Reductive amination of carboxylic acids and [^{11}C]magnesium halide carboxylates

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The reductive amination of carboxylic acids was shown to be promoted by 2-chloropyridine hydrochloride (3 eq). It allowed the one-pot preparation of *N*-alkylamines in yields up to 93% from carboxylic acid (1 eq), amine (1 eq) and sodium borohydride (5 molar eq). The reaction, carried out with [^{11}C]magnesium halide carboxylates (^{11}C, β^+, $t_{1/2}$: 20 min), led to *N*-[^{11}C]alkylamines in 20–25% radiochemical yields (decay corrected to the end of bombardment, 30 min preparation time from [^{11}C]CO_2). In this case, the addition of pyridinium salts led only to the corresponding [^{11}C]carboxylic acids.

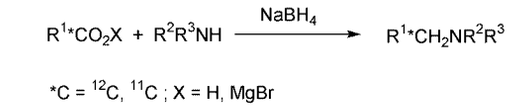
Introduction

Positron emission tomography is a unique technique used to study a wide range of physiological and biochemical processes in several major organs. It allows visualization and quantification of receptors of the different neurotransmitters in living human brain. Its development strongly depends on the availability of new radiotracers labelled with a positron emitter,[1–3] for example carbon-11 ($t_{1/2}$ = 20.4 min) or fluorine-18 ($t_{1/2}$ = 109.6 min). Due to the difficulties encountered in the incorporation of fluorine-18 into a molecule, the labelling of biologically active compounds with carbon-11 is largely employed. However, the preparation of radiotracers is governed by the following constraints: the short half life of carbon-11, the submicromolar amount of the [^{11}C]precursor available from the cyclotron ([^{11}C]CO_2 or [^{11}C]CH_4) and the need for exclusion of stable isotopes in order to obtain tracers of high specific radioactivity. Finally, all the manipulations have to be as simple as possible in order to be remote-controlled for routine production of the tracer under safe conditions. All these aspects require rapid and efficient syntheses with economy of reagents, of reaction steps and of purifications. These requirements could also satisfy some industrial demands.

N-Substituted amines are probably the most common functional groups in drugs and biologically active compounds. Alkylation of a "nor" amine (primary or secondary amine precursor of the alkylated amine) using alkyl iodides, alkyl bromides or triflates[4a] is often used to introduce a substituent on the nitrogen atom. Amidation followed by a reduction,[4b] which is more time consuming, is also a common way to access amines. Reductive aminations of aldehydes or ketones[4c] are well known alternative methods. Reductive carbonations of silylated amines[5] lead only to *N*-methylated amines. All these methods have been used in carbon-11 chemistry,[1–3,6–9] the *N*-[^{11}C]alkylation of amines being, so far, the preferred route to [^{11}C]tracers. However, the latter route requires a multistep procedure from [^{11}C]CO_2 and no simple and short procedure, except for methylation, has been developed for the alkylation of amines.

Although more readily available than alkyl iodides, aldehydes or amides, carboxylic acids[10–14] and esters,[15–17] have been rarely employed to alkylate amines under reductive conditions. The need for a large excess of acid or ester was probably the major limitation of this reaction both for its use in synthesis and for its application to the preparation of [^{11}C]amines.

We previously noticed that *N*-[^{11}C]alkylations of amines[18] took place when [^{11}C]carboxylates and amines were heated in the presence of sodium borohydride. This reaction was unexpected owing to the fact that the reaction conditions differed strongly from those previously described.[10–14] Indeed, the [^{11}C]carboxylate was used in submicromolar amounts[19] compared to the nor-amine and the reducing agent. Moreover, [^{11}C]amides, formed by direct reaction of [^{11}C]carboxylates and amines,[20] could not be reduced by $NaBH_4$. These observations prompted us to study the reductive amination of carboxylic acids both in stable isotope and carbon-11 chemistries. We describe here the one pot synthesis of tertiary amines from carboxylic acids (1 eq) and secondary amines (1 eq) and the radiosynthesis of [^{11}C]amines directly from [^{11}C]magnesium halide carboxylates (Scheme 1).



Scheme 1 Reductive amination of carboxylic acids and [^{11}C]-carboxylates.

Results and discussion

Reductive amination of carboxylic acids under stoichiometric conditions

Reductive amination of carboxylic acids[10–14] was reported as an attractive and efficient method for the preparation of secondary or tertiary alkyl- and arylamines. It only required the heating of a nor-amine with a carboxylic acid (neat or in solution in toluene, dioxane or THF) in the presence of a mild reducing agent (*i.e.* $NaBH_4$). In all cases, an excess of acid (>20 eq) was used. In a first experiment, the reported conditions were applied to the reaction of amine **2** in acetic acid **1a** with $NaBH_4$ (5 molar eq). The amine **9a** was formed in high yield (66–72%). The amine–borane complex **15** (2–5%) and the amide **12a** (5–13%) were also isolated. Similar results were obtained whatever the order of addition of the reagents, although it was reported[11] to be of prime importance. The yield in amine **9a** decreased to 50% when 2.5 molar eq of $NaBH_4$ were used while the yield of the amide **12a** increased up to 41%. The reductive amination of

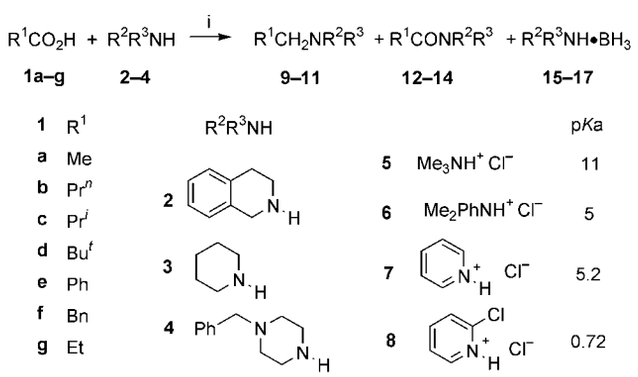
Table 1 Yields in amines **9**–**11** as a function of the reaction conditions

Entry	R^2R^3NH	R^1CO_2H	Method	**8**/$NaBH_4$ (mmol)	Solvent	$R^2R^3NCH_2R^1$	Yield (%)[a]
1	**2**	**1a**	A	3:5	THF	**9a**	93
2		**1a**	A	3:5	toluene	**9a**	0[b]
3		**1a**	A	3:5	CH_2Cl_2	**9a**	0[c]
4		**1a**	B	3:2.5	THF	**9a**	21[d]
5		**1a**	B	3:2.5	toluene	**9a**	19[d]
6		**1a**	B	3:5	THF	**9a**	41[d]
7		**1a**	B	3:5	toluene	**9a**	32[d]
8		**1a**	B	3:5	CH_2Cl_2	**9a**	42[d]
9		**1a**	B	3:5	dioxane	**9a**	44[d]
10		**1a**	B	3:10	toluene	**9a**	27[d]
11		**1a**	B	3:20	toluene	**9a**	12[d]
12		**1a**	B	6:5	THF	**9a**	0[b]
13		**1b**	A	3:5	THF	**9b**	73
14		**1c**	A	3:5	THF	**9c**	71
15		**1d**	A	3:5	THF	**9d**	19[d]
16		**1e**	A	3:5	THF	**9e**	43[d]
17		**1f**	A	3:5	THF	**9f**	78
18	**3**	**1a**	A	3:5	THF	**10a**	87
19		**1b**	A	3:5	THF	**10b**	79
20	**4**	**1b**	A	3:5	THF	**11b**	68
21		**1g**	A	3:5	THF	**11g**	76

[a] Isolated yields. [b] **2** was quantitatively recovered. [c] **15** was quantitatively formed. [d] Side products: **12a** 51% (entry 5), 58% (entry 7), 27% (entry 10) and 10% (entry 11) yields and **15**.

acid **1a** (1 eq) with amine **2** (1 eq) and $NaBH_4$ (2–5 molar eq) was then attempted in different solvents (THF, dioxane, Et_2O, toluene or CH_2Cl_2). In all cases, the amine–borane complex **15** was quantitatively produced.

The need for a proton source in the reaction mixture and the possibility of activation of an acid function with pyridinium salts[21] led us to add an ammonium salt to the reaction medium (Scheme 2). Trimethylamine **5**, *N*,*N*-dimethylaniline **6**, pyridine



Scheme 2 *Reagents and conditions*: i, $NaBH_4$, salt **5**–**8**, solvent, Δ 15 h.

7 and 2-chloropyridine **8** hydrochlorides were chosen because of their range of pK_a values[22,23] (Scheme 2). The yields of amines **9**–**11** were strongly dependent on the ammonium salt added to the reaction mixture, on the solvent and on the order of addition of the reagents. The reaction was carried out according to two procedures. In method A, $NaBH_4$ was added to acid **1**, amine **2**–**4** and salt **5**–**8**. In method B, amine **2**–**4** and salt **5**–**8** were added to a mixture of acid **1** and $NaBH_4$.

Method A gave the best results (Table 1). Yields of amines **9**–**11** ranged from 43–93% (except for **1d**: 19%, entry 15) with THF as the solvent, 2-chloropyridine hydrochloride **8** as the salt and a 1:1:3:5 molar ratio of acid–amine–salt **8**–$NaBH_4$ (entries 1, 13–14, 16–21). Using larger excesses of $NaBH_4$ led to an increased amount of complexes **15**–**17** (up to 80%) whereas the starting amines **2**–**4** were recovered quantitatively if salt **8** was added in excess in comparison with $NaBH_4$. Pyridine or *N*,*N*-dimethylaniline hydrochlorides **7** and **6** were less efficient (yields of amines **9**–**11** <65%, results not presented). The reactions carried out in the presence of trimethylammonium hydrochloride **5** gave mainly **15**–**17**. The reactivity of salts **5**–**8** appeared thus directly related to their pK_a values. A strong solvent influence was observed. Complexes **15**–**17** were the only products formed in CH_2Cl_2 (entry 3) whereas in toluene (entry 2) the amines **2**–**4** were recovered quantitatively.

Using method B, yields of amines **9**–**11** were significantly lower (<45%, entries 4–12) and the formation of the amine–borane complex **15**–**17** was largely favoured (45–90%). The best results were obtained with a 1:1:3:5 molar ratio of acid–amine–salt **8**–$NaBH_4$ in THF, CH_2Cl_2 or dioxane. No improvement was observed by using the salts **5**–**7** or by modifying the ratio of reagents. In toluene, which gave no reductive amination when method A was used, amines **9**–**11** (yields up to 32%) were formed together with large amounts of amides **12**–**14** (up to 58%). Attempts to improve the yields of amines **9**–**11** by using larger amounts of $NaBH_4$ or by adding $LiAlH_4$ to the reaction mixture 1 h before quenching, failed. In Et_2O, no alkylation was observed, and **15**–**17** were formed. In EtOH, DMSO or DMF, no alkylation occurred whatever the conditions and the amines **2**–**4** were quantitatively recovered. This method B appeared less sensitive to the solvent than method A but led to a mixture of products.

In summary, the use of an excess of carboxylic acid in the reductive amination of acids could be avoided by addition of salt **8**. Alkylation of amines occurred in moderate to high yields when $NaBH_4$ (5 eq) was allowed to react with a mixture of acid (1 eq), amine (1 eq) and salt **8** (3 eq) in THF.

Reductive amination of [^{11}C]carboxylic acid salts

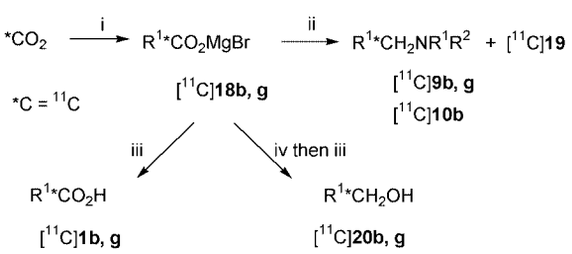
Reductive amination of [^{11}C]carboxylates **18b** or **18g** was carried out as follows. [^{11}C]Carboxylates **18b** or **18g**, formed by trapping [^{11}C]CO_2 with the corresponding Grignard reagent in THF, was transferred under nitrogen into a reactor containing the reducing agent with or without a salt **6** or **8** in a solvent (THF, toluene, HMPT, DMF or diglyme). After stirring for 1 min, amine **2** or **3** was added and the mixture was heated for 10 or 20 min. After hydrolysis, the crude product was analysed by radioTLC and GC. In order to have an efficient [^{11}C]CO_2 trapping (>90%), 0.275 mmol of Grignard reagent was used. The estimated amount of [^{11}C]carboxylates **18b** or **18g** produced was lower than 1 μmol.[19] An excess of nor-amine (0.375 mmol) was chosen as it gave highest yields in direct amidation of [^{11}C]carboxylates.[20] The quantities of salt **5**–**8** and of reducing agent were varied.

Table 2 Reductive amination of carboxylates [^{11}C]**18**

Entry	R^2R^3NH	$R^1[^{11}C]O_2MgX$	R^1	$NaBH_4$ (mmol)	$R^2R^3N[^{11}C]H_2R^1$	Yield (%)[a]	[^{11}C]**19**	Yield (%)[a]
1	**2**	**18b**	*n*-Pr	0.375	**9b**	10	**19b**	63
2				0.750		14		40
3	**2**	**18g**	Et	0.375	**9g**	14	**19g**	36
4	**4**	**18b**	*n*-Pr	0.375	**10b**	22	**19b**	36

[a] Isolated radiochemical yields, corrected for decay, 25 min from [^{11}C]CO_2.

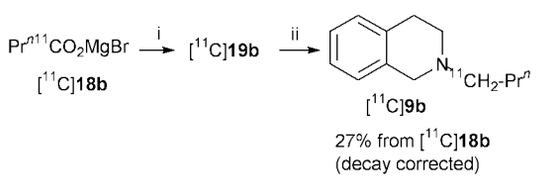
The reductive amination of carboxylates [^{11}C]**18b** and [^{11}C]**18g** was highly dependent of the reducing agents. The radiochemical yields in amines [^{11}C]**9b**, [^{11}C]**9g** and [^{11}C]**10b** decreased in the following order: $NaBH_4 > LiBH_4 > KBH_4 > Zn(BH_4)_2$. Reactions using $Zn(BH_4)_2$ led to alcohol [^{11}C]**20b** or [^{11}C]**20g** in up to 90% (results not shown). Among the several solvents tested, THF gave the best results. Conversely to stable isotope chemistry, the yields in amines [^{11}C]**9**,**10** were higher when no salt was added. They ranged from 10 to 22% when 0.375 mmol of $NaBH_4$ was used (Table 2, entries 1, 3 and 4). Carboxylic acids [^{11}C]**1b** or [^{11}C]**1g** (27–50%, from [^{11}C]CO_2) resulting from the hydrolysis of the carboxylates [^{11}C]**18b** or [^{11}C]**18g**, and a radioactive compound [^{11}C]**19** of low polarity (36–63%, from [^{11}C]CO_2), were also formed (Scheme 3). Reactions using lower amounts of $NaBH_4$ led to



Scheme 3 *Reagents and conditions*: i, R^1MgBr, THF, 0 °C, 3 min; ii, $NaBH_4$, R^2R^3NH, (**5**–**8**), THF, Δ, 10 or 20 min; iii, aq NH_4Cl; iv, $LiAlH_4$, 70 °C, 5 min.

acids [^{11}C]**1** in large quantities (>65%, data not presented). The same result was observed when the salts **6** and **8** were used in small amounts (0.032 mmol). Using a large excess of $NaBH_4$ or sonication did not improve the yields significantly (entry 2). No [^{11}C]amides from direct reaction between [^{11}C]carboxylates and amines[20] were formed.

Identification of [^{11}C]acids and [^{11}C]alcohols was achieved from their unambiguous syntheses (respectively by hydrolysis and by reduction with $LiAlH_4$ of the starting carboxylates [^{11}C]**18b** or [^{11}C]**18g**) (Scheme 3). The radioactive compound [^{11}C]**19b** was found to be the reaction product of carboxylate [^{11}C]**18b** with $NaBH_4$ (25% radiochemical yield from [^{11}C]CO_2, 10 min reaction time) and an intermediate in the reductive amination. Indeed, the reaction of [^{11}C]**19b** with tetrahydroisoquinoline **2** for 10 min led to the corresponding amine [^{11}C]**9b** in 27% radiochemical yield (Scheme 4, compared to



Scheme 4 *Reagents and conditions*: i, $NaBH_4$, THF, Δ, 10 min; ii, amine **2**, THF, Δ 10 min.

10%, entry 1 Table 2). The formation of [^{11}C]**19b** appeared thus crucial to obtain the amine [^{11}C]**9b** in an optimum yield. However, the kinetics of its formation remained slow, and that could explain the final low yields observed. In conclusion, the reductive amination of carboxylates [^{11}C]**18b** and [^{11}C]**18g** can be carried out in THF in the presence of $NaBH_4$. Radiochemical yields in amines [^{11}C]**9b**, [^{11}C]**9g** and [^{11}C]**10b** were ranged from 15 to 25% (decay corrected, [^{11}C]CO_2) after 20 min of reaction.

Conclusion

We have shown carboxylic acids can alkylate secondary amines under stoichiometric conditions. The reaction required an excess of $NaBH_4$ (5 eq), the presence of 2-chloropyridine hydrochloride (3 eq) and THF as the solvent. The order of addition of the reagents was crucial for the reaction efficiency. Under the appropriate conditions, the yields were moderate to high and similar to those reported when an excess of acid was used.

The reaction was successfully applied to carbon-11 chemistry but the differences in the reductive amination conditions were noteworthy. The [^{11}C]carboxylates led to [^{11}C]amines in yields up to 25% (from [^{11}C]CO_2 in 30 min total time synthesis) if no pyridinium salt was added. In the presence of salt **8**, the main reaction product was the [^{11}C]carboxylic acid **18b** or **18g**.

Finally, the method described here could be a good alternative to the use of alkyl iodides, especially when they are of high molecular weight or of low stability. Due to the fact that the alkylation is direct from the carboxylic acids or their salts, this route could be very attractive for the preparation of amines labelled with carbon-14. Alkylation of functionalised substrates and the use of polymer supported reagents (pyridine hydrochloride and $NaBH_4$) are underway.

Experimental

THF was dried by reflux over benzophenone and sodium and Et_2O by reflux over $LiAlH_4$. They were distilled under a nitrogen atmosphere. Solutions of Grignard reagents were obtained from magnesium turnings and alkyl halides in freshly distilled THF or Et_2O under nitrogen. *N*,*N*-Dimethylaniline **6** and 2-chloropyridine **8** hydrochlorides were prepared as described[24] just before use. All other reagents were used as received from commercial sources (purity >98% Janssen Chimica, Aldrich or Sigma). Compounds **11b** and **11g** were prepared as references by alkylation of 4-benzylpiperazine. IR spectra were recorded on a Perkin-Elmer 16 PC FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained from solutions in $CDCl_3$ on a Bruker AC-250 spectrometer (250 MHz ^{1}H, 62 MHz ^{13}C) with Me_4Si as internal standard. ^{11}B NMR spectra were obtained from solutions in $CDCl_3$ on a Bruker DRX 400 spectrometer at 128 MHz with $BF_3{\cdot}Et_2O$ as external reference. All chemical shifts (δ) are quoted in parts per million. All *J* values are in Hz. Mass spectra were recorded on a Nermag R10 (EI, 70 eV) spectrometer and high resolution mass spectra were measured with a JEOL JMDS 300 spectrometer. Column chromatography was carried out on silica gel 60 (70–230 mesh ASTM, Merck). Thin layer chromatography was performed on silica gel $60F_{254}$ (1.1 mm, Merck). Gas chromatography analyses were carried out on a DELSI apparatus.

[^{11}C]Carbon dioxide was prepared by the ^{14}N(p, α)^{11}C nuclear reaction using nitrogen gas target and a baby cyclotron (CGR

MeV 325). Bombardment was carried out for 1 to 2 min with a 1 to 2 μA beam of 16 MeV protons yielding 150–580 MBq of [^{11}C]carbon dioxide. Radioactivity was measured with a Capintec Radioisotope Calibrator (CRC-12). Identification of the labelled compounds and determination of the radiochemical purity were carried out by radio-TLC using a Berthold automatic TLC-linear analyser and authentic stable isotope samples as references.

Reductive amination of carboxylic acid 1: general procedure

Method A. To a mixture of carboxylic acid **1** (4 mmol), amine **2**–**4** (4 mmol), salt **5**–**8** (12 mmol) in THF, dichloromethane or toluene (15 cm^3), $NaBH_4$ (0.760 g, 20 mmol) was added at 50 °C over a period of 15 min. After heating at 70 °C for 15 h, the suspension was cooled to room temperature and hydrolysed with sodium hydroxide (5%, 20 cm^3). After extraction with dichloromethane (3 × 20 cm^3), the organic phase was dried over magnesium sulfate, filtered and evaporated. The crude product was purified by column chromatography to yield the desired *N*-alkylated amines **9**–**11**, the amine–borane complexes **15**–**17** or the starting amines **2**–**4** (Scheme 2, Table 1).

Method B. Carboxylic acid **1** (4 mmol) was added dropwise at 0 °C to a suspension of $NaBH_4$ (0.760 g, 20 mmol) in a solvent (15 cm^3) (THF, diethyl ether, dioxane, dichloromethane, toluene, ethanol, *N*,*N*-dimethylformamide or dimethyl sulfoxide). After stirring for 15 min, salt **5**–**8** (12 mmol) then amine **2**–**4** (4 mmol) were added. The mixture was heated at 70 °C for 15 h, cooled to room temperature and then hydrolysed with sodium hydroxide (5%, 20 cm^3). After extraction with dichloromethane (3 × 20 cm^3), the organic phase was dried over magnesium sulfate, filtered and evaporated. The crude product was purified to yield the desired amines **9**–**11**, the corresponding amides **12**–**14**, the amine–borane complexes **15**–**17** and the starting amines **2**–**4** (see Results and discussion, Scheme 2, Table 1).

2-Ethyl-1,2,3,4-tetrahydroisoquinoline 9a [11,25]

Purification by column chromatography using dichloromethane–methanol (90 : 10) as eluent yielded **9a** as a yellow oil, R_f 0.4 (dichloromethane–methanol, 90 : 10); ν_{max} (NaCl)/cm^{-1} 2968, 2932, 2800, 2768, 1452 and 740; δ_H ($CDCl_3$) 1.1 (3H, t, *J* 7.2), 2.49 (2H, q, *J* 7.2), 2.65 (2H, t, *J* 5.9), 2.84 (2H, t, *J* 5.9), 3.55 (2H, s), 6.92–7.03 (4H, m); δ_C ($CDCl_3$) 12.4, 29.1, 50.7, 52.2, 55.8, 125.7, 126.7, 127.2, 128.7, 134.3 and 134.7; *m*/*z* 161 ($M^{+\bullet}$, 1%), 146 ($M^+ - CH_3$, 9), 132 ($M^+ - C_2H_5$, 18) and 41 (100).

2-Butyl-1,2,3,4-tetrahydroisoquinoline 9b [25]

Purification by column chromatography using light petroleum–ethyl acetate (30 : 70) as eluent gave the pure title compound **9b** as a yellow oil, R_f 0.8 (light petroleum (bp 35–60 °C)–ethyl acetate, 30 : 70); ν_{max} (NaCl)/cm^{-1} 2954, 2930, 1454 and 740; δ_H ($CDCl_3$) 0.9 (3H, t, *J* 7.4), 1.25–1.34 (2H, m), 1.45–1.58 (2H, m), 2.43 (2H, t, *J* 7.4), 2.65 (2H, t, *J* 5.9), 2.84 (2H, t, *J* 5.9), 3.55 (2H, s), 6.92–7.03 (4H, m); δ_C ($CDCl_3$) 14.2, 20.9, 29.2, 29.5, 51.1, 56.3, 58.4, 125.7, 126.2, 126.7, 128.7, 134.5 and 134.9; *m*/*z* 189 ($M^{+\bullet}$, 5%), 146 ($M^+ - C_3H_7$, 83), 132 ($M^+ - C_4H_9$, 8) and 41 (100).

2-(2-Methylpropyl)-1,2,3,4-tetrahydroisoquinoline 9c [26]

Purification by column chromatography using dichloromethane–methanol (90 : 10) as eluent gave the pure title compound **9c** as a yellow oil, R_f 0.8 (dichloromethane–methanol, 90 : 10); ν_{max} (NaCl)/cm^{-1} 2952, 2924, 1464 and 740; δ_H ($CDCl_3$) 0.95 (6H, d, *J* 6.6), 1.90 (1H, m), 2.26 (2H, d, *J* 7.3), 2.68 (2H, t, *J* 5.8), 2.89 (2H, t, *J* 5.8), 3.58 (2H, s), 7.0–7.1 (4H, m); δ_C ($CDCl_3$) 21.1, 25.8, 29.3, 47.5, 51.2, 56.8, 125.6, 126.1, 127.2, 128.8, 134.8 and 135.4; *m*/*z* 189 ($M^{+\bullet}$, 2%), 146 ($M^+ - C_3H_7$, 72), 132 ($M^+ - C_4H_9$, 5) and 41 (100). Addition of anhydrous hydrogen chloride (1 M) in diethyl ether to a solution of **9c** in diethyl ether yielded quantitatively, after evaporation of the solvent, 2-(2-methylpropyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride as a white solid (mp 201–203 °C, lit.,[26] 205 °C).

2-(2,2-Dimethylpropyl)-1,2,3,4-tetrahydroisoquinoline 9d [27]

Purification by column chromatography using dichloromethane–methanol (90 : 10) as eluent gave the pure title compound **9d** as a yellow oil, R_f 0.4 (dichloromethane–methanol, 90 : 10); ν_{max} (NaCl)/cm^{-1} 2952, 2862, 1464 and 744; δ_H ($CDCl_3$) 0.90 (9H, s), 2.2 (2H, s), 2.6 (2H, t, *J* 5.8), 2.8 (2H, t, *J* 5.8), 3.65 (2H, s), 7.0–7.1 (4H, m); δ_C ($CDCl_3$) 27.9, 29.6, 33.3, 53.7, 58.6, 70.1, 125.5, 125.9, 126.6, 128.8, 134.8 and 137.0; *m*/*z* 203 ($M^{+\bullet}$, 1%) and 146 ($M^+ - C_4H_9$, 100).

2-Benzyl-1,2,3,4-tetrahydroisoquinoline 9e [28]

Purification by column chromatography using dichloromethane–methanol (90 : 10) as eluent gave the pure title compound **9e** as a white solid (mp 37 °C), R_f 0.5 (dichloromethane–methanol, 90 : 10); ν_{max} (NaCl)/cm^{-1} 3084, 3062, 3024, 2918, 2800, 2756, 1496, 1454, 1094, 740 and 698; δ_H ($CDCl_3$) 2.75 (2H, t, *J* 5.7), 2.91 (2H, t, *J* 5.7), 3.64 (2H, s), 3.69 (2H, s), 6.7–7.4 (9H, m); δ_C ($CDCl_3$) 29.3, 50.8, 56.3, 62.9, 125.7, 126.2, 126.7, 127.2, 128.4, 128.7, 129.2, 134.5, 135.1 and 138.5; *m*/*z* 223 ($M^{+\bullet}$, 8%), 146 ($M^{+\bullet} - C_6H_5$, 68), 132 ($M^{+\bullet} - C_7H_7$, 13) and 41 (100). Addition of anhydrous hydrogen chloride (1 M) in diethyl ether to a solution of **9e** in diethyl ether yielded quantitatively, after evaporation of the solvent, 2-benzyl-1,2,3,4-tetrahydroisoquinoline hydrochloride as a white solid (mp 203–204 °C, lit.[28] 204 °C).

2-(2-Phenylethyl)-1,2,3,4-tetrahydroisoquinoline 9f [29]

Purification by column chromatography using dichloromethane–methanol (90 : 10) as eluent gave the pure title compound **9f** as a yellow oil, R_f 0.67 (dichloromethane–methanol, 90 : 10); ν_{max} (NaCl)/cm^{-1} 3024, 2928, 1672 and 740; δ_H ($CDCl_3$) 2.7–2.8 (4H, m), 2.8–2.9 (4H, m), 3.72 (2H, s), 7.0–7.3 (9H, m); δ_C ($CDCl_3$) 29.2, 34.1, 51.1, 56.2, 60.5, 125.7, 126.2, 126.3, 126.7, 127.2, 128.5, 132.3, 134.9, 134.8 and 140.5.

1-Ethylpiperidine 10a [12]

Purification by column chromatography using dichloromethane–cyclohexane–methanol–NH_4OH (68 : 15 : 15 : 2) as eluent gave the pure title compound **10a** as a yellow oil, R_f 0.5 (dichloromethane–cyclohexane–methanol–NH_4OH, 68 : 15 : 15 : 2); δ_H ($CDCl_3$) 0.91 (3H, t, *J* 7.2), 1.4–1.6 (7H, m), 2.3 (5H, m); δ_C ($CDCl_3$) 24.8, 26.9, 29.5, 54.9 and 59.7.

1-Butylpiperidine 10b [30]

Purification by column chromatography using dichloromethane–cyclohexane–methanol–NH_4OH (68 : 15 : 15 : 2) as eluent gave the pure title compound **10b** as a yellow oil, R_f 0.5 (dichloromethane–cyclohexane–methanol–NH_4OH, 68 : 15 : 15 : 2); δ_H ($CDCl_3$) 0.91 (3H, t, *J* 7.2), 1.3 (2H, sextet, *J* 7.2), 1.5 (5H, m), 1.6 (4H, m), 2.3 (m, 5H); δ_C ($CDCl_3$) 14.2, 21.2, 24.6, 26.1, 29.2, 54.8 and 59.5.

1-Benzyl-4-butylpiperazine 11b

Purification by column chromatography using dichloromethane–methanol (90 : 10) as eluent gave the pure title compound **11b** as a yellow oil, R_f 0.66 (dichloromethane–methanol, 90 : 10) (Found: $M^{+\bullet}$, 232.1922. $C_{15}H_{24}N_2$ requires *M*, 232.1934); δ_H ($CDCl_3$) 0.83 (3H, t, *J* 7.3), 1.28–1.36 (2H, m), 1.4–1.6 (2H, m), 2.2–2.3 (2H, m), 2.5–2.6 (8H, m), 3.5 (2H, s), 7.2–7.3 (5H, m); δ_C ($CDCl_3$) 14.1, 20.6, 29.3, 53.5, 53.9, 60.7, 63.3, 127.5, 128.3, 129.4 and 138.1.

Table 3 R_f and R_t of ^{11}C-compounds

^{11}C-Compounds		R_f		R_t/min	
		Eluant A[a]	Eluant B[b]	Conditions C[c]	Conditions D[d]
Acids	[^{11}C]**1b**	—	0.45	—	—
	[^{11}C]**1g**	—	0.40	—	—
Alcohols	[^{11}C]**20b**	0.85	0.50	2	—
	[^{11}C]**20g**	0.85	0.50	1	2
Amines	[^{11}C]**9b**	0.20	0.60	4	—
	[^{11}C]**9g**	0.15	0.50	3	—
	[^{11}C]**10b**	—	0.35	—	7
Low polar compounds	[^{11}C]**19b**	0.90	0.50	13	15
	[^{11}C]**19g**	0.90	0.50	13	—

[a] Dichloromethane–methanol 98:2. [b] Ethyl acetate–methanol 50:50. [c] Column SE 30 (silicone 2 M, 2 m), oven: 220 °C, injector and detector: 300 °C, P_{He}: 1.5 bar. [d] Column DC 550 (chromosorb GAW, 2 m), oven: 160 °C, injector and detector: 200 °C, P_{He}: 1.25 bar.

1-Benzyl-4-propylpiperazine 11g

Purification by column chromatography using dichloromethane–methanol (90:10) as eluent gave the pure title compound **11g** as a yellow oil, R_f 0.66 (dichloromethane–methanol, 90:10) (Found: $M^{+\bullet}$, 218.1756. $C_{14}H_{22}N_2$ requires *M*, 218.1778); δ_H ($CDCl_3$) 0.89 (3H, t, *J* 7.3), 1.4–1.6 (2H, m), 2.2–2.3 (2H, m), 2.5–2.6 (8H, m), 3.5 (2H, s), 7.2–7.3 (5H, m); δ_C ($CDCl_3$) 12.1, 20.2, 53.2, 53.3, 60.9, 63.2, 127.1, 128.3, 129.4 and 138.3.

Borane complexes

These compounds were isolated in low amount and characterized only by the following data.

1,2,3,4-Tetrahydroisoquinoline–borane complex 15. Purified with dichloromethane–methanol (95:5) as eluent to give the pure title compound **15** as a white solid (mp 117.4 °C), R_f 0.85 (dichloromethane–methanol, 95:5); ν_{max} (KBr)/cm^{-1} 3190 and 1166; δ_H ($CDCl_3$) 1.0–2.0 (3H, m), 2.8–3.2 (3H, m), 3.5–3.6 (1H, m), 3.9–4.1 (1H, m), 4.2–4.3 (2H, m), 7.0–7.3 (4H, m); δ_C ($CDCl_3$) 27.7, 50.5, 54.5, 126.4, 126.9, 127.7, 129.0, 131.3 and 131.5; δ_B ($CDCl_3$) −14.9 (q, *J* 81); *m*/*z* 146 ($M - 1^{+\bullet}$, [$^{12}C_9{}^1H_{13}{}^{11}B^{14}N$], 48%), 145 ($M - 1^{+\bullet}$, [$^{12}C_9{}^1H_{13}{}^{10}B^{14}N$], 15%), 132 (84), 117 (58), 104 (100), 91 (33), 78 (18) and 42 (51).

Piperidine–borane complex 16.[31] Purified with dichloromethane–methanol (95:5) as eluent to give the pure title compound **16** as a white solid (mp 82 °C, lit.[31] 81–83 °C), R_f 0.8 (dichloromethane–methanol, 95:5); ν_{max} (KBr)/cm^{-1} 3400 and 1145; δ_H ($CDCl_3$) 1.20–1.45 (4H, m), 1.48–1.85 (5H, m), 2.40–2.57 (2H, m), 3.20–3.25 (2H, m), 4.2 (1H, s, NH); δ_C ($CDCl_3$) 22.6, 25.7 and 53.4; δ_B ($CDCl_3$) −15.4 (q, *J* 89); *m*/*z* 98 ($M - 1^{+\bullet}$, [$^{12}C_5{}^1H_{13}{}^{11}B^{14}N$], 88%), 97 ($M - 1^{+\bullet}$, [$^{12}C_5{}^1H_{13}{}^{10}B^{14}N$], 28%), 84 (38) and 42 (100).

4-Benzylpiperazine–borane complex 17. Purified with dichloromethane–methanol (95:5) as eluent to give the pure title compound **17** as a white solid (mp 125 °C), R_f 0.9 (dichloromethane–methanol, 95:5); ν_{max} (KBr)/cm^{-1} 3400 and 1155; δ_H ($CDCl_3$) 1.80–2.10 (8H, m), 2.7 (1H, m), 3.2–3.25 (3H, m), 3.5 (2H, s), 7.2–7.4 (5H, m); δ_C ($CDCl_3$) 55.5, 61.2, 127.3, 128.6, 129.9 and 138.6; δ_B ($CDCl_3$) −14.3 (q, *J* 82).

Synthesis of carboxylic acids [^{11}C]1b and [^{11}C]1g:[20] general procedure

[^{11}C]Carbon dioxide was bubbled at 0 °C for 3 min through a Grignard reagent (1.47 M in THF; 0.190 cm^3, 0.275 mmol) in THF (0.1 cm^3) leading to the carboxylates [^{11}C]**18b** or [^{11}C]**18g**. The mixture was then hydrolyzed at 0 °C with NH_4Cl (saturated solution; 1.5 cm^3). After addition of a solution of NaOH (saturated solution; 1 cm^3) until pH 14, the crude reaction mixture was counted and analysed by radio TLC (Table 3). Carboxylic acids [^{11}C]**1b** (94 MBq, >99% radiochemical purity) and [^{11}C]**1g** (98 MBq, >99% radiochemical purity) were obtained respectively in 91% and 96% radiochemical yields (decay corrected to the end of bombardment starting from 150–155 MBq of [^{11}C]CO_2) within 12 min.

Synthesis of alcohols [^{11}C]20b[32] and [^{11}C]20g:[33] general procedure

To the solution of carboxylates [^{11}C]**18b** or [^{11}C]**18g** in THF prepared as described earlier, a solution of $LiAlH_4$ in THF (0.3 cm^3, 1.3 M) was added under nitrogen at 0 °C. After heating for 5 min at 70 °C, the mixture was cooled to RT and then quenched with NH_4Cl (saturated solution, 1.5 cm^3). After extraction with dichloromethane (2 cm^3), the organic and aqueous layers were separated, counted and analysed by radio TLC or GC (Table 3). Alcohols [^{11}C]**20b** or [^{11}C]**20g** and acids [^{11}C]**1b** or [^{11}C]**1g** were the only radioactive products detected respectively in the organic and aqueous layers. Alcohols [^{11}C]**20b** (139 MBq, >98% radiochemical purity) and [^{11}C]**20g** (162 MBq, >96% radiochemical purity) were obtained respectively in 45% and 52% radiochemical yields (decay corrected to the end of bombardment starting from 570–575 MBq of [^{11}C]CO_2) within 18 min.

Reductive amination of carboxylates [^{11}C]18b and [^{11}C]18g: general procedure

The carboxylates [^{11}C]**18b** or [^{11}C]**18g** in THF prepared as described earlier, were transferred under nitrogen into a second vial containing the reducing agent (0.125, 0.165, 0.375 or 0.75 mmol), a solvent (THF, HMPT, DMF or diglyme, 0.3 cm^3), and a possible salt **6** or **8** (0.032 or 0.44 mmol). After addition of the amine (0.375 mmol) and heating for 10 or 20 min at 70 or 90 °C, the mixture was cooled to RT and then quenched with 10% HCl (0.8 cm^3). After addition of NaOH (saturated solution, 1 cm^3) until pH 14 and extraction with dichloromethane (2 cm^3), the organic and aqueous layers were separated, counted and analysed by radio TLC or GC (Table 3). Acid [^{11}C]**1** was the only radioactive product detected in the aqueous layer. A mixture of amine [^{11}C]**9**,**10** and of compound [^{11}C]**19b** or [^{11}C]**19g** were revealed in the organic phase (Scheme 3, Table 2).

Preparation of [^{11}C]19b

The carboxylate [^{11}C]**18b** in THF (0.3 cm^3), prepared as described above, was transferred under nitrogen into a vial containing $NaBH_4$ (14 mg, 0.375 mmol) in a suspension in THF (1 cm^3). After heating at 70 °C for 10 min, the mixture was cooled to RT and quenched with 10% HCl (0.8 cm^3). After addition of NaOH (saturated solution, 1 cm^3) until pH 14 and extraction with dichloromethane (2 cm^3), the organic and aqueous phases were separated, counted and analysed by radio TLC (Table 3).

Acid [^{11}C]**1b** and compound [^{11}C]**19b** were the only products detected respectively in the aqueous and organic phases. Compound [^{11}C]**19b** (25 MBq, >92% radiochemical purity) was obtained in 25% radiochemical yields (decay corrected to the end of bombardment starting from 275 MBq of [^{11}C]CO_2) within 20 min.

Reductive amination *via* the formation of [^{11}C]19b

The carboxylate [^{11}C]**18b** in THF (0.3 cm^3), prepared as described above, was transferred under nitrogen into a vial containing $NaBH_4$ (14 mg, 0.375 mmol) in a suspension in THF (1 cm^3). After heating at 70 °C for 10 min, the amine **2** (0.375 mmol) was added. The mixture was heated for 10 min at 70 °C, cooled to RT and then quenched with concentrated HCl (0.8 cm^3). After addition of NaOH (saturated solution, 1 cm^3) until pH 14 and extraction with dichloromethane (2 cm^3), the organic and aqueous phases were separated, counted and analysed by radio-TLC or GC (Table 3). Analysis of the aqueous phase revealed only the presence of acid [^{11}C]**1b** whereas analysis of the organic phase (79 MBq), revealed the presence of a mixture of amine [^{11}C]**9b** and of compound [^{11}C]**19b** in a 54 : 46 ratio. Amine [^{11}C]**9b** was obtained in 27% radiochemical yield (decay corrected to the end of bombardment starting from 500 MBq of [^{11}C]CO_2) within 35 min.

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