{C}H_3(CH_2)_3$), 23.5 ($CH_3\underline{C}H_2(CH_2)_2$), 23.8 (2x$CH_2\underline{C}H(CH_3)_2$), 25.5 (2x$CH_2CH(\underline{C}H_3)_2$), 26.3 ($CH_2\underline{C}H_2CH_2CH_3$), 40.9 ($\underline{C}H_2(CH_2)_2CH_3$), 49.7 (2x$\underline{C}H_2CH(CH_3)_2$), 55.1 ($CNH_2$). Anal. ($C_{17}H_{33}NO_4$). Calcd. C, 64.73; H, 10.54; N, 4.44. Found C, 64.34; H, 10.08; N, 4.81.

2-Methyl-tricyclo[3.3.1.1^{3,7}]decan-2-amine 8d. Tertiary alcohol **8b** was obtained after treating a solution of adamantanone (**5a**) **(**500 mg, 3.33 mmol) in dry THF (30% solution w/v) with 2-molar excess CH_3MgI (obtained from 20% solution w/v solution of CH_3I (940 mg, 6.67 mmol) in dry ether and 1.3 equivalents of Mg (210 mg, 8.67 mmol)) under argon atmosphere and stirring the mixture overnight. After treating the mixture with saturated ammonium chloride the organic phase was separated and the aqueous phase was extracted twice with an equal volume of diethyl ether. The combined organic phase was washed with water and brine, dried (Na2SO4) and evaporated to afford the corresponding tertiary alcohol **8b**; yield 525 mg (95 %); IR (Nujol) ν(OH) 3423 cm^{-1}; ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 27.2,27.5 (5,7 adamantane-C), 27.4 (CH_3), 33.1 (8,10 adamantane-C), 35.2 (4,9 adamantane-C), 38.4 (1,3 adamantane -C), 39.3 (6 adamantane-C), 74.0 (2 adamantane-C).

To a stirred mixture of sodium azide (187 mg, 2.88 mmol) and dry dichloromethane (5 mL), trifluoroacetic acid (0.8 mL, 9.6 mmol) was added at 0 °C. The resulting mixture was stirred for 10 min at 0 °C and a solution

of the tertiary alcohol **8b** (160 mg, 0.96 mmol) in 5 mL of dichloromethane was added dropwise. The mixture was stirred at 0-5 °C for 4 h and 24 h at ambient temperature. The mixture was made alkaline by adding NH_3 12 % (30 mL) and the organic phase was separated. The aqueous phase was extracted with dichloromethane and the combined organic phases were washed with water, brine and dried (Na_2SO_4). Solvent was evaporated in vacuo to afford azide **8c** yield 0.161g (88 %); IR (Nujol) $\nu(N_3)$ 2213cm^{-1}.

To a stirred suspension of $LiAlH_4$ (127 mg, 3.35 mmol) in dry ether (10 mL) was added dropwise at 0 °C a solution of the azide **8c** (160 mg, 0.84 mmol) in dry ether (5 mL). The mixture was refluxed for 5 h and then was treated with water, NaOH 10 % and water. The insoluble inorganic material was filtered-off, washed with ether and the filtrate was extracted with HCl 6%. The aqueous phase was made alkaline with solid sodium carbonate and was extracted with diclhoromethane or ether. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated in vacuo to afford the amine **8d**; yield 117 mg, (83 %); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.17 (br s, 3H, CH_3), 1.46-1.48 (d, J=12.1 Hz, 2H, 4eq,9eq adamantane-H), 1.54 (d, J=12.1 Hz, 2H, 8eq,10eq adamantane-H), 1.56-1.63 (br m, 4H, 1,3,6 adamantane-H), 1.76 (br s, 2H, 5,7 adamantane-H), 1.93 (d, J=12.1 Hz, 2H, 8ax,10ax adamantane-H), 2.01 (d, J=12.1 Hz, 2H, 4ax,9ax adamantane-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 27.3 (7 adamantane-C), 27.7 (5 adamantane-C), 27.9 (CH_3), 33.2 (4,9 adamantane-C), 34.7 (8,10 adamantane-C), 38.9 (6 adamantane-C), 39.6 (1,3 adamantane-C), 52.9 (2 adamantane-C). Hydrochloride: mp > 250 ºC (EtOH-Et_2O); Anal. ($C_{11}H_{20}ClN$) C, H, N. Calcd. C, 65.49; H, 9.99; N, 6.94. Found C, 65.34; H, 10.08; N, 6.64.

2-Ethyl-tricyclo[3.3.1.1^{3,7}]decan-2-amine 9d. Tertiary alcohol **9b** was obtained after treating a solution of adamantanone (**5a**) **(**500 mg, 3.33 mmol) in dry THF (30% solution w/v) with n-ethyllithium (0.5 M in benzene), (20 mL, 10,0 mmol) at 0 °C and stirring the mixture overnight; yield 560 mg (94%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.86 (t, J=7.0 Hz, $CH_2C\underline{H}_3$), 1.40-1.70 (m, 10 H, 1,3, 4eq,9eq,6,8eq,10eq adamantane-H, $C\underline{H}_2CH_3$), 1.75-1.83 (m, 2H, 5,7 adamantane-H),1.94 (d, J=12.1 Hz, 2H, 8ax,10ax adamantane-H), 2.07 (d, J=12.1 Hz, 2H, 4ax,9ax adamantane-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 6.4 ($CH_2\underline{C}H_3$), 27.4, 27.5 (5,7 adamantane-C), 30.6 ($\underline{C}H_2CH_3$), 33.0 (8,10 adamantane -C), 34.6 (4,9 adamantane-C), 36.6 (1,3 adamantane-C), 38.5 (6 adamantane-C), 74.9 (2 adamantane-C).

The tertiary azide **9c** was prepared by treatment of the tertiary alcohol **9b** (0.180g, 1.0mmol with CH_2Cl_2 (5 mL) / NaN_3 (195 mg, 3.00 mmol) / TFA (0.8 mL, 10.0 mmol) according to the same procedure followed for the azide **8c**.; yield 0.160 g (80%); IR (Nujol) $\nu(N_3)$ 2100 cm^{-1}.

The oily amine **9d** was prepared through $LiAlH_4$ (0.120 g, 0.78 mmol) reduction of azide **9c** (160 mg, 3.12 mmol) in refluxing ether (10 mL) for 5h according to the same procedure followed for amine **8d**; yield 100 mg (71%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.85 (t, J=7.1 Hz, 3H, $CH_2C\underline{H}_3$), 1.55 (br s, 2H, 1,3 adamantane-H), 1.58-1.68 (m, 7H, 4eq,9eq-H, 8eq, 6 adamantane-H, $C\underline{H}_2CH_3$), 1.78 (br s, 1H, 5 adamantane-H), 1.81 (br s, 1H, 7 adamantane-H), 1.93 (d, J=12.1Hz, 2H, 8ax,10ax adamantane-H), 2.06 (d, J=12.1 Hz, 2H, 4ax,9ax adamantane-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 6.5 ($CH_2\underline{C}H_3$), 27.2, 27.6 (5,7 adamantane-C), 30.7 ($\underline{C}H_2CH_3$), 33.0 (4,9 adamantane-C), 33.8 (8,10 adamantane-C), 36.6 (1,3 adamantane-C), 38.5 (6 adamantane-C), 74.9 (2 adamantane-C). Hydrochloride: mp > 250 ºC (EtOH-Et_2O); Anal. ($C_{12}H_{22}ClN$). Calcd. C, 66.80; H, 10.28. Found C, 67.01; H, 10.08.

2-*n*-Propyl-tricyclo[3.3.1.1^{3,7}]decan-2-amine 10d. The $CH_2CH{=}CH_2MgBr$ reagent was obtained by adding a 20% solution w/v solution of $CH_2CH{=}CH_2Br$ (1.6 g, 13.34 mmol) in dry ether to 1.05 equivalents of Mg (340 mg, 14.01 mmol) under argon atmosphere. Tertiary alcohol was obtained after adding a solution of adamantanone **11** (1000 mg, 6.67 mmol) in dry diethyl ether (30% solution w/v) to the above prepared $CH_2CH{=}CH_2MgBr$ under argon atmosphere and stirring the mixture overnight. After treating the mixture with saturated ammonium chloride following usual workup the corresponding tertiary unsaturated alcohol; yield 1.1

g, (89%); δ (ppm) 1.52 (d, J=12.1 Hz, 2H, 4eq,9eq adamantane-H), 1.53-1.90 (m, 10H, 1,3,5,6,7,8eq,10eq,8ax,10ax adamantane-H), 2.15 (d, J=12.1 Hz, 1H, 4ax,9ax-H), 2.40 (d, J=5.8 Hz, 2H, $C\underline{H}_2CH=CH_2$), 5.05-5.15 (m, 2H, $CH_2CH=C\underline{H}_2$), 5.75-6.0 (m, 1H, $CH_2C\underline{H}=CH_2$).

The unsaturated alcohol was hydrogenated under PtO_2 (catalyst was used in 1/20 percentage to the weight of the unsaturated compound) to afford the n-propyl alcohol **10b**; yield quant.: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.92 (t, J=7.0 Hz, 3H, $CH_2CH_2C\underline{H}_3$), 1.30-1.40 (m, 2H, $CH_2C\underline{H}_2CH_3$), 1.52 (d, J=12.1 Hz, 2H, 4eq,9eq adamantane-H), 1.58-1.61 (m, 2H, $C\underline{H}_2CH_2CH_3$), 1.68 (d, J=12.1 Hz, 2H, 8eq,10eq adamantane-H), 1.67 (br s, 2H, 6 adamantane-H), 1.68 (br s, 2H, 1,3 adamantane -H), 1.79 (m, 2H, 5,7 adamantane-H), 1.83 (d, J=12.1 Hz, 2H, 8ax,10ax adamantane-H), 2.16 (d, J=12.1 Hz, 2H, 4ax,9ax adamantane-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.9 ($CH_2CH_2\underline{C}H_3$), 15.4 ($CH_2\underline{C}H_2CH_3$), 27.4, 27.6 (5, 7 adamantane-C), 33.1 ($\underline{C}H_2CH_2CH_3$), 34.7 (4, 9 adamantane-C), 37.1 (8, 10 adamantane-C), 38.5 (1, 3 adamantane-C), 40.9 (6 adamantane-C), 75.2 (2 adamantane-C).

The tertiary azide **10c** was prepared by treatment of the tertiary alcohol **10b** (640 mg, 3.27 mmol with CH_2Cl_2 (20 mL)/NaN_3 (640 mg, 9.83 mmol)/TFA (2.6 mL, 32.7 mmol) according to the same procedure followed for the azide **8c**; yield 470 mg (66%); IR (Nujol) ν(N_3) 2100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.96 (t, J=7.1 Hz, 3H, $CH_2CH_2C\underline{H}_3$), 1.42 (m, 2H, $CH_2C\underline{H}_2CH_3$), 1.59 (d, J=12.1 Hz, 2H, 8eq,10eq adamantane-H), 1.68 - 2.03 (m, 12H, $C\underline{H}_2CH_2CH_3$, 1,3,4eq,5,7,8ax,9eq,10ax adamantane-H), 2.10 (d, J=12.1 Hz, 2H, 4ax,9ax adamantane-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.7 ($CH_2CH_2\underline{C}H_3$), 16.4 ($CH_2\underline{C}H_2CH_3$), 27.2, 27.4 (5, 7 adamantane-C), 33.8 ($\underline{C}H_2CH_2CH_3$) 34.4 (4, 9 adamantane-C), 37.9 (8, 10 adamantane-C), 38.5 (1, 3 adamantane-C), 40.0 (6 adamantane -C), 69.7 (2 adamantane -C).

The oily amine **10d** was prepared through $LiAlH_4$ (390 mg, 10.3 mmol) reduction of azide **10c** (490 mg, 2.57 mmol) in refluxing ether (10 mL) for 5h according to the same procedure followed for amine **10d**; yield 350 mg (74%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.92 (t, J=7 Hz, 3H, $CH_2CH_2C\underline{H}_3$), 1.29-1.40 (m, 2H, $CH_2C\underline{H}_2CH_3$), 1.52 (d, J=12.1 Hz, 2H, 4eq,9eq adamantane-H), 1.58-1.61 (m, 2H, $C\underline{H}_2CH_2CH_3$), 1.67 (d, J=12.1 Hz, 2H, 8eq,10eq adamantane-H), 1.66 (br s, 2H, 6 adamantane-H), 1.68 (br s, 2H, 1,3 adamantane-H), 1.78 (br s, 2H, 5,7 adamantane-H), 1.83 (d, J=12.1 Hz, 2H, 8ax,10ax adamantane-H), 2.16 (d, J=12.1 Hz, 1H, 4ax,9ax adamantane-H); Hydrochloride: mp> 250 ºC (EtOH-Et_2O); Anal. ($C_{13}H_{24}ClN$). Calcd. C, 67.95; H, 10.53; N, 6.10. Found C, 68.15; H, 10.28; N, 6.50.

2-*n*-Butyl-(tricyclo[3.3.1.1^{3,7}]decan)-2-amine 11d. The 2-*n*-Butyl-tricyclo[3.3.1.1^{3,7}]decan-2-azide **11c** was prepared by treatment of the tertiary alcohol **11b** (300 mg, 1.44 mmol) with CH_2Cl_2 (20 mL) / NaN_3 (281 mg, 4.32 mmol)/TFA (1.2 mL, 14.4 mmol) according to the same procedure followed for azide **8c**. Yield 255 mg, (76%); IR (Nujol) ν(N_3) 2088 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.96 (t, J = 7 Hz, 3H, $C\underline{H}_3CH_2CH_2CH$), 1.32-1.42 (m, 4H, $CH_3C\underline{H}_2C\underline{H}_2CH_2$), 1.62 (d, J=12.1 Hz, 2H, 4eq,9eq adamantane-H), 1.70-1.93 (m, 12H, adamantane-H, $CH_3CH_2CH_2C\underline{H}_2$), 2.14 (d, J=12.1 Hz, 2H, 4ax,9ax adamantane-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.2 ($\underline{C}H_3CH_2CH_2CH_2$), 23.3 ($CH_2\underline{C}H_2CH_2CH_3$), 24.9 ($CH_3CH_2\underline{C}H_2CH_3$), 27.2, 27.4 (5,7-adamantane C), 33.8 (4,9-adamantane C), 33.7 (8,10-adamantane C), 34.4 (1,3-adamantane C), 35.2 ($CH_3CH_2CH_2\underline{C}H_2$), 38.5 (6-adamantane C), 69.7 (2-adamantane C). The oily amine **11d** was prepared through $LiAlH_4$ (130 mg, 3.43 mmol) reduction of azide **11c** (200 mg, 0.860 mmol) in refluxing ether (15 mL) for 5h according to the same procedure followed for amine **8d**. Yield 41 mg, (23%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.88 (t, J=7.1 Hz, 3H, $C\underline{H}_3CH_2CH_2CH$), 1.18-1.32 (m, 4H, $CH_3C\underline{H}_2C\underline{H}_2CH_2$), 1.45-165 (m, 10H, adamantane-H, $CH_3CH_2CH_2CH_2$), 1.77 (br s, 2H, 5,7 adamantane-H), 1.93 (d, J=12.1 Hz, 2H, 8ax,10ax adamantane-H), 2.03 (d, J=12.1 Hz, 2H, 4ax,9ax adamantane-H), 2,13 (br s, 2H, NH_2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 14.3 ($\underline{C}H_3CH_2CH_2CH_2$), 23.7 ($CH_2\underline{C}H_2CH_2CH_3$), 24.6 ($CH_3CH_2\underline{C}H_2CH_3$), 27.5, 27.8 (5,7 adamantane-C), 34.1 (4,9 adamantane-C), 33.2 (8,10 adamantane-C), 37.5 (1,3 adamantane-C), 38.6 (6

adamantane-C), 39.1 ($CH_3CH_2CH_2\underline{C}H_2$), 54.5 (2 adamantane-C). Fumarate: mp 220 ^oC (EtOH-Et_2O); Anal. ($C_{18}H_{29}NO_4$). Calcd. C, 66.84; H, 9.04; N, 4.33; Found C, 66.34; H, 9.22; N, 4.84.

2-Phenyl-(tricyclo[3.3.1.1^{3,7}]decan)-2-amine 12d. The 2-Phenyl-tricyclo[3.3.1.1^{3,7}]decan-2-azide **12c** was prepared by treatment of the tertiary alcohol **12b** (300 mg, 1.32 mmol) with CH_2Cl_2 (20 mL) / NaN_3 (265 mg, 3.95 mmol)/TFA (1.1 mL, 13.2 mmol) according to the same procedure followed for azide **8c**. Yield 290 mg, (95%); IR (Nujol) $\nu(N_3)$ 2098 cm^{-1}; ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 26.8, 27.4 (5,7-adamantane-C), 33.1 (4,9-adamantane-C), 33.4 (8,10-adamantane-C), 34.1 (1,3-adamantane-C), 37.7 (6-adamantane-C), 70.3 (2-adamantane-C), 125.6, 127.3, 127.8, 128.9, 140.3 (phenyl).

The oily amine **12d** was prepared through $LiAlH_4$ (897 mg, 3.95 mmol) reduction of azide **12c** in refluxing ether (15 mL) for 5h according to the same procedure followed for amine **8d.** Yield 123 mg, (55%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.53 (br s, 2H, 6 adamantane-H), 1.61-1.80 (m, 6H, adamantane-H), 1.90 (br s, 2H, 5,7 adamantane-H), 2.33 (d, J=12.1 Hz, 1H, 4ax,9ax adamantane-H), 2.45 (br s, 2H, 1,3 adamantane-H), 7.18-7.25 (m, 5H, phenyl-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 27.2, 27.6 (5,7 adamantane-C), 32.9 (4,9 adamantane-C), 34.6 (8,10 adamantane-C), 35.8 (1,3 adamantane-C), 38.2 (6 adamantane-C), 57.8 (2 adamantane-C), 125.2, 126.2, 128.8, 148.7 (Ph). Hydrochloride: mp> 265 ^oC (EtOH-Et_2O); Anal. ($C_{16}H_{22}ClN$) Calcd. C, 72.84; H, 8.41; N, 5.31. Found C, 72.12; H, 8.32; N, 5.02.

2-Benzyl-(tricyclo[3.3.1.1^{3,7}]decan)-2-amine 13d. The 2-Benzyl-tricyclo[3.3.1.1^{3,7}]decan-2-azide **13c** was prepared by treatment of the tertiary alcohol **13b** (500 mg, 2.07 mmol) with CH_2Cl_2 (25 mL)/NaN_3 (540 mg, 8.28 mmol)/TFA (1.7 mL, 20.7 mmol) according to the same procedure followed for azide **8c**. Yield 280 mg, (50%); IR (Nujol) $\nu(N_3)$ 2096 cm^{-1}; ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 27.1, 27.4 (5,7-adamantane C), 33.7 (4,9-adamantane C), 33.8 (8,10-adamantane C), 34.1 (1,3-adamantane C), 38.4 (6-adamantane C), 41.4 (CH_2Ph), 69.8 (2-adamantane C), 126.7, 128.2, 130.3, 136.6 (Ph).

The oily amine **13d** was prepared through $LiAlH_4$ reduction of azide **13c** in refluxing ether for 5h according to the same procedure followed for amine **8d**. Yield 45%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.61 (d, J=12.1 Hz, 2H, 4eq, 9eq adamantane-H), 1.61 (br s, 1H, 6 adamantane-H), 1.73 (br s, 1H, 5,7 adamantane-H), 1.78 (d, J=12.1 Hz, 2H, 8eq,10eq adamantane-H), 1.87 (br s, 1H, 3 adamantane-H), 1.97 (br s, 1H, 1 adamantane-H), 2.09 (d, J=12.1 Hz, 1H, 8ax,10ax adamantane-H), 2.29 (d, J=12.1 Hz, 1H, 4ax,9ax adamantane-H), 2.97 (s, 2H, CH_2Ph), 7.10-7.32 (m, 5H, phenyl-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 27.6, 27.8 (5,7-adamantane C), 33.2 (4,9- adamantane C), 34.3 (8,10-adamantane C), 37.3 (1,3-adamantane C), 39.2 (6-adamantane C), 44.2 (CH_2Ph), 55.1 (2-adamantane C), 126.3, 128.1, 130.7, 138.4 (Ph). Fumarate: mp 205 ^oC (EtOH-Et_2O); Anal. ($C_{21}H_{27}NO_4$). Calcd. C, 70.56; H, 8.41; N, 5.31. Found C, 70.99; H, 8.53; N, 5.02.

2-(p-Methoxy)benzyl-(tricyclo[3.3.1.1^{3,7}]decan)-2-amine 14d. 2-(p-Methoxy)benzyl-2-adamantanol **14b** was obtained after adding dropwise a solution of 2-adamantanone (500 mg, 3.33 mmol) in dry THF (6 mL) to a solution of pMeOBnMgCl (0.25 M in THF, 27 mL, 6.66 mmol) at room temperature and under argon atmosphere. The resulting mixture was stirred overnight and then heated at 45 ^oC for 2 hours. After treating the mixture with saturated ammonium chloride following usual workup the corresponding tertiary alcohol **14b** was obtained. Yield 725 mg, (80%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.48 (d, J=12.1 Hz, 2H, 4eq,9eq adamantane-H), 1.53 (br s, 1H, OH), 1.66 (br s, 1H, 6 adamantane-H), 1.71 (br s, 1H, 5,7 adamantane-H), 1.77 (br s, 1H, 3 adamantane-H), 1.80 (d, J=12.1 Hz, 2H, 8eq,10eq adamantane-H), 1.91 (br s, 1H, 1 adamantane-H), 2.08 (d, J=12.1 Hz, 1H, 8ax,10ax adamantane-H), 2.22 (d, J=12.1 Hz, 1H, 4ax,9ax adamantane-H), 2.93 (s, 2H, CH_2Ar), 3.79 (s, 3H, OCH_3), 6.85 (d, J = 6 Hz, 2H, phenyl-H), 7.15 (d, J = 6 Hz, 2H, phenyl-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 27.4, 27.5 (5,7 adamantane-C), 33.1 (4,9 adamantane-C), 34.7 (8,10 adamantane-C), 36.9 (1,3 adamantane-C), 38.5 (6 adamantane-C), 43.9 (CH_2Ar), 74.7 (2 adamantane-C), 126.5, 128.3, 130.7, 137.4 (Ar).

The corresponding azide **14c** was prepared from alcohol **14b** (720 mg, 2.64 mmol) according to the same procedure followed for azide **8c** using CH_2Cl_2 (30 mL)/NaN_3 (515.5 mg, 7.93 mmol)/TFA (3.01 mg, 26.4 mmol). Yield 730mg, (93 %).

The oily amine **14d** was prepared through $LiAlH_4$ (358 mg, 9.43 mmol) reduction of azide **14c** (700 mg, 2.36mmol) in refluxing THF (20 mL) for 5h. Yield 307 mg, (48%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.62 (d, *J*=12 Hz, 2H, 4eq,9eq adamantane-H), 1.73 (d, *J*=12.1 Hz, 2H, 8eq,10eq adamantane-H), 1.77 (br s, 1H, 5,7 adamantane-H), 1.84 (br s, 1H, 6 adamantane-H), 1.93 (br s, 1H, 3 adamantane-H), 1.97 (br s, 1H, 1 adamantane-H), 2.09 (d, *J*=12.1 Hz, 1H, 8ax,10ax adamantane-H), 2.24 (d, *J*=12.1 Hz, 1H, 4ax,9ax adamantane-H), 2.93 (s, 2H, CH_2Ar), 3.80 (s, 3H, OCH_3), 6.84 (d, *J*=6.2 Hz, 2H, phenyl-H), 7.15 (d, *J*=6.2 Hz, 2H, phenyl-H). Fumarate: mp 205 °C (EtOH–Et_2O). Anal. ($C_{21}H_{36}NO_5$) Calcd. C, 65.94; H, 9.49; N, 3.66. Found C, 65.05; H, 9.58; N, 3.72.

1-Adamantyl-2-propanol (AdMe$_2$COH) 15b. Methylmagnesium iodide was prepared from magnesium turnings (1.99 g, 83.1mmol) and methyl iodide (10.7 g, 75.6mmol) in 40 mL of dry diethyl ether. A solution of 1-adamantanecarbonyl chloride (**6a**) (2.5 g, 12.6 mmol) in 60 mL of dry diethyl ether was added dropwise under Ar atmosphere and stirring. The reaction mixture was heated at gentle reflux for 4h under stirring and Ar atmosphere. The mixture was treated with an equal volume of saturated solution of ammonium chloride under ice-cooling. The organic layer was separated and the aqueous phase was extracted with diethyl ether 2 times. The combined organic phases were washed with water and brine, dried (Na_2SO_4) and evaporated under vacuum to yield a white solid residue of 2-(1-adamantyl)-propan-2-ol **15b**. Yield 2.09 g (85.5%); IR (Nujol) ν(OH) 3400 (br s, OH) cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$) δ (ppm) 1.12 (s, 6H, 2xCH_3), 1.62-1.69 (m, 12H, 2,4,6,8,9,10 adamantane-H), 1.99 (br s, 3H, 3,5,7 adamantane-H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 24.34 (CH_3), 28.74 (3,5,7-C, adamantane C), 36.35 (2,8,9-C, adamantane C), 37.22 (4,6,10-C, adamantane C), 38.84 (1-C, adamantane C), 74.88 (C-OH).

2-(1-adamantyl)-2-azidopropane (AdMe$_2$CN$_3$) 15c. The oily 2-(1-adamantyl)-2-azidopropane **3c** was prepared by treatment of the tertiary alcohol **15b** with CH_2Cl_2/NaN_3/TFA. To a stirring mixture of sodium azide (503 mg, 7.74 mmol) and dry dichloromethane (15 mL), trifluoroacetic acid (2.94 g, 25.8mmol) was added at 0 °C. The resulting mixture was stirred for 10 min at 0 °C and a solution of 2-(1-adamantyl)-propan-2-ol **15b** (500 mg, 2.58 mmol) in 15mL of dry dichloromethane was added dropwise under ice-cooling. The mixture was stirred vigorously at 0-5 °C for 4 h and additional 24 h at ambient temperature. The mixture was made alkaline by adding NH_3 12 % (40 mL) and the organic phase was separated and washed with 30 mL of water two times. The aqueous phase was extracted two times with dichloromethane (30 mL) and the combined organic phases were washed with water, brine and dried (Na_2SO_4). Solvent was evaporated in vacuo to afford 2-(1-adamantyl)-propan-2-azide **15c**. Yield: 80%; IR (Nujol) ν(N_3) 2098 cm^{-1} (s); ^{1}H-NMR (400MHz, $CDCl_3$) δ (ppm) 1.23 (s, 6H, 2xCH_3), 1.60-1.71 (m, 12H, 2,4,6,8,9,10 adamantane-H), 2.0 (br s, 3H, 3,5,7 adamantane-H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 20.79 (CH_3), 28.66 (3,5,7-C, adamantane C), 36.56 (2,8,9-C, adamantane C), 37.07 (4,6,10-C, adamantane C), 39.10 (1-C, adamantane C), 67.57 (C-N).

2-(1-adamantyl)-propan-2-amine (AdMe$_2$CNH$_2$) 15d. A solution of 2-azido-2-(1-adamantyl)propane **15c** (250 mg, 1.14 mmol) in 10 mL of dry diethyl ether was added dropwise to a solution of lithium aluminum hydride (173 mg, 4.56mmol) in 10 mL of dry diethyl ether under ice-cooling. The mixture was heated at reflux for 5 h under stirring. Then the mixture was hydrolyzed with a dropwise addition of 2 mL water, 2 mL of sodium hydroxide 10% w/v solution and 6 mL water under stirring and ice-cooling. The mixture was filtered under vacuum and the residue was washed 2 times with diethyl ether. Another 30 mL of diethyl ether was added to the ethereal filtrate and the solution was extracted with 60 mL (2×30 mL) of hydrochloric acid 6% w/v. The aqueous phase was separated and made alkaline through-addition of an excess solid sodium carbonate under ice-

cooling. The aqueous phase was extracted two times with 30 mL of dichloromethane. The combined organic extracts were dried (Na_2SO_4) and evaporated under vacuum, to yield a light yellow colored solid residue of 2-(1-adamantyl)-propan-2-amine **15d**. Yield: 73%; IR (Film) ν(NH_2) 3373 cm^{-1} (s); ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 0.99 (s, 6H, 2xCH_3), 1.60-1.68 (m, 12H, 2,4,6,8,9,10 adamantane-H), 1.99 (br s, 3H, 3,5,7 adamantane-H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 25.30 (CH_3), 28.87 (3,5,7-C, adamantane C), 36.23 (2,8,9-C, adamantane C), 37.26 (4,6,10-C, adamantane C), 38.12 (1-C, adamantane C), 53.68 (C-N). Hydrochloride (EtOH-Ether); Anal. ($C_{13}H_{24}ClN$). Calcd. C, 61.51; H, 9.96; N, 5.12. Found C, 61.66; H, 10.06; N, 5.13.

3-(1-adamantyl)-pentan-3-ol (AdEt$_2$COH) 16b. A solution of 1-adamantanecarbonyl chloride (**6a**) (700 mg, 3.53 mmol) in 25 mL of dry diethyl ether was added dropwise under Ar atmosphere and stirring, to a solution of 5 mL ethyl lithium (0.5 M in benzene/cyclohexane, 12.5 mmol). The mixture was stirred for 26 h under Ar atmosphere at room temperature. The reaction mixture was hydrolyzed with an equal volume of saturated ammonium chloride solution under ice-cooling. The organic layer was separated and the aqueous phase was extracted with diethyl ether two times. The combined organic phase was washed two times with a solution of sodium hydroxide 3% w/v, water and brine, and dried over anhydrous sodium sulfate. After evaporation of the solvent under vacuum, a light yellow coloured solid residue of the alcohol **16b** was obtained. Yield 357 mg (45.5%); IR (Nujol) *ν*(OH) 3502 cm^{-1} (br s); ^{1}H-NMR (400MHz, $CDCl_3$) *δ* (ppm) 0.93 (t, *J*=7.0 Hz, 6H, 2xCH_3), 1.56 (q, *J*=7.0 Hz, 4H, 2x$CH_3C\underline{H_2}$), 1.61-1.70 (m, 12H, 2,4,6,8,9,10 adamantane-H), 2.05 (br s, 3H, 3,5,7 adamantane-H); ^{13}C-NMR (50 MHz, $CDCl_3$) *δ* (ppm) 9.47 (CH_3), 25.93 ($CH_3\underline{C}H_2$), 28.90 (3,5,7 adamantane C), 36.71 (2,8,9 adamantane C), 37.40 (4,6,10 adamantane C), 38.51 (1 adamantane C), 40.48 (C-OH).

3-(1-adamantyl)-pentan-3-amine (AdEt$_2$CNH$_2$) 16d. The oily 3-(1-adamantyl)-3-azidopentane **16c** was prepared by treatment of the tertiary alcohol **16b** with CH_2Cl_2/NaN_3/TFA according to the same procedure followed for 2-(1-adamantyl)-2-azido-propane **15d**. The reaction afforded an oily mixture of azide **16c** along with 3-(1-adamantyl)-pent-2-ene as an elimination by-product. The yield of the azide preparation was 65 % based on the integration of ^{13}C NMR peaks. The crude oily mixture was used without further purification for the $LiAlH_4$ reduction step.

3-(1-Adamantyl)-3-pentanamine **16d** was prepared through $LiAlH_4$ reduction of azide **16c** in refluxing ether for 5h according to the same procedure followed for 2-(1-adamantyl)-propan-2-amine **15d**. Amine **16d** was afforded as light yellow colored oil. Yield: 10.9%; MS 222.4; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ* (ppm) 0.88 (t, *J*=7.1 Hz, 6H, 2xCH_3), 1.08 (br s, 2H, NH_2), 1.33-1.52 (m, 2H, 2x$CH_3\underline{CH_2}$), 1.60-1.69 (m, 12H, 2,4,6,8,9,10 adamantane-H), 1.97 (br s, 3H, 3,5,7 adamantane-H); ^{13}C-NMR (50 MHz, $CDCl_3$) *δ* (ppm) 9.90 (CH_3), 26.73 ($CH_3\underline{C}H_2$), 29.04 (3,5,7 adamantane C), 36.75 (2,8,9 adamantane C), 37.45 (4,6,10 adamantane C), 38.60 (1 adamantane C), 39.86 (CNH_2). Fumarate (EtOH-Ether). Anal. ($C_{19}H_{31}NO_4$). Calcd. C, 67.63; H, 9.26; N, 4.15. Found C, 67.33; H, 9.06; N, 4.35.

1-1-adamantyl)-1-allylbut-3-enyl azide (AdAllyl$_2$COH) 17b. Allylmagnesium bromide was prepared from magnesium turnings (1.33 g, 55.4 mmol) and allyl bromide (6.1 g, 50.4 mmol) in 60 mL of dry diethyl ether. A solution of 1-adamantanecarbonyl chloride (**6a**) (2 g, 10.1 mmol) in 60 mL of dry diethyl ether was added dropwise to the first solution, under Ar atmosphere and stirring. The reaction mixture was heated at gentle reflux for 4h under stirring and Ar atmosphere and an additional 24 h at room temperature under stirring and Ar atmosphere. The mixture was hydrolyzed with an equal volume of saturated solution of ammonium chloride under ice-cooling. The organic layer was separated and the aqueous phase was extracted with diethyl ether two times. The combined organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated under vacuum to yield a yellow colored oil residue of 1-(1-adamantyl)-1-allylbut-3-enol **17b**. Yield: 1.74 g (70%); IR (Film) *ν*(OH) 3568 cm^{-1} (s), *ν*(=C-H) 3074 cm^{-1} (s), 3008 cm^{-1} (m), *ν*(C=C) 1636 cm^{-1} (s); ^{1}H-NMR (400MHz,

$CDCl_3$) δ (ppm) 1.70 (m, 12H, 2,4,6,8,9,10 adamantane-H), 1.99 (br s, 3H, 3,5,7 adamantane-H), 2.28-2.40 (m, J=7.1 Hz, 4H, 3,5-CH_2), 5.09 (t, J=7.1 Hz, 4H, 2xCH_2=), 5.88-5.98 (m, J=7 Hz, 2H, 2xCH=); ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 28.81 (3,5,7-C, adamantane C), 36.57 (2,8,9-C, adamantane C), 37.29 (4,6,10-C, adamantane C), 39.29 (CH_2), 40.34 (1-C, adamantane C), 76.08 (C-OH), 118.11 (=CH_2), 135.82 (CH=).

4-(1-adamantyl)-hept-1,6-dien-4-azide (AdAllyl$_2$C-N$_3$) 17c. The 4-(1-Adamantyl)-hept-1,6-dien-4-azide **17c** was prepared by treatment of the tertiary alcohol **17b** (500 mg, 2.03 mmol) with CH_2Cl_2 (20 mL) / NaN_3 (396 mg, 6.09 mmol) / TFA (1.6 mL, 20.3 mmol) according to the same procedure followed for azide **15c**. Yield 265 mg, (44%); ^{1}H-NMR (400MHz, $CDCl_3$) δ (ppm) 1.64-1.75 (m, 12H, 2,4,6,8,9,10 adamantane-H), 1.82 (br s, 3H, 3,5,7 adamantane-H), 1.99-2.20 (m, 4H, 3,5-CH_2), 5.09 (t, J=7.1 Hz, 4H, 2xCH_2=), 5.90-5.98 (m, 2H, 2xCH=); ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 28.78 (3,5,7-C, adamantane-C), 36.57 (2,8,9-C, adamantane-C), 37.01 (4,6,10-C, adamantane-C), 39.28 (CH_2), 41.09 (1-C, adamantane-C), 55.14 (C-N_3), 118.06 (=CH_2), 135.61 (CH=).

1-(1-Adamantyl)cyclopentanamine 19d. The corresponding cyclopentanol **19b** used as a starting material was prepared from ethyl 1-adamantanecarboxylate **17** and 1,4-bis(bromomagnesiobutane) in dry ether with a 70% yield according to a published procedure;[21] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.30-1.40 (m, 2H, cyclopentane-H), 1.50-1.80 (m, 18H, adamantane-H, cyclopentane-H), 1.98 (br s, 3H, 3,5,7 adamantane-H), 2.16 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.2 (3,4 cyclopentane-C), 28.6 (3,5,7 adamantane-C), 33.8 (2,5-cyclopentane-C), 37.1 (4,6,10 adamantane-C), 37.3 (2,8,9 adamantane-C), 39.5 (1 adamantane -C), 87.6 (1 cyclopentane-C).

To a stirred mixture of NaN_3 (0.270 g, 4.08mmol) and dry dichloromethane (40 mL) at 0 °C, TFA (13.6mmol) was added. To the stirred mixture a solution of tertiary alcohol **19b** (0.300 g, 1.36 mmol) in dry dichloromethane (20 mL) was added and stirring was maintained at 0 °C for 4 h. The mixture was stirred at ambient temperature for 24 h and then was treated with NH_3 12% (30 mL) at 0 °C. The organic phase was separated and the aqueous phase was extracted twice with an equal volume of dichloromethane. The combined organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated to afford oily azide **19c**; yield 0.290 g (88%); IR (Nujol) ν(N_3) 2097 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50-1.80 (m, 20H, adamantane-H, cyclopentane-H), 1.99 (br s, 3H, 3,5,7 adamantane-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.2 (3,4-cyclohexane-C), 28.6 (3,5,7 adamantane-C), 30.7 (2,5 cyclohexane-C), 37.1 (4,6,10 adamantane -C), 36.7 (2,8,9 adamantane-C), 41.8 (1 adamantane-C), 81.2 (1 cyclopentane-C).

To a stirred suspension of $LiAlH_4$ (161 mg, 4.24 mmol) in dry ether (20 mL) was added, drop-wise at 0 °C, a solution of the azide **19c** (260 mg, 1.06 mmol) in dry ether (10 mL). The reaction mixture was refluxed for 5 h (TLC monitoring) and then hydrolyzed with water and NaOH (15%) under ice cooling. The inorganic precipitate was filtered off and washed with ether, and the filtrate was extracted with HCl (6%). The aqueous layer was made alkaline with solid Na_2CO_3 and the mixture was extracted with ether. The combined ether extracts were washed with water and brine and dried (Na_2SO_4). After evaporation of the solvent the oily amine **19d** was obtained; yield: 151 mg (65%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.08-1.18 (m, 4H, 3,4 cyclopentane-H), 1.50-1.80 (m, 18H, adamantane-H, cyclopentane-H, NH_2), 1.98 (br s, 3H, 3,5,7 adamantane-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 24.9 (3,4-cyclopentane-C), 28.8 (3,5,7 adamantane-C), 34.4 (2,5 cyclopentane-C), 37.0 (4´,6´,10´-C), 37.4 (2,8,9 adamantane-C), 39.0 (1 adamantane-C), 66.8 (1 cyclopentane-C). Fumarate: mp 255 ºC (EtOH-Et_2O).

1-(1-Adamantyl)cyclohexanamine (20d). Tertiary alcohol **21** was obtained from 1-adamantyl lithium (formed by 1-bromoadamantane and lithium wire under sonication) and cyclohexanone in dry THF according to a published procedure with 70% yield.[49,50] To a stirred mixture of NaN_3 (0.170 g, 2.61mmol) and dry dichloromethane (20 mL) at 0 °C, TFA (8.70mmol) was added. To the stirred mixture a solution of tertiary alcohol **20b** (0.204 g, 0.87 mmol) in dry dichloromethane (10 mL) was added and stirring was maintained at 0

°C for 4 h. The mixture was stirred at ambient temperature for 24 h and then was treated with NH_3 12% (30 mL) at 0 °C. The organic phase was separated and the aqueous phase was extracted twice with an equal volume of dichloromethane. The combined organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated to afford oily azide **20c**; yield 0.140 g (60%); IR (Nujol) $\nu(N_3)$ 2101 cm^{-1}; ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 21.9 (4 cyclohexane-C), 25.6 (3,5 cyclohexane-C), 28.8 (3,5,7 adamantane-C), 30.8 (2,6 cyclohexane-C), 35.7 (4,6,10 adamantane-C), 37.2 (2,8,9 adamantane-C), 42.0 (1 adamantane-C), 70.1 (1-cyclohexane-C).

To a stirred suspension of $LiAlH_4$ (65 mg, 1.70mmol) in dry ether (7 mL) was added, drop-wise at 0 °C, a solution of the azide **20c** (110 mg, 0.425mmol) in dry ether (5 mL). The reaction mixture was refluxed for 5 h (TLC monitoring) and then hydrolyzed with water and NaOH (15%) under ice cooling. The inorganic precipitate was filtered off and washed with ether, and the filtrate was extracted with HCl (6%). The aqueous layer was made alkaline with solid Na_2CO_3 and the mixture was extracted with ether. The combined ether extracts were washed with water and brine and dried (Na_2SO_4). After evaporation of the solvent the oily amine **20d** was obtained; yield: 50 mg (30%); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.35-1.42 (m, 6H, 3,4,5 cyclohexane-H), 1.48-1.55 (m, 3H, 2,8,9 adamantane-H), 1.56-1.70 (m, 12H, 2,6 cyclohexane-H, 4,6,10 adamantane-H, NH_2), 1.98 (br s, 3H, 3,5,7 adamantane-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 22.1 (4-cyclohexane-C), 26.4 (3,5-cyclohexane-C), 29.0 (3′,5′,7′-C), 30.5 (2,6-cyclohexane-C), 35.7 (4,6,10 adamantane-C), 37.5 (2,8,9 adamantane-C), 38.7 (1 adamantane-C), 54.5 (1 cyclohexane-C). Fumarate: mp 264 ºC (EtOH-Et_2O); Anal. ($C_{20}H_{31}NO_4$) Calcd. C, 68.74; H, 8.94; N, 4.01. Found C, 68.43; H, 9.06; N, 4.35.

2-(p-Hydroxy)benzyl-(tricyclo[3.3.1.1^{3,7}]decan)-2-amine (21). 2-(p-hydroxy)benzyl-2-adamantanamine **21** was obtained after deprotection of amine 14d (120 mg, 0.44 mg) using BBr_3 at -80°C. Yield 90 mg (80%); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.48 (m, 2H, 4eq,9eq adamantane-H), 1.71-1.80 (m, 7H, 3,5,6,7,8eq,10eq adamantane-H), 1.93-2.0 (m, 3H, 1,8ax,10ax adamantane-H), 2.24 (d, *J*=12.1 Hz, 1H, 4ax,9ax adamantane-H), 2.92 (s, 2H, CH_2Ar), 3.58 (s, 1H, OH), 6.73 (d, *J*=6.2 Hz, 2H, phenyl-H), 7.06 (d, *J*=6.2 Hz, 2H, phenyl-H). Fumarate (EtOH–Et_2O). Anal. ($C_{20}H_{34}NO_5$) Calcd: C, 65.19; H, 9.30; N, 3.80. Found: C, 65.05; H, 9.58; N, 3.72.

Procedure B (standard Ritter reaction)

4-Ethyloctan-4-amine (BuEtPrCNH$_2$) 1d. A solution of conc. H_2SO_4 (6 mL) and AcOH (6 mL) was added dropwise to a mixture of alcohol **1b** (500 mg, 3.16 mmol), AcOH (6 mL) and KCN (258 mg, 3.96 mmol) at 70 °C and heating was maintained for 2 h. The resulting mixture was treated with water (10 mL) and NaOH 10% (10 mL) and stirred for 15 min. The mixture was extracted with ether (2x15 mL), the combined organic phases were washed with water and the solvent was evaporated in vacuo to afford the amine **1d** acetamide. A mixture of the amine **1d** acetamide (430 mg, 2.32 mmol) and KOH (1.04 g, 18.6 mmol) in di(ethylene glycol) (2 mL) was heated for 24h in a sealed tube at 180 °C. After cooling, the tube was opened and the mixture poured into water (50 mL). The mixture was extracted with diclhoromethane (3x20 mL) and washed with HCl 6%. The aqueous phase was made alkaline with solid sodium carbonate and was extracted with diclhoromethane. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated in vacuo to afford the 4-ethyloctan-4-amine **1d**; Yield 47%. Amine **3d** was prepared according to the same procedure; Characterization of compound **1d** is included in compounds synthesized by Procedure A.

5-Butylnonan-5-amine (Bu$_3$CNH$_2$) 3d. The amine **3d** acetamide was prepared as above for the preparation of tert-alkyl amine **1d** through treatment of alcohol **3b** (500 mg, 2.50 mmol), with conc.H_2SO_4 (6 mL) / AcOH (6 mL) / KCN (203 mg, 3.13 mmol). The amine **3d** was prepared through treatment of **3d** acetamide (400 mg, 1.76

mmol) with KOH (780 mg, 18.6 mmol) in di(ethylene glycol) (2 mL) and following the same workup. Yield 20 mg (4%). Characterization of compound **3d** is included in compounds synthesized by Procedure A.

Procedure B (modified Ritter reaction)

4-propylheptan-4-amine (Pr_3CNH_2) 2d. To a mixture of the alcohol **2b** (300 mg, 1.90 mmol) and $ClCH_2CN$ (287 mg, 3.80 mmol), AcOH (0.3 mL, 5.25 mmol) was added and the mixture was cooled to 0-3 °C. H_2SO_4 (0.3 mL, 5.70 mmol) was added dropwise keeping the temperature below 10 °C. The reaction mixture was allowed to reach rt, stirred for 24 h and poured into ice water (10 mL). Chloroacetamide **22** was extracted with ether (3 × 10 mL). The combined extracts were washed with $NaHCO_3$ 10% and brine, and dried ($NaSO_4$). Solvent was evaporated in vacuo to afford compound **22** which was used without further purification for the next step. Yield 200 mg (45%); IR (Nujol) ν(C=O) 1668 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.96 (t, J=7.1 Hz, 9H, 3x$CH_2CH_2C\underline{H}_3$), 1.33-1.47 (m, 12H, 3x$C\underline{H}_2CH_2CH_3$, 3x$CH_2C\underline{H}_2CH_3$), 4.27 (s, $COCH_2Cl$).

A solution of the amide **22** (180 mg, 0.772 mmol) and thiourea (70.6 mg, 0.927 mmol) in EtOH (6 mL)/AcOH (1.2 mL) was refluxed for 10 h. Then water (15 mL) was added to the reaction mixture and the resulting precipitate was filtered off. The filtrate was made alkaline with NaOH 20%, washed with ether (3 × 30 mL) and extracted with HCl 6%. The aqueous phase was made alkaline with solid sodium carbonate and was extracted with dichloromethane or ether. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated in vacuo to afford the amine **2d.** Yield 100 mg (80 %); Characterization of compound **2d** is included in compounds synthesized by Procedure A.

5-Butylnonan-5-amine (Bu_3CNH_2) 3d. Chloroacetamide **23** was prepared through treatment of tributylsubstituted methanol **3b** (300 mg, 1.50 mmol) with $NCCH_2Cl$ (282 mg, 3.00 mmol), H_2SO_4 (0.3 mL, 5.70 mmol) / AcOH (0.3 mL, 5.25 mmol) according to the same procedure followed for the chloroacetamide **22**. Yield 252 mg, (61%); IR (Nujol) ν(C=O) 1689 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.97 (t, J=7.1 Hz, 9H, 3x$C\underline{H}_3CH_2CH_2CH_2$), 1.29-1.35 (m, 12H, 3x$CH_3CH_2CH_2C\underline{H}_2$, 3x $CH_3CH_2\underline{CH}_2CH_2$), 1.38-1.47 (m, 6H, 3x $CH_3\underline{CH}_2CH_2CH_2$), 4.27 (s, $COCH_2Cl$). The amine **3d** was prepared as above for the preparation of tert-alkyl amine **2d** through treatment of **23** (200 mg, 0.725 mmol) with thiourea (66 mg, 0.871 mmol) in EtOH (6 mL)/AcOH (1.2 mL) and following the same workup. Yield 19 mg (13%). Characterization of compound **3d** is included in compounds synthesized by Procedure A.

2-*n*-Butyl-(tricyclo[3.3.1.1^{3,7}]decan)-2-amine 11d. Chloroacetamide **24** was prepared through treatment of *tert*-alkyl alcohol **11b** (300 mg, 1.44 mmol) with $NCCH_2Cl$ (271 mg, 2.88 mmol), H_2SO_4 (0.3 mL, 5.70 mmol) / AcOH (0.3 mL, 5.25 mmol) according to the same procedure followed for the chloroacetamide **22**. Yield 209 mg, (51%); IR (Nujol) ν(C=O) 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.96 (t, J=7.1 Hz, 3H, $C\underline{H}_3CH_2CH_2CH$), 1.35-1.45 (m, 4H, $CH_3C\underline{H}_2C\underline{H}_2CH_2$), 1.63 (d, J=12.1 Hz, 2H, 4eq,9eq-adamantane-H), 1.76-2.02 (m, 12H, adamantane-H, $CH_3CH_2CH_2C\underline{H}_2$), 2.05 (d, J=12.1 Hz, 2H, 4ax,9ax adamantane-H), 4.32 (s, $COCH_2Cl$). The amine **11d** was prepared as above for the preparation of tert-alkyl amine **2d** through treatment of **24** (200 mg, 0.704 mmol) with thiourea (67 mg, 0.880 mmol) in EtOH (6 mL)/AcOH (1.2 mL) and following the same workup. Yield 57 mg (39%). Characterization of compound **11d** is included in compounds synthesized by Procedure A.

2-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)-propan-2-amine 15d. Chloroacetamide **25** was prepared through treatment of *tert*-alkyl alcohol **15b** (300 mg, 1.55 mmol) with $NCCH_2Cl$ (290 mg, 3.09 mmol), H_2SO_4 (0.3 mL, 5.70 mmol) / AcOH (0.3 mL, 5.25 mmol) according to the same procedure followed for the chloroacetamide **22**. Yield 42 mg, (10%); IR (Nujol) ν(C=O) 1673 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.80 (s, 6H, 2xCH_3), 1.58-1.70 (m, 12H, 2,4,6,8,9,10 adamantane H), 2.01 (br s, 3H, 3,5,7 adamantane H), 4.30 (s, $COCH_2Cl$). The amine **15d** was prepared in traces as above for the preparation of tert-alkyl amine **2d** through treatment of **23** (40 mg, 0.150

mmol) with thiourea (9 mg, 0.118 mmol) in EtOH (3 mL)/AcOH (0.6 mL) and following the same workup. Yield traces.

4-(Tricyclo[3.3.1.1^{3,7}]dec-1-yl)-heptan-4-amine 18d. Chloroacetamide **26** was prepared through treatment of *tert*-alkyl alcohol **18d** (300 mg, 1.20 mmol) with $NCCH_2Cl$ (226 mg, 2.40 mmol), H_2SO_4 (0.3 mL, 5.70 mmol) / AcOH (0.3 mL, 5.25 mmol) according to the same procedure followed for the chloroacetamide **22**. Yield 144 mg, (37%); IR (Nujol) ν(C=O) 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.92 (t, J=7.1 Hz, 6H, 2xCH_3), 1.35-1.43 (m, 8H, 2x $C\underline{H}_2C\underline{H}_2CH_3$), 1.63-1.70 (m, 12H, 2,4,6,8,9,10 adamantane H), 2.01 (br s, 3H, 3,5,7 adamantane H), 4.28 (s, $COCH_2Cl$). The amine **18d** was prepared in traces as above for the preparation of tert-alkyl amine **2d** through treatment of **26** (140 mg, 0.430 mmol) with thiourea (26 mg, 0.344 mmol) in EtOH (3 mL)/AcOH (0.6 mL) and following the same workup.

Procedure C

4-Propylheptan-4-amine (Pr_3CNH_2) 2d. To a stirred mixture of 4-heptanone **2a** (224 mg, 1.97 mmol) and $Ti(EtO)_4$ (900 mg, 3.93 mmol) in dry THF (4 mL), *tert*-butanesulfinamide (250 mg, 2.06 mmol) was added and the resulting reaction mixture was refluxed overnight. The mixture was cooled at 0 ºC and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel (40-63 μm) using 40:60 Et_2O/hexane as an eluent to afford the sulfinyl ketimine **28**. Yield 48%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.88-0.98 (m, 6H, $(CH_2)_2C\underline{H}_3$), 1.20 (s, 9H, $C(C\underline{H}_3)_3$), 1.56-1.60 (sex, J=7.1, 4H $CH_2C\underline{H}_2CH_3$), 2.32-2.38 (m, 2H, $C\underline{H}_2CH_2CH_3$), 2.54-2.71 (m, 2H, $C\underline{H}_2CH_2CH_3$).

Propylmagnesium bromide (2.07 mmol) (obtained from 20% solution w/v 1-bromopropane in dry ether and 1.3 equivalents of Mg) was cooled at -78 °C and treated dropwise with a solution of the *tert*-butyl sulfinyl ketimine **28** (205 mg, 0.942 mmol) in dry ether (2 mL). The resulting mixture was stirred for 1 h at -78°C and then allowed to reach slowly ambient temperature and stirred for additional 15 h. The mixture was then cooled at 0 °C, treated with sat. aq. Na_2SO_4 (5 mL) and stirred for 10 min. After suction filtration, the mixture was extracted with ethyl acetate (2 x 15 mL) and the organic phase was washed with brine, dried (Na_2SO_4) and evaporated in vacuo to afford crude *tert*-butyl sulfinamide **30** which was used without further purification for the next step.

A solution of sulfinamide **30** (121 mg, 0.463 mmol) in dioxane (1 mL) was cooled at 0 ºC and treated dropwise with HCl 2.5 M in ethanol (4.0 mL, 2.31 mmol). The resulting solution was allowed to reach ambient temperature and stirred for 40 min. The solution was concentrated under vacuum to a volume of 1 mL and 2 mL of ether was added to afford amine **2d** hydrochloride as a precipitate. Yield 13 mg (18%); Characterization of compound **2d** is included in compounds synthesized by Procedure A.

5-Butylnonan-5-amine (Bu_3CNH_2) 3d. *Tert*-butyl sulfinyl ketimine **29** was prepared according to the same procedure followed for *tert*-butyl sulfinyl ketimine **10**. Yield 77% ; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.89 (t, J = 7, 6H, $(CH_2)_3C\underline{H}_3$), 1.19 (s, 9H, $C(C\underline{H}_3)_3$), 1.33 (sextet, J=7, 4H, $(CH_2)_2C\underline{H}_2CH_3$), 1.54 (q, J=7.1, 4H, $CH_2C\underline{H}_2CH_2CH_3$), 2.38 (t, J=7.1, 2H, $C\underline{H}_2(CH_2)_2CH_3$), 2.58-2.73 (m, 2H, $C\underline{H}_2(CH_2)_2CH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 13.9 (2x$(CH_2)_3\underline{C}H_3$), 22.3 ($C(\underline{C}H_3)_3$), 23.0 (2x$(CH_2)_2\underline{C}H_2CH_3$), 27.8 ($CH_2\underline{C}H_2CH_2CH_3$), 29.6 ($CH_2\underline{C}H_2CH_2CH_3$), 36.4 (2x$\underline{C}H_2CH_2CH_2CH_3$), 56.2 ($\underline{C}(CH_3)_3$), 189.1 (C=N).

A 0.7 M solution of sulfinyl ketimine **29** (387 mg, 1.58 mmol,) in dry toluene (2 mL) was cooled at -78 °C and treated dropwise with a 2M solution of $AlMe_3$ in toluene (0.8 mL, 1.1 molar excess). The mixture was stirred for 5 min and a solution of 1.6M n-butyl lithium in hexanes (2 mL, 0.4 M in toluene, 2.2 molar excess) was added dropwise at -78 ºC. The resulting mixture was stirred for additional 4 h at -78 °C and then allow to reach 0 ºC. The mixture was treated with sat. aq. Na_2SO_4 (5 mL) and stirred for 10 min. After suction filtration, the mixture was extracted with ethyl acetate (2 x 15 mL) and the organic phase was washed with brine, dried

(Na_2SO_4) and evaporated in vacuo to afford crude *tert*-butyl sulfinamide **31** which was used without further purification for the next step.

A solution of sulfinamide **31** (227 mg, 0.750 mmol) in dioxane (1 mL) was cooled at 0 ºC and treated dropwise with HCl 2.5 M in ethanol (6.5 mL, 3.75 mmol). The resulting solution was allowed to reach ambient temperature and stirred for 40 min. The solution was concentrated under vacuum to a volume of 1 mL and 2 mL of ether was added to afford amine **3d** hydrochloride as a precipitate. Yield 45 mg (25 %); Characterization of compound **3d** is included in compounds synthesized by Procedure A.

Procedure D

5-Propyl-nonan-5-amine (Bu_2PrCNH_2) 6d. Kulinkovich-de Meijere reaction protocol: A solution of butanenitrile (**34**) (1.0 g, 14.5 mmol) in 40 mL anhydrous ether was added dropwise to a 3.2 molar excess of BuMgBr (3M in dry ether, obtained from 1-bromobutane (5.9 g, 46.4 mmol) with 1.2 equivalents of Mg (1.4 g, 55.7 mmol)). After stirring the mixture for 30 min, 1 equiv of $Ti(iPrO)_4$ (4.1 g, 14.5 mmol) was added successively at rt and the reaction mixture was gently refluxed for 24 h. After treating the mixture with NaOH 10%, following usual workup the corresponding amine **6d** was obtained. Yield 670 mg (25%), (Table 5, entry 1); Characterization of compound **6d** is included in compounds synthesized by Procedure A.

5-Butyl-nonan-5-amine (Bu_3CNH_2) 3d. Kulinkovich-de Meijere reaction protocol: A solution of pentanenitrile **35** (1.0 g, 12.0 mmol) in 40 mL anhydrous ether was added dropwise to a 3.2 molar excess of BuMgBr (3M in dry ether, obtained from 1-bromobutane (4.9 g, 36.0 mmol) and 1.2 equivalents of Mg (1.0 g, 43.2 mmol)). After stirring the mixture for 30 min, 1 equiv of $Ti(iPrO)_4$ (3.4 g, 12.0 mmol) was added successively at rt and the reaction mixture was gently refluxed for 24 h. After treating the mixture with NaOH 10% following usual workup the corresponding amine **3c** was obtained. Yield 510 mg (20%), (Table 5, entry 2); characterization of compound **3d** is included in compounds synthesized by Procedure A.

4-(*Tert*-butyl)-heptane-4-amine ($tBuMe_2CNH_2$) (38). Kulinkovich-de Meijere reaction protocol: *Tert*-alkyl amine **38** was prepared through the reaction of pivalonitrile (**36**) (500 mg, 6.02 mmol) in 30 mL of anhydrous diethyl ether with a 3M PrMgBr in dry ether (obtained from PrBr (2.20 g, 18.07 mmol) and 1.2 equivalents of Mg (520 mg, 21.7 mmol)) and $Ti(iPrO)_4$ (2.0 g, 7.22 mmol) according to the same procedure described above for the amines **3d** and **6d**. Fumaric salt formation and recrystallization afforded 340 mg of fumaric salt of amine **38**. Yield 20%, (Table 5, entry 3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.84-0.90 (m, 15H, $(CH_2)_2C\underline{H}_3$, $(CH_2)_2C\underline{H}_3$, $C(C\underline{H}_3)_3$), 1.28-1.40 (m, 8H, $(C\underline{H}_2)_2CH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ (ppm) 15.37 ($2x(CH_2)_2\underline{C}H_3$), 18.62 ($2xCH_2\underline{C}H_2CH_3$), 26.3 ($C(\underline{C}H_3)_3$), 38.9 ($2x\underline{C}H_2CH_2CH_3$), 42.2 ($\underline{C}(CH_3)_3$), 57.5($CNH_2$).

3-(1-Adamantyl)-propan-2-amine ($AdMe_2CNH_2$) 15d. Kulinkovich-de Meijere reaction protocol: A solution of 3M MeMgBr (1 mL, 3.11 mmol) in diethyl ether was added dropwise to 1-adamantanecarbonitrile (**37**) (500 mg, 3.11 mmol) in ether (30 mL). After stirring the mixture for 30 min, 1.2 equiv of $Ti(iPrO)_4$ (975 mg, 3.43 mmol) was added successively at rt. The mixture was allowed to stir at room temperature under argon atmosphere for 1 h. Then, 4 mL of methylithium solution (1.6 M in diethyl ether, 6.22 mmol) was added dropwise and the reaction mixture was gently refluxed for 24 h. After treating the mixture with NaOH 10% following usual workup the corresponding amine **15d** was obtained. Yield 60 mg (10%), (Table 5, entry 7); Characterization of compound **15d** is included in compounds synthesized by Procedure A.

3-(1-Adamantyl)-propan-2-amine ($AdMe_2CNH_2$) 15d. Kulinkovich-de Meijere reaction protocol: A solution of 3M MeMgBr (1 mL, 3.11 mmol) in diethyl ether was added dropwise to 1-adamantanecarbonitrile (**37**) (500 mg, 3.11 mmol) in ether (30 mL). After stirring the mixture for 30 min, 1.2 equiv of $Ti(iPrO)_4$ (975 mg, 3.43 mmol) was added successively at rt. The mixture was allowed to stir at room temperature under argon atmosphere for 1 h. Then, 2.1 mL of MeMgBr solution (3 M in diethyl ether, 6.22 mmol) was added dropwise and the reaction mixture was gently refluxed for 24 h. After treating the mixture with NaOH 10% following

usual workup the corresponding amine **15d** was obtained. Yield 60 mg (10%), (Table 5, entry 9); Characterization of compound **15d** is included in compounds synthesized by Procedure A.

3-(1-Adamantyl)-propan-2-amine ($AdMe_2CNH_2$) 15d. Kulinkovich-Szymoniak reaction protocol: Tetraisopropoxy titanium (975 mg, 3.43 mmol) was added in a solution of 1-adamantanecarbonitrile (**37**) (500 mg, 3.11 mmol) in 30 mL of anhydrous diethyl ether, under stirring and argon atmosphere. After 20 min, 1 mL of MeMgBr solution in diethyl ether (3 M, 6.22 mmol) was added dropwise and the mixture was allowed to stir at room temperature under argon atmosphere for 1 h. Then, 4 mL of methylithium solution (1.6 M in diethyl ether, 6.22 mmol) was added dropwise and the reaction mixture was gently refluxed for 24 h. After treating the mixture with NaOH 10% following usual workup the corresponding amine **15d** was obtained. Yield 66 mg (11%), (Table 5, entry 7); Characterization of compound **15d** is included in compounds synthesized by Procedure A.

3-(1-Adamantyl)-propan-2-amine ($AdMe_2CNH_2$) 15d. Kulinkovich-Szymoniak reaction protocol: A solution of 3M MeMgBr (2.1 mL, 6.22 mmol) in diethyl ether was added dropwise to 1-adamantanecarbonitrile (**37**) (500 mg, 3.11 mmol) in ether (30 mL). After stirring the mixture for 30 min, 1.2 equiv of $Ti(iPrO)_4$ (975 mg, 3.43 mmol) was added successively at rt. The mixture was allowed to stir at room temperature under argon atmosphere for 1 h. Then, 1 mL of MeMgBr solution (3 M in diethyl ether, 3.11 mmol) was added dropwise and the reaction mixture was gently refluxed for 24 h. After treating the mixture with NaOH 10% following usual workup the corresponding amine **15d** was obtained. Yield 60 mg (10%), (Table 5, entry 9); Characterization of compound **15d** is included in compounds synthesized by Procedure A.

3-(1-Adamantyl)-propan-2-amine ($AdMe_2CNH_2$) 15d. $CeCl_3$ applied protocol: Commercial dry $CeCl_3$ (2.37 g, 9.61 mmol) was further subjected to stirring at 140-150 ºC (0.1 mm) for 3 h. Argon was added slowly, and the flask was cooled in an ice bath. Anhydrous THF (20 mL) was added, and the suspension was stirred at 25 ºC for 2 h. Then MeLi (6 mL of a 1.6 M solution in ether, 9.61 mmol) was added keeping the temperature at -78 ºC with a dry ice/acetone bath. The mixture was stirred in the dry ice/acetone bath for 30 min, and 1-adamantanecarbonitrile (**37**) (0.500 g, 3.10 mmol) in 2 mL of THF was added. Stirring at -65 ºC was continued for *5* h. Concentrated NH_3 (10 mL) was added at less than -40 ^oC, and the mixture was brought to 25 ºC and filtered with the aid of Celite. The solids were washed several times with dichloromethane, and the aqueous layer of the filtrates was extracted twice with dichloromethane. The combined organic phases were dried and concentrated. The residue was taken up in 10 mL of toluene and stirred with 10 mL of 3% H_3P0_4 for 20 min. The toluene layer was extracted with two l0 mL portions of water, and the combined aqueous phases were washed once with toluene and made basic with conc. NH_3. The mixture was extracted several times with dichloromethane, and the residue was obtained on removal of the solvent from the dried (Na_2SO_4) extracts; Yield 70 mg (12%) of **15d**. (Table 5, entry 10)

3-(1-Adamantyl)-pentan-3-amine ($AdEt_2CNH_2$) 16d. Kulinkovich-de Meijere reaction protocol using 3 eq. EtMgBr. Amine **16d** was prepared through the reaction of 1-adamantanecarbonitrile (**37**) (500 mg, 3.11 mmol) in 30 mL of anhydrous diethyl ether with EtMgBr 3M in dry ether (obtained from EtBr (1.02 g, 9.33 mmol) and 1.2 equivalents of Mg (672 mg, 28.0 mmol) and $Ti(iPrO)_4$ (970 mg, 3.42 mmol) according to the same procedure described above for the amines **3d** and **6d** to afford 120 mg of mixture. For purification of the crude product 2 mL of an ethanolic solution of fumaric acid (66 mg, 0.569 mmol) was added to a solution of the crude amine in 2 mL ethanol. The mixture was evaporated under vacuum, to yield a white colored crystal residue which was treated with diethyl ether and filtered under vacuum to afford a non-separable mixture of AdEtCH-NH_2 (**40**) in 3% yield and $AdEt_2C$-NH_2 **16d** in a 4% yield (ratio 60:40 according to ^{13}C NMR spectrum), (Table 5, entry 5). Characterization of compound **16d** is included in compounds synthesized by Procedure A.

3-(1-Adamantyl)-pentan-3-amine ($AdEt_2CNH_2$) 16d. Kulinkovich-de Meijere reaction protocol using EtMgBr and EtLi. Amine **16d** was prepared through the reaction of 1-adamantanecarbonitrile (**37**) (500 mg, 3.11 mmol) in 30 mL of anhydrous diethyl ether with EtMgBr 3M in dry ether (obtained from EtBr (340 mg, 3.11 mmol) and 1.2 equivalents of Mg (90 mg, 3.73 mmol) and $Ti(iPrO)_4$ (970 mg, 3.42 mmol) according to the same procedure described above for the amines **3d** and **6d**. The mixture was allowed to stir at room temperature under argon atmosphere for 1 h. Then, 12 mL of ethyllithium solution (0.5 M in cyclohexane/benzene, 6.22 mmol) or 6.22 mmol of ethyl magnesium bromide solution was added dropwise and the reaction mixture was gently refluxed for 24 h. After treating the mixture with NaOH 10% following usual workup the corresponding amine **16d** was obtained. Yield 70 mg (10%), (Table 5, entry 8); Characterization of compound **16d** is included in compounds synthesized by Procedure A.

3-(1-Adamantyl)-pentan-3-amine ($AdEt_2CNH_2$) 16d. Kulinkovich-Szymoniak reaction protocol: Tetraisopropoxy titanium (975 mg, 3.43 mmol) was added in a solution of 1-adamantanecarbonitrile (**37**) (500 mg, 3.11 mmol) in 30 mL of anhydrous diethyl ether, under stirring and argon atmosphere. After 20 min, 3.1 mL of ethyl magnesium bromide solution in diethyl ether (1 M, 3.11 mmol) was added dropwise and the mixture was allowed to stir at room temperature under argon atmosphere for 1 h. Then, 12 mL of ethyllithium solution (0.5 M in cyclohexane/benzene, 6.22 mmol) was added dropwise and the reaction mixture was gently refluxed for 24 h. After treating the mixture with NaOH 10% following usual workup to yield 300 mg of a yellow oily product, which was purified by recrystallization; 2 mL of an ethanolic solution of fumaric acid (166 mg, 1.43 mmol) was added to a solution of the crude amine in 2 mL ethanol. The mixture was evaporated under vacuum, to yield a white colored crystal residue which was treated with diethyl ether and filtered under vacuum to afford 60 mg (yield 10%) of the fumarate salt of amine **16d**; Yield 65 mg (10%), (Table 5, entry 8); Characterization of compound **16d** is included in compounds synthesized by Procedure A.

1-(1-adamantyl)cyclopentanamine 19d. Kulinkovich-de Meijere reaction protocol: A solution of 1-adamantanecarbonitrile (**37**) (300 mg, 1.86 mmol) in ether (5 mL) was added dropwise to a 2 molar excess of $BrMg(CH_2)_2MgBr$ (3M in dry ether, obtained from dibromobutane with 2.2 equivalents of Mg). After stirring the mixture for 30 min, 1 equiv of $Ti(iPrO)_4$ (529 mg, 1.86 mmol) was added successively at rt and the reaction mixture was allowed to stir at room temperature under argon atmosphere for 24 h. After a dropwise addition of an equal volume of a sodium hydroxide 10% w/v solution under ice cooling, the mixture was stirred for 30 min and filtered under vacuum. The filtrate was extracted with diethyl ether (2x10mL). The combined ethereal phases were extracted with 30 mL (2x15 mL) of hydrochloric acid 6% w/v. The aqueous phase was separated and made alkaline through addition of an excess solid sodium carbonate under ice-cooling. The aqueous phase was extracted two times with 15 mL of dichloromethane. The combined organic extracts were washed 2 times with an equal volume of water and brine, dried (Na_2SO_4) and evaporated under vacuum to yield 173 mg of a yellow oily product, which was purified by recrystallization; 2 mL of an ethanolic solution of fumaric acid (94 mg, 0.829 mmol) was added to a solution of the crude amine in 2 mL ethanol. The mixture was evaporated under vacuum, to yield a white colored crystal residue which was treated with diethyl ether and filtered under vacuum to afford 60 mg (yield 10%) of the fumarate salt of 3-(1-adamantyl)-pentan-3-amine **19d**. (Table 5, entry 6). Characterization of compound **19d** is included in compounds synthesized by Procedure A.

Author Information

‡: These authors contributed equally to the work.

This research is part of C.T. Ph.D thesis and part of A.D. Master's thesis. A.D. current address: Chair of Pharmaceutical and Medicinal Chemistry, Institute of Pharmacy and Food Chemistry, Julius-Maximilians-Universität Würzburg, Am Hubland, 97074 Würzburg, Germany. A.K. designed this research project. C.T. and A.D. performed the synthesis work. Ath. K. performed some reactions. I.S. did the calculations. A.K. and A.D. wrote the manuscript.

7 Achnowlegments

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8 Suppementary Information

Figures S1-S9, Tables S1-S4

9 References

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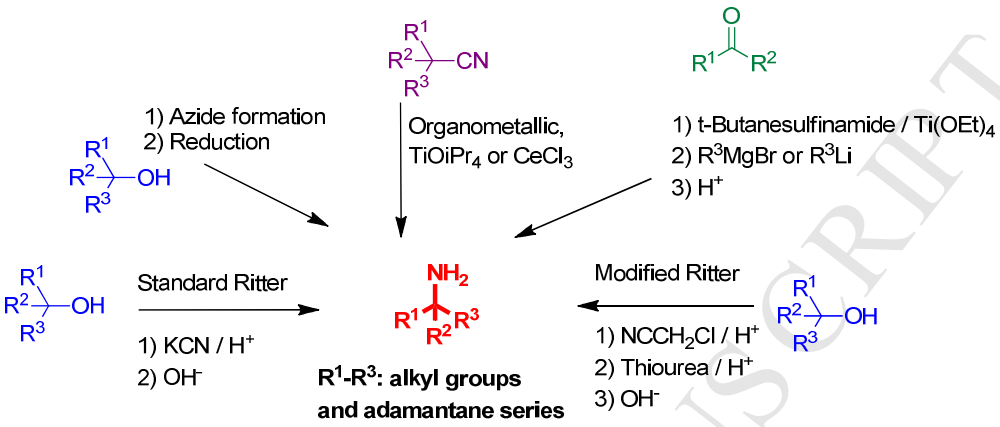
TOC Graphic

Approaches to primary tert-alkyl amines as building blocks

Christina Tzitzoglaki[‡], Antonios Drakopoulos[‡], Athina Konstantinidi, Ioannis Stylianakis, Antonios Kolocouris



Although, the synthetic procedures in the scheme are known and efficient for the synthesis of amines RCH_2NH_2 and $RR'CHNH_2$, they were not studied systematically for the primary *tert*-alkyl amines $RR'R''CNH_2$. The reaction conditions and substrate limitations for the synthesis of primary *tert*-alkyl amines in aliphatic series, including adamantane adducts, were studied herein. The procedure via azide formation and reduction provedthe more general and applicable also for compounds bearing bulky adducts. The findings are important for Organic Chemistry literature.