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One-pot solvent-free reductive amination with a solid ammonium carbamate salt from CO_2 and amine†

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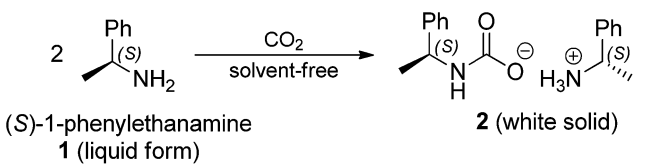
Many amines are liquid and their handling is inconvenient compared with the corresponding solids. We transformed a liquid (*S*)-(−)-1-phenylethylamine **1** to the corresponding neutral solid form **2** by reacting with carbon dioxide. We performed reductive amination of **2** with various aldehydes **3** under solvent-free conditions to provide secondary amines **5** in high yields.

Environmental issues are of growing concern and scientists are trying to eliminate extra steps in reactions and also avoid extra reagents including unwanted by-products. In typical organic reactions, large amounts of organic solvents are used universally. Even if they are recycled with suitable treatment, they contribute to environmental and energy-related problems. Many efforts have been made to design environmentally benign processes to eliminate or reduce hazardous substances during organic syntheses.[1] Among those, solvent-free condition is a very attractive from both environmental and economic points of view. Very recently, we reported some advantages of solvent-free reactions in terms of selectivity as well as reaction rates.[2]

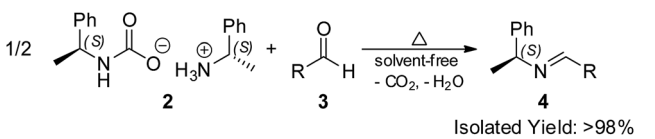
Amine is a ubiquitous functional group, whose derivatives are versatile building blocks for the synthesis of natural products, pharmaceuticals, and fine chemicals.[3] Since liquid free amines are inconvenient to handle and also prone to oxidation, it is common to convert liquid amines to the corresponding acid salts. However, this necessitates a neutralization step with a base when we need to use free amines. Alternately, the carbamic acid forms of amines have been generated by reaction with toxic or cumbersome reagents including phosgene[4] and its derivatives[5] or carbon monoxide.[6] Therefore, it is convenient to convert liquid amines to the corresponding neutral solids, which are expected to show the same reactivity as parent amine.

Carbon dioxide (CO_2) has been efficiently used as an alternative for the synthesis of carbamates.[7] Although Aresta *et al.* reported the synthesis of carbamate salts with carbon dioxide,[8] most researchers have used CO_2 for the synthesis of carbamate esters by reacting the amine, CO_2 and an electrophile such as alkyl halide, epoxide or terminal alkynes with transition metal catalysts.[9] Recently, Peeters *et al.* employed CO_2 as a temporary amine protecting group as well.[10]

In this report we demonstrate the direct use of neutral ammonium carbamate salts in solvent-free reductive amination reactions. The reductive amination reaction is useful for the synthesis of medicinally relevant enzyme inhibitors,[11] dendritic polyglycerols,[12] and highly functionalized amine derivatives.[13] Hence, the reductive amination reaction remains one of the most powerful and widely utilized transformation that allows the direct conversion of carbonyl compounds into amines using simple operations.[14] We employed previously reported methods[15,16] to prepare a stable neutral solidified ammonium



Scheme 1 Solid ammonium carbamate formation of (*S*)-(−)-1-phenylethylamine with CO_2.



Scheme 2 Solvent-free imine formation.

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† Electronic supplementary information (ESI) available: Experimental procedures, compound characterization data (^{1}H and ^{13}C NMR spectra, TGA, IR spectra, XRD data for compounds **2** as well as ^{1}H NMR and ^{13}C NMR spectra for **4a**, and **5a–5r**). CCDC 953131. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra07558g

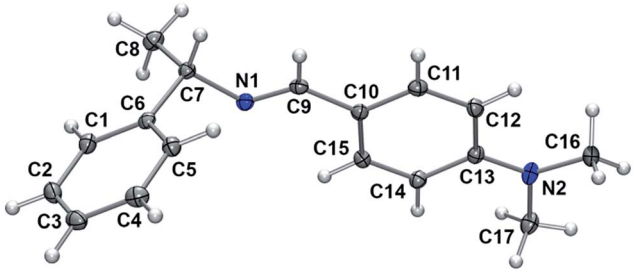
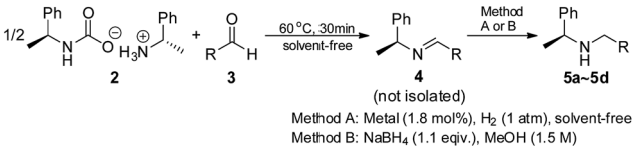


Fig. 1 ORTEP plot of (*S*,*E*)-*N*,*N*-dimethyl-4-((1-phenylethyl-imino) methyl)aniline **4a**, at 30% probability level of the thermal ellipsoids. Hydrogen atoms are not labeled for clarity.



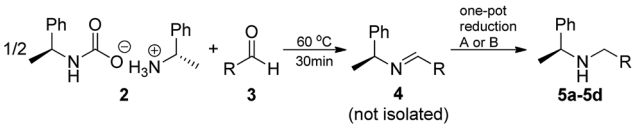
Scheme 3 One-pot solvent-free reductive amination of aldehydes.

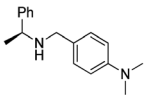
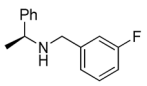
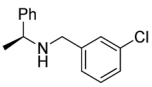
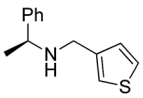
carbamate salt of (*S*)-(−)-1-phenylethylamine by reacting liquid (*S*)-(−)-1-phenyl-ethylamine with CO_2. Then we applied the solid amine equivalent to form imines using various aldehydes in the absence of solvent.[16a] We recently found that the solid amine formation could be successfully performed with dry ice (solid CO_2) at 1 atm and 50 mmol scale reductive amination also proceeded without any difficulties.[16b,c] We carried out the catalytic hydrogenation of the imines with Adams' catalyst (PtO_2) under 1 atm of H_2 without solvents. Here, we report a highly effective, convenient and environmentally benign process for the preparation of secondary amines *via* one-pot solvent-free reductive amination of aldehydes.

We prepared a stable solid (*S*)-(−)-1-phenylethylamine carbamate ammonium salt **2** by reacting liquid (*S*)-(−)-1-phenylethylamine **1** with CO_2 to produce a white solid (Scheme 1) and this salt is stable enough to store at room temperature in air.[2]

We proposed the structure of the salt **2** based on the following observations: 1 equiv. of **2** reacted with 2 equiv. of an aldehyde to give the corresponding imine as the sole product. Additionally, we characterized **2** by elemental analysis, ^{1}H NMR, ^{13}C NMR, thermal gravimetric analysis (TGA), IR spectroscopy, and X-ray powder diffraction (XRD) (ESI Fig. S1–S4†). TGA data for **2** show that **2** completely disappears above 105 °C (ESI Fig. S3†), indicating that **2** is sublimed below that temperature. Interestingly, the boiling point of **1** is 187 °C, which is much higher than the sublimation temperature of the solid congener **2**. The sublimation of **2** is presumably due to the easy dissociation of CO_2 in **2**. Decarboxylation of **2** liberates free amine,

Table 1 One-pot solvent-free reductive amination *via* catalytic hydrogenation with various catalysts[a]

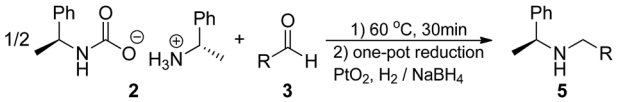


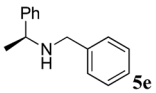
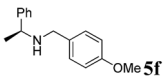
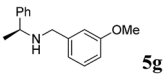
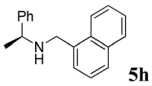
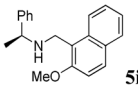
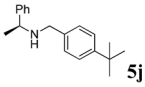
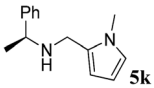
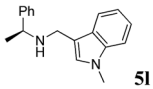
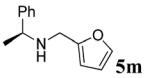
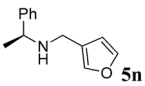
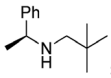
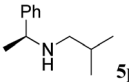
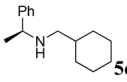
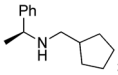
Entry	Aldehyde **3**	Product **5**	Reducing agent[b]	Time[c] (h)	Yield[d] (%)
1	4-(Dimethylamino)-benzaldehyde **3a**	 **5a**	PtO_2	16	90
			Pt/C	12	85
			Pd/C	6	49
			$NaBH_4$	0.5	87
2	3-Fluoro-benzaldehyde **3b**	 **5b**	PtO_2	14	97
			Pt/C	20	89
			Pd/C	14	98
			$NaBH_4$	0.5	91
3	3-Chloro-benzaldehyde **3c**	 **5c**	PtO_2	14	95
			PtO_2[e]	26	91
			PtO_2[f]	7	94
			Pt/C	20	92
			Pd/C	36	48
			$NaBH_4$	0.5	88
4	3-Thiophene-carboxaldehyde **3d**	 **5d**	PtO_2[g]	20	96
			Pt/C[g]	20	38
			Pd/C[g]	20	5
			$NaBH_4$	0.5	91

[a] Method A: solvent-free catalytic hydrogenation, Method B: stoichiometric reduction with $NaBH_4$ in MeOH. [b] Metal catalyst (1.8 mol%), $NaBH_4$ (1.1 equiv.), MeOH (1.5 M, 0.67 mL) at 25 °C. [c] Reaction time for hydrogenation or reduction of imine. [d] Isolated yield. [e] 0.60 mol%. [f] 2.9 mol%. [g] At 40 °C.

which is less likely to experience close interaction among themselves, unlike neat liquid amine. This supports remarkably high reactivity of **2** towards aldehydes even in the solid state. Upon heating the mixture (>60 °C) of solidified amine **2** and aldehyde without stirring, **2** is converted to the reactive free amine, which readily reacts with an aldehyde to yield the corresponding imine.

Table 2 One-pot reductive amination with diverse aldehydes using PtO_2 and $NaBH_4$



Entry	Aldehyde **3**	Product **5**	Time[a] (h)	Yield[b] (%)
1	Benzaldehyde **3e**[c]	 **5e**	10/0.5	98[d]/93[e]
2	4-Anisaldehyde **3f**[c]	 **5f**	13/0.5	97[d]/96[e]
3	3-Methoxy-benzaldehyde **3g**[c]	 **5g**	13/0.5	95[d]/87[e]
4	1-Naphthaldehyde **3h**[c]	 **5h**	26/0.5	95[d]/95[e]
5	2-Methoxy-1-naphthaldehyde **3i**[f]	 **5i**	26/0.5	96[d]/96[e]
6	4-*tert*-Butyl-benzaldehyde **3j**[c]	 **5j**	8/0.5	97[d]/90[e]
7	1-Methylpyrrole-2-carboxaldehyde **3k**[c]	 **5k**	15/0.5	93[d]/88[e]
8	1-Methylindole-3-carbaldehyde **3l**[f,g]	 **5l**	43/0.5	96[d]/84[e]
9	2-Furaldehyde **3m**[c]	 **5m**	30/0.5	95[d]/96[e]
10	3-Furaldehyde **3n**[c]	 **5n**	35/0.5	93[d]/94[e]
11	Trimethylacetaldehyde **3o**[c]	 **5o**	3/0.5	96[d]/93[e]
12	Isobutyraldehyde **3p**[c]	 **5p**	3/0.5	98[d]/92[e]
13	Cyclohexanecarbox-aldehyde **3q**[c]	 **5q**	3/0.5	92[d]/88[e]
14	Cyclopentanecarbox-aldehyde **3r**[c]	 **5r**	3/0.5	93[d]/84[e]

[a] Reaction time for catalytic hydrogenation/$NaBH_4$ reduction of imine. [b] Isolated yield. [c] Imine synthesis: 60 °C, 30 min. [d] Yield of catalytic hydrogenation using PtO_2 (1.8 mol%). [e] Yield of reduction with $NaBH_4$ (1.1 equiv.) and MeOH (1.5 M, 0.67 mL). [f] Imine synthesis: 100 °C, 1 h. [g] Trace amount of MeOH (20–30 μL) was added for mixing of the corresponding imine and PtO_2 catalyst.

Solvent-free imine formation was achieved by combining the solidified amine **2** and aldehydes **3** with 1 : 2 molar ratio and warming the mixture to 60 or 100 °C under air without stirring (Scheme 2). We observed water formation within 20 min, which was the sign of the conversion of the aldehyde to the corresponding imine **4** by dehydration. We did the comparison experiments with a 1 : 1 mixture of neat (*S*)-1-phenylethylamine and aldehydes to obtain the corresponding imine with some side products. The reason for the clean reaction with the solid amine equivalent is the presence of a small amount of the amine in the reaction mixture from the gradual decarboxylation of the ammonium salt upon heating the mixture. As a representative example of the imine formation reactions, 2 equiv. of 4-(dimethylamino)benzaldehyde **3a** was reacted with 1 equiv. of **2**, to produce (*S*,*E*)-*N*,*N*-dimethyl-4-((1-phenylethylimino)-methyl)aniline **4a** almost quantitatively without any side product.‡

We confirmed the structure of the imine **4a** using a single crystal X-ray diffraction (see ESI Table S1–S3†). Single crystals for the diffraction study were grown from a methylene chloride–hexane (1 : 4) solution. Fig. 1 shows the ORTEP diagram of **4a**, which is based on the amine and aldehyde units linked by an imine (–N=C–) group, and the configuration of **1** (*S*) has not been changed during the formation of this imine *via* compound **2**.

The bond distance of N1–C9 in the imine group is 1.266 Å which is similar to those of typical N=C double bonds.[17,18] The bond angles of C7–N1–C9 and N1–C9–C10 are 117.00° and 123.50°, respectively (see Table S2 and S3,† ESI). Detailed data are presented in Table S3 (see ESI†).

After obtaining the imine **4** from the reaction of 1 equiv. of solidified amine **2** with 2 equiv. of aldehyde **3**, a catalytic amount of PtO_2, Pt/C, or Pd/C was added with an atmospheric pressure of H_2. The one-pot catalytic hydrogenation proceeded in the absence of solvent to produce the secondary amine in high yields.[19] For comparison, the reduction of the imine with 1.1 equiv. of $NaBH_4$ was conducted in the presence of MeOH (1.5 M, 0.67 mL) (Scheme 3) and those results were summarized in Table 1. Table 1 shows that PtO_2 is better than Pt/C and Pd/C in terms of reaction time and chemical yield. The entire reaction proceeded in the absence of solvent, which resulted in secondary amines smoothly even in the case of solid imines (Table 1, entry 1). Although reduction with $NaBH_4$ was completed within 0.5 h, it was performed in MeOH to mix the imine and $NaBH_4$, which led to extra purification step. When we used 4-(dimethylamino)-benzaldehyde **3a** and Pd/C, we obtained 49% yield of the desired product **5a** with 41% of the debenzylation product, 4-(aminomethyl)-*N*,*N*-dimethylaniline.[20] On the other hand, using PtO_2 and Pt/C catalysts under the same conditions provided much higher yield without forming the over reduction product (Table 1 entry 1). In addition, Pd/C is not appropriate in the reaction with halogen substituted aromatic aldehyde due to the hydrogenolysis of the halogen (Table 1, entry 3).[21] For imines containing sulfur, catalytic hydrogenation proceeded with 5% conversion using Pd/C and 38% with Pt/C. The low conversions are mainly due to the poisoning of Pd and Pt surfaces by sulfur. However, the PtO_2 catalyst provided high yield as anticipated (Table 1, entry 4).[22] Furthermore, it seems that the amount of PtO_2 is related to reaction time: when 2.9 mol% of PtO_2 was used, reaction was completed in 7 h, giving 94% yield; otherwise using 0.60 mol% of PtO_2 took 26 h with 91% yield (Table 1, entry 3).

We extended this solvent-free PtO_2 reduction system to other aldehydes since PtO_2 provides better results in reducing functionalized imines. Reaction time is not affected by placement of –OMe substituents on aromatic rings (Table 2, entries 2 and 3). The fused ring system, naphthyl, significantly retards the catalytic hydrogenation (Table 2, entries 4 and 5) while alkyl substitution on the phenyl ring speeds catalytic hydrogenation (Table 2, entry 6). In case of the heteroaromatic rings such as pyrrole, indole, and furan give a much slower reaction rate (Table 2, entries 7–10). On the other hand, aliphatic imines are converted to secondary amines within short reaction time (Table 2, entries 11–14).

We demonstrated that a solidified amine **2**, prepared from the reaction of a liquid amine with CO_2, could be used as a stable precursor for the reductive amination process. The overall reaction proceeded in one-pot and solvent-free condition and we successfully tested the reaction with a variety of aldehydes. This reaction system is convenient and environmentally benign to be a general method for reductive amination with a wide range of aldehydes.[23]

Acknowledgements

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Notes and references

‡ X-ray crystallographic data for (*S*,*E*)-*N*,*N*-dimethyl-4-(((1-phenylethyl)imino)methyl)aniline **4a**: $C_{17}H_{20}N_2$, monoclinic, $P2(1)$, $Z = 2$, $a = 8.5299(3)$, $b = 6.0689(2)$, $c = 13.7293(5)$ Å, $\beta = 91.554(2)°$, $V = 710.46(4)$ Å^3, $\mu = 0.070$ mm^{-1}, $\rho_{calcd} = 1.180$ g cm^{-3}, $R_1 = 0.0353$, and $wR_2 = 0.0930$ for 3410 unique reflections and 175 variables.

1 (*a*) Y. Monguchi, Y. Fujita, S. Hashimoto, M. Ina, T. Takahashi, R. Ito, K. Nozaki, T. Maegawa and H. Sajiki, *Tetrahedron*, 2011, **67**, 8628; (*b*) P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University, Oxford, 1998; (*c*) J. Bonnamour, T.-X. Métro, J. Martinez and F. Lamaty, *Green Chem.*, 2013, **15**, 1116; (*d*) M. Li, X.-L. Lv, L.-R. Wen and Z.-Q. Hu, *Org. Lett.*, 2013, **15**, 1262.
2 B. Lee, P. Kang, K. H. Lee, J. Cho, W. Nam, W. K. Lee and N. H. Hur, *Tetrahedron Lett.*, 2013, **54**, 1384.
3 (*a*) E. M. Brzostowska and A. Greer, *J. Am. Chem. Soc.*, 2003, **125**, 396; (*b*) T. Doi, M. Yoshida, K. Shin-ya and

T. Takahashi, *Org. Lett.*, 2006, **8**, 4165; (*c*) X. Feng, S. Chen, Y. Xu, W. Du, Q. Luo and B.-F. Liu, *J. Sep. Sci.*, 2008, **31**, 824.

4 D. P. N. Satchell and R. S. Satchell, *Chem. Soc. Rev.*, 1975, **4**, 231.

5 S. Raucher and D. S. Jones, *Synth. Commun.*, 1985, **15**, 1025.

6 (*a*) T. W. Leung and B. D. Dombek, *J. Chem. Soc., Chem. Commun.*, 1992, 205; (*b*) T. Mizuno, J. Takahashi and A. Ogawa, *Tetrahedron*, 2002, **58**, 7805.

7 (*a*) D. Chaturvedi and S. Ray, *Monatsh. Chem.*, 2006, **137**, 127; (*b*) E. Quaranta and M. Aresta, *Carbon Dioxide as Chemical Feedstock*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2010, and references cited therein.

8 (*a*) M. Aresta and E. Quaranta, *Tetrahedron*, 1992, **48**, 1515; (*b*) M. Aresta, D. Ballivet-Tkatchenko, D. B. Dell'Amico, M. C. Bonnet, D. Boschi, F. Calderazzo, R. Faure, L. Labella and F. Marchetti, *Chem. Commun.*, 2000, 1099.

9 (*a*) Y. Yoshida, S. Ishii and T. Yamashita, *Chem. Lett.*, 1984, 1571; (*b*) Y. Yoshida, S. Ishii, M. Watanabe and T. Yamashita, *Bull. Chem. Soc. Jpn.*, 1989, **62**, 1534; (*c*) Y. Yoshida and S. Inoue, *Chem. Lett.*, 1978, 139; (*d*) Y. Yoshida and S. Inoue, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 559; (*e*) Y. Yoshida and S. Inoue, *J. Chem. Soc., Perkin Trans. 1*, 1979, 3146; (*f*) F. Kojima, T. Aida and S. Inoue, *J. Am. Chem. Soc.*, 1986, **108**, 391; (*g*) W. D. McGhee, D. P. Riley, M. E. Christ and K. M. Christ, *Organometallics*, 1993, **12**, 1429; (*h*) M. Aresta and E. Quaranta, *Chem.Tech.*, 1997, **27**, 32; (*i*) P. G. Jessop, T. Ikariya and R. Noyori, *Chem. Rev.*, 1995, **95**, 259.

10 A. Peeters, R. Ameloot and D. E. De Vos, *Green Chem.*, 2013, **15**, 1550.

11 J. Samanen, T. Cash, D. Narindray, E. Brandeis, W. Adams Jr, H. Weideman, T. Yellin and D. Regoli, *J. Med. Chem.*, 1991, **34**, 3036.

12 F. Koç, M. Wyszogrodzka, P. Eilbracht and R. Haag, *J. Org. Chem.*, 2005, **70**, 2021.

13 (*a*) V. I. Tararov, R. Kadyrov, T. H. Riermeier and A. Börner, *Chem. Commun.*, 2000, 1867; (*b*) R. Apodaca and W. Xiao, *Org. Lett.*, 2001, **3**, 1745; (*c*) B. Basu, S. Jha, Md. M. H. Bhuiyan and P. Das, *Synlett*, 2003, 555; (*d*) T. Gross, A. M. Seayad, M. Ahmad and M. Beller, *Org. Lett.*, 2002, **4**, 2055; (*e*) K. Miura, K. Ootsuka, S. Suda, H. Nishikori and A. Hosomi, *Synlett*, 2001, 1617; (*f*) I. Shibata, T. Suwa, E. Sugiyama and A. Baba, *Synlett*, 1998, 1081.

14 B. Sreedhar, P. S. Reddy and D. K. Devi, *J. Org. Chem.*, 2009, **74**, 8806.

15 (*a*) B. Lee, S. H. Kang, D. Kang, K. H. Lee, J. Cho, W. Nam, O. H. Han and N. H. Hur, *Chem. Commun.*, 2011, **47**, 11219; (*b*) B. Lee, K. H. Lee, J. Cho, W. Nam, O. H. Han and N. H. Hur, *Org. Lett.*, 2011, **13**, 6386.

16 (*a*) B. Lee, K. H. Lee, B. Y. Lim, J. Cho, W. Nam and N. H. Hur, *Adv. Synth. Catal.*, 2013, **355**, 389; (*b*) Preparation of **2** in multi gram scale. A glass vial was charged with 6.1 g (50 mmol) of (*S*)-1-phenylethanamine **1** and dry ice (20 g). After 1 hour, the liquid (*S*)-1-phenylethanamine **1** was transformed to a white solid powder of **2** quantitatively. The weight change from **1** to **2** was 1.1 g which means CO_2 (25 mmol) reacted with **1** in 2 : 1 ratio; (*c*) 4-Anisaldehyde (4.76 g, 4.30 mL, 2.00 mmol) was placed in a round-bottomed flask and the solidified amine **2** (5.00 g, 1.00 mmol) was added. The flask was warmed to 60 °C for 6 hours and the condensed water vapor was wiped then allowed to cool to room temperature. To the flask was added PtO_2 (198 mg, 5 mol%) and the hydrogenation proceeded at room temperature under 1 atm of H_2 for 15 hours to provide 95% of the reductive amination product with no side product.

17 (*a*) N. Arai, N. Utsumi, Y. Matsumoto, K. Murata, K. Tsutsumi and T. Ohkuma, *Adv. Synth. Catal.*, 2012, **354**, 2089; (*b*) J. Waser, B. Gaspar, H. Nambu and E. M. Carreira, *J. Am. Chem. Soc.*, 2006, **128**, 11693; (*c*) J. F. Larrow, E. N. Jacobsen, Y. Gao, Y. Hong, X. Nie and C. M. Zepp, *J. Org. Chem.*, 1994, **59**, 1939; (*d*) H. N. Khatri, *U.S. Pat.*, 4997945, 1991.

18 H.-K. Fun, H. Kargar and R. Kia, *Acta Crystallogr., Sect. E: Struct. Rep. Online*, 2008, **64**, o1894.

19 (*a*) B. T. Cho and S. K. Kang, *Tetrahedron*, 2005, **61**, 5725; (*b*) B. T. Cho and S. K. Kang, *Synlett*, 2004, **9**, 1484.

20 S. Ram and L. D. Spicer, *Synth. Commun.*, 1987, **17**, 415.

21 (*a*) M. A. Aramendía, V. Borau, I. M. García, C. Jiménez, A. Marinas, J. M. Marinas and F. J. C. Urbano, *R. Acad. Sci. Paris, Série IIc.*, 2000, **3**, 465; (*b*) F. J. Urbano and J. M. Marinas, *J. Mol. Catal. A: Chem.*, 2001, **173**, 329; (*c*) B. Sreedhar and V. S. Rawat, *Synth. Commun.*, 2012, **42**, 2490.

22 (*a*) P. Albers, J. Pietsch and S. F. Parker, *J. Mol. Catal. A: Chem.*, 2001, **173**, 275; (*b*) J. K. Dunleavy, *Platinum Met. Rev.*, 2006, **50**, 110.

23 We also prepared many ammonium carbamate salts from various alkyl primary amines successfully. However, we could not prepare stable salts from secondary amines and aromatic amine.