Tetrahedron Letters 55 (2014) 1379–1383

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A novel one-pot synthesis of oxazolidinones through direct introduction of CO_2 into allylamine derivatives

Laura Soldi, Chiara Massera, Mirco Costa, Nicola Della Ca' *

Dipartimento di Chimica and CIRCC, Parco Area delle Scienze 17/A, I-43124 Parma, Italy

ARTICLE INFO

Article history:
Received 21 November 2013
Revised 20 December 2013
Accepted 8 January 2014
Available online 15 January 2014

Keywords:
Oxazolidinone
Allylamine
Carbon dioxide fixation
One-pot synthesis
Supercritical fluids

ABSTRACT

1,3-Oxazolindin-2-one derivatives were obtained for the first time through carboxylative cyclization of allylamines in the absence of any metal or base catalyst. An electron-withdrawing substituent on the allylic double bond is crucial for the reaction success. Allylamines react with CO_2 in MeCN/MeOH mixture and in $scCO_2$ giving satisfactory results.

The efficient reconversion of carbon dioxide into organic molecules is currently one of the most important targets in synthetic organic chemistry. Since CO_2 is an ubiquitously available raw material, its utilization in the production of fine-chemicals, fuels, and materials is of considerable interest.[1] Environmentally impacting processes, such as those concerning the synthesis of organic carbonates, methanol, or some pharmaceutical specialities, could be replaced by more friendly methodologies based on the use of CO_2.

The widespread use of oxazolidin-2-ones as chiral auxiliaries and antimicrobials since their first report in 1981[2] induced many researchers to look for new ways for their preparation avoiding the traditional and more direct ones between amino alcohols and either phosgene or diethyl carbonate. Over the years attractive synthetic methodologies based on the use of carbon oxides have been developed. Thus, oxazolidin-2-ones were obtained in excellent yields with high catalytic efficiencies by direct PdI_2/KI-catalyzed oxidative carbonylation of the readily available 2-amino-1-alkynols.[3] CO_2 has been also employed as source for oxazolidinone formation. In fact the direct addition of CO_2 to β-amino alcohols at high pressure and temperature to give these target compounds has been reported for the first time in 1959.[4] More recently, many researchers described the efficient conversion of aziridines into oxazolidinones by CO_2 incorporation[5] even in the absence of catalysts and/or under supercritical conditions.[6] Moreover, 5-methylene-1,3-oxazolidin-2-ones can be obtained by either reacting alkynes, primary amines, and CO_2 in the presence of copper(I) catalyst under solvent-free conditions[7] or starting from N-substituted propargylamines and CO_2 using ruthenium, copper, or silver complexes as catalysts.[8] Some years ago we reported the direct introduction of CO_2 into secondary acetylenic amines, via intramolecular cyclization to 5-methylene-1,3-oxazolidin-2-ones in the absence of metals.[9] The reaction is based on the formation of carbamate salts in the presence of catalytic amounts of strong organic bases such as pentaalkylguanidines. Subsequently, secondary propargyl amines were found to react smoothly with CO_2 under supercritical conditions to give 5-methyleneoxazolidinones even in the absence of any metal or base catalyst.[10]

On the ground of the reported behavior of the N-substituted propargyl amines with CO_2,[9,10] we verified the feasibility of incorporating CO_2 into allylamines in order to obtain oxazolidin-2-ones. The addition of carbamic acid derivatives to C=C double bonds has been scarcely investigated. We mention for example the stoichiometric transformation of ammonium carbamates and cyclic diolefins bound to a Pd center,[11] and a three-component reaction involving CO_2, secondary amines, and vinyl ethers.[12] In general catalysts, such as palladium or guanidine bases, or iodo derivatives, such as iodine or *t*BuOI, are mandatory to enable the reaction between allylamines and CO_2.[13]

We now report a convenient one-pot synthesis of oxazolidin-2-ones through the direct incorporation of carbon dioxide into allylamine derivatives in the absence of any base or catalyst.

In our initial study allylamines were allowed to react in an autoclave under 40 bar of CO_2 (measured at room temperature) at 90 °C for 24 h in MeCN, MeOH, and their mixtures. While allylamines

* Corresponding author. Tel.: +39 0521 905676; fax: +39 0521 905472.
E-mail address: nicola.dellaca@unipr.it (N. Della Ca').

0040-4039/$ - see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2014.01.029

bearing hydrogen, alkyl, or aryl groups on the terminal carbon of the double bond (R^1 = H, alkyl, aryl) failed to react, on the contrary, very good results were obtained for the first time with an alkoxycarbonyl moiety as an activating substituent (EWG). At first the reaction of substrate **1a** with CO_2 was considered in order to find out the appropriate conditions (Table 1). Only moderate yield of **2a** was obtained in pure MeCN while even worse in pure MeOH. Mixtures with different MeCN/MeOH vol/vol ratio were also tested and, in particular, those with MeCN/MeOH in 1:1 (vol/vol) ratio led to an excellent result (Table 1, entry 3). In addition, CO_2 pressure affects positively the yield of **2a** until 40–50 bar, when a plateau is reached (Table 1, entries 3 and 6–8).

The aprotic polar solvent MeCN, able to dissolve the carbamate salt formed from secondary allylamines, carbon dioxide and the same protonated amine, promotes its dissociation by stabilization of the ammonium cation and simultaneously frees up its counterpart (the carbamate anion) promoting the intramolecular nucleophilic attack of the double bond. On the other hand, the protic polar solvent is able to dissolve a larger amount of CO_2. The mixture causes a beneficial effect on the process.

Allylamines with R^1 and R^2 of different nature were caused to react under the previously optimized reaction conditions.[14] The results, reported in Table 2, show that an EWG on the double bond is crucial for the success of the reaction. Substrates bearing the CO_2Me moiety on the double bond, such as **1a**, **1b**, and **1d**, gave excellent yields of the corresponding products **2a**, **2b**, and **2d** (Table 2, entries 1, 2, 5 and 6). A confirmation of the structure of compound **2b** (5-(carbomethoxymethyl)-3-cyclohexyloxazolidin-2-one) was obtained by the X-ray diffraction analysis on a single crystal (Fig. 1).

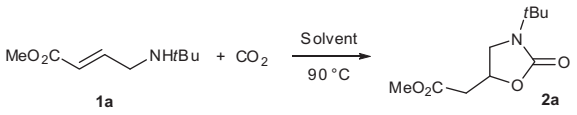
The substrate **1c**, in spite of the presence of the CO_2Me group, showed a lower reactivity (Table 2, entry 3) even at a higher temperature (Table 2, entry 4) probably owing to the sterically encumbered NR^2 moiety combined with its lower basicity. On the other hand, it was proved that substrate **1e** did not react under the reported conditions, recovering the unconverted reagent (entry 7). Only a strong EWG on the double bond was able to promote the cyclization step and to this end an aryl bearing a nitro group in *ortho* or in *para* position was employed as R^1 substituent. The substrate **1f** (R^1 = 2-nitrophenyl, R^2 = *t*Bu) was caused to react under the same conditions leading to product **2f** in low yield (entry 8). Substrate **1g** showed an analogous behavior (entry 9), even at higher temperature (110 °C, entry 10). The nitro group in *ortho* position could interfere with the amine moiety preventing the carbamate formation and consequently the cyclization. Carboxylation reactions carried out with **1h** and **1i**, bearing a nitro substituent in *para* position, led to better yields of the corresponding oxazolidinone derivatives **2h** and **2i** (Table 2, entries 11 and 12).

The formation of carbamate anions through CO_2 addition to a secondary amine, taking place under widely different conditions of temperature and CO_2 pressure, is the first step of the process. Its concentration and stability are determined by the nature of both the counterion and the solvent.[15] The tendency of the oxygen of the carbamate anion to attack the C=C unsaturation leading to an intramolecular cyclization, is favored by the electrophilic character of the double bond. Moreover, the substrate reactivity is influenced by R^2 substituents, in fact a more electron withdrawing group (R^2 = $MeCHCO_2Me$, Table 2, entry 4) is less effective than other alkyl substituents, probably because of the reduced nucleophilicity of the nitrogen atom.

At this point we considered the possibility to eliminate the organic solvent mixture, carrying out the reactions in supercritical CO_2 ($scCO_2$) due to its tunable intrinsic properties such as polarity, density, and environmental advantages.[16] Its behavior can affect the solubility of organic compounds and, as a consequence, the reaction course. The dense CO_2 medium can facilitate the formation of carbamic acid intermediates, leading to a marked improvement of the cyclic urethane formation. The increased activity in $scCO_2$ is not unprecedented. Recently, efficient syntheses of urethanes have been achieved by using $scCO_2$ as reactant and reaction medium.[17] However, the CO_2 chemical fixation under $scCO_2$ conditions often needs longer reaction times extending to several hours the achievement of satisfactory results.[16] Preliminary experiments, carried out with $scCO_2$ as both reagent and reaction medium, showed that the best yields were obtained at 80–90 bar of CO_2 pressure. The reaction of allylamines **1a–i** (2.0 mmol) and 12 g of liquid CO_2 was performed into a stainless steel autoclave under stirring (45 mL) at 110 °C for 48–72 h. The results collected in the Table 3 show that in $scCO_2$ substrates **1a**, **1b**, and **1d** (Table 3, entries 1, 2, 4 and 5) gave yields slightly better with respect to the ones obtained in MeCN/MeOH mixtures, while with substrates **1c**, **1f–i** (Table 3, entries 3 and 7–10) a noticeable increase of the yields was achieved. Improvement of the reaction performance may lie in increasing the density of $scCO_2$ and the solvation effect, eventually leading to a liquid phase able to dissolve the reactants and ammonium carbamate salts derived from CO_2, where the neat reaction might proceed. As previously reported, no product was obtained with substrate **1e** (Table 3, entry 6).

Substrates **1d**, **1g**, and **1i**, containing a chiral (±) center in R^2 group, reacted with CO_2 leading to two diastereoisomers of oxazolidinone derivatives in 1:1 molar ratio (Table 2, entries 3, 5, 9, 10 and 12). The evidence for a diastereoselective control in the

Table 1
Optimization of reaction conditions for the synthesis of **2a**[a]

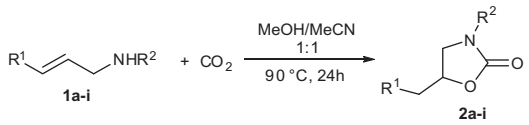


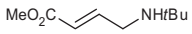
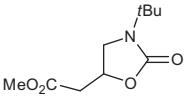
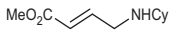
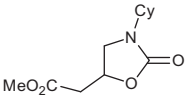
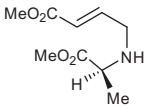
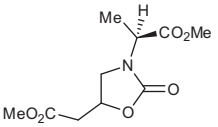
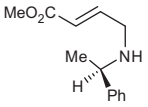
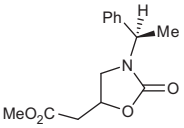
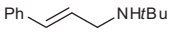
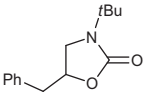
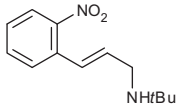
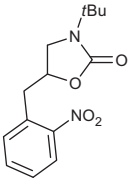
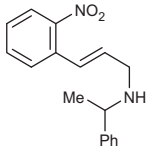
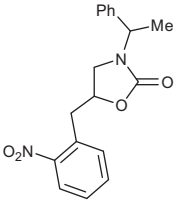
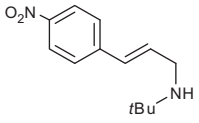
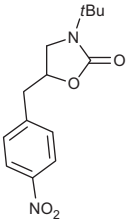
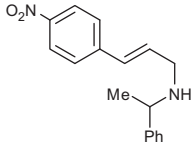
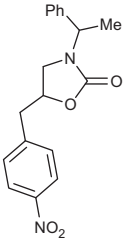
1a **2a**

Entry	MeCN (ml)	MeOH (ml)	CO_2 (bar)	Conversion[b] of **1a** (%)	Yield[b] of **2a** (%)
1	4	—	40	90	42
2	3	1	40	92	61
3	2	2	40	96	92
4	1	3	40	90	23[c]
5	—	4	40	87	6[c]
6	2	2	20	82	74
7	2	2	30	94	87
8	2	2	50	96	91

[a] Reaction and conditions: **1a** (2.0 mmol), MeOH/MeCN (4.0 mL, 1/1 vol/vol), CO_2 (pressure measured at room temperature), 90 °C, 24 h.
[b] Determined by ^{1}H NMR.
[c] Residual unknown oligomeric material was present in the crude reaction mixture.

Table 2
Synthesis of *N*-alkyl-1,3-oxazolidin-2-one derivatives **2** from allylamines **1** and CO_2[a]



Entry	Substrate **1**	T (°C)	Conv.[b] of **1** (%)	Product **2**	Yield[b,c] of **2** (%)
1	**1a** 	90	96		**2a** 92(86)[c]
2	**1b** 	90	98		**2b** 95(88)[c]
3	(L)-**1c** 	90	68		**2c** 35[d]
4	(L)-**1c**	110	49		**2c** 44[d]
5	**1d** 	90	93		**2d** 88[e](81)[c]
6	(R)-**1d**	90	96		**2d** 77[e](70)[c]
7	**1e** 	90	0		**2e** 0
8	**1f** 	90	35		**2f** 18
9	**1g** 	90	15		**2g** 14
10	**1g**	110	18		**2g** 15[e]
11	**1h** 	90	60		**2h** 51
12	**1i** 	90	60		**2i** 31[e]

[a] Reaction conditions: **1** (2.0 mmol), MeOH/MeCN (4.0 mL, 1/1 vol/vol), CO_2 (45–60 bar, measured at room temperature), 24 h.
[b] Determined by ^1H NMR.
[c] Isolated yield.
[d] A 1.5:1 mixture of two diastereoisomers.
[e] A 1:1 mixture of two diastereoisomers.

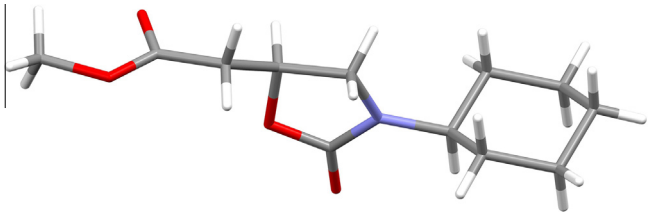


Figure 1. Single-crystal X-ray diffraction analysis for **2b**.

Table 3
Synthesis of *N*-alkyl-1,3-oxazolidin-2-one derivatives **2** from allylamines **1** and CO_2 in $scCO_2$[a]

Entry	**1**	*P*[b] (bar)	Time (h)	Conv.[c] of **1** (%)	Yield[c] of **2** (%)
1	**1a**	90	48	100	**2a** 98(96)
2	**1b**	98	48	100	**2b** 96(94)
3	(*L*)-**1c**	86	72	80	**2c** 64(60)[d]
4	**1d**	92	72	89	**2d** 75(71)[e]
5	(*R*)-**1d**	92	72	94	**2d** 73(69)[e]
6	**1e**	94	72	0	2e 0
7	**1f**	90	72	93	**2f** 83(78)
8	**1g**	86	72	91	**2g** 80(76)[e]
9	**1h**	86	72	100	**2h** 99(97)
10	**1i**	88	72	93	**2i** 83(78)[e]

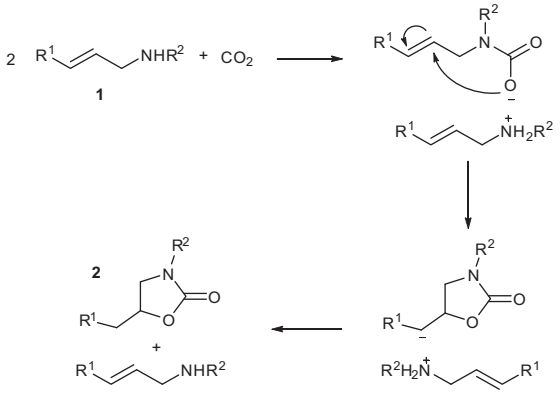
[a] Reaction conditions: **1** (2.0 mmol), liquid CO_2 (12.0 g), 24 h, 110 °C.
[b] Pressure at reaction temperature.
[c] Determined by ^1H NMR (isolated yield in brackets).
[d] A 1.5:1 mixture of two diastereoisomers.
[e] A 1:1 mixture of two diastereoisomers.

synthesis could be provided starting from (*L*)-**1c** and (*R*)-**1d** obtained using the corresponding chiral amines, such as (*L*)-alanine methyl ester and (*R*)-methylbenzyl amine, respectively. In both cases two diastereoisomers were obtained and the relative quantities were determined by gas chromatographic and ^1H NMR analyses. With the substrate (*L*)-**1c** a moderate excess of one diasteroisomer (1.5:1 in molar ratio) was observed (Table 2, entries 3 and 4 and Table 3, entry 3), whereas with the substrate (*R*)-**1d** the two diastereoisomers were present at about the same amount (Table 2, entry 6 and Table 3, entry 5). These results prove that, with regard to substrates (*L*)-**1c** and (*R*)-**1d**, only a poor influence of the chiral center bonded to the nitrogen (R^2) was produced, probably because it is too far from the prochiral center.

The selective formation of *N*-alkyl-1,3-oxazolidin-2-one derivatives **2** implies that the reaction mechanism involves a base-assisted nucleophilic attack of the carbamate anion[18] to an activated C=C double bond, leading to the intramolecular cyclization. Under CO_2 atmosphere, the starting amine **1** is in equilibrium with the corresponding ammonium carbamate; an intramolecular nucleophilic attack of the carbamate anion to the internal carbon of the double bond, generates a cyclic carbanion which, due to its major basicity, is neutralized by the ammonium counterpart, providing compound **2** (Scheme 1).

The importance of this kind of compounds is further remarked by the fact that products **2a–d** can be easily converted to useful intermediate employed for the synthesis of the biologically active 4-amino-3-hydroxy butanoic acid (GABOB).[19]

In summary, an efficient synthesis of 1,3-oxazolidin-2-one derivatives by carboxylative cyclization of allylamines in the absence of any metal or base catalyst has been proposed for the first time. An EWG on the allylic double bond is necessary for the reaction success, whereas substituents able to increase the amine basicity can help the process. Allylamines react with CO_2 in MeCN/MeOH mixture and in $scCO_2$ with very satisfactory results. The latter procedure gives excellent results and provides an effective and



Scheme 1. Formation pathway for oxazolidinones **2**.

straightforward method for the green synthesis of substituted five membered cyclic urethanes useful as intermediates in many research fields.

Acknowledgments

This work was supported by MIUR and Parma University. The NMR instrumentation was provided by Centro Interdipartimentale 'Giuseppe Casnati' of Parma University.

Supplementary data

Supplementary data (experimental details and the characterization data for starting materials **1a–i** and products **2a–i**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.029.

References and notes

1. (a)*Carbon Dioxide as Chemical Feedstock*; Aresta, M., Ed.; Wiley-VCH: Weinheim, 2010; (b) Aresta, M.; Dibenedetto, A. *Dalton Trans.* **2007**, 2975–2992; (c) Darensbourg, D. J. *Chem. Rev.* **2007**, *107*, 2388–2410; (d) Ackermann, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3842–3844; (e) Zhang, Y.; Riduan, S. N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6210–6212; (f) Liu, A.-H.; Li, Y.-N.; He, L.-N. *Pure Appl. Chem.* **2012**, *84*, 581–602.
2. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
3. (a) Gabriele, B.; Mancuso, R.; Salerno, G.; Costa, M. *J. Org. Chem.* **2003**, *68*, 601–604; (b) Gabriele, B.; Salerno, G.; Brindisi, D.; Costa, M.; Chiusoli, G. P. *Org. Lett.* **2000**, *2*, 625–627.
4. (a) Lynn, J. W. U.S. Patent 2,975,187, 1961; (b) Steele, A. B. U.S. Patent 2,868,801, 1959.
5. (a) Song, Q.-W.; Zhao, Y.-N.; He, L.-N.; Gao, J.; Yang, Z.-Z. *Curr. Catal.* **2012**, *1*, 107–124; (b) Wu, Y.; Liu, G. *Tetrahedron Lett.* **2011**, *52*, 6450–6452.
6. (a) Phung, C.; Ulrich, R. M.; Ibrahim, M.; Tighe, N. T. G.; Lieberman, D. L.; Pinhas, A. R. *Green Chem.* **2011**, *13*, 3224–3229; (b) Jiang, H.-F.; Ye, J.-W.; Qi, C.-R.; Huang, L.-B. *Tetrahedron Lett.* **2010**, *51*, 928–932; (c) Kawanami, H.; Matsumoto, H.; Ikushima, Y. *Chem. Lett.* **2005**, *34*, 60–61; (d) Kawanami, H.; Ikushima, Y. *Tetrahedron Lett.* **2002**, *43*, 3841–3844.
7. Zhao, J.; Jiang, H. *Tetrahedron Lett.* **2012**, *53*, 6999–7002.
8. (a) Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *Tetrahedron Lett.* **1987**, *28*, 4417–4418; (b) Dimroth, P.; Pasedach, H. (BASF) *Ger. Patent* (DAS) 1,098,953, 1961; *Chem. Abstr.* **1962**, *56*, 2453; (c) Dimroth, P.; Pasedach, H. *Ger. Patent* (DAS) 1,164,411, 1964; *Chem. Abstr.* **1964**, *60*, 14510; (d) Bruneau, C.; Dixneuf, P. H. *J. Mol. Catal.* **1992**, *74*, 97–107. and references therein; (e) Yoshida, S.; Fukui, K.; Kikuchi, S.; Yamada, T. *Chem. Lett.* **2009**, *38*, 786–787.
9. (a) Costa, M.; Chiusoli, G. P.; Rizzardi, M. *Chem. Commun.* **1996**, 1699–1700; (b) Costa, M.; Chiusoli, G. P.; Taffurelli, D.; Dalmonego, G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1541–1546.
10. Kayaki, Y.; Yamamoto, M.; Suzuki, T.; Ikariya, T. *Green Chem.* **2006**, *8*, 1019–1021.
11. McGhee, W. D.; Riley, D. P. *Organometallics* **1992**, *11*, 900–907.
12. Yoshida, Y.; Inoue, S. *Chem. Lett.* **1977**, *6*, 1375–1376.
13. (a) Yoshida, M.; Ohsawa, Y.; Sugimoto, K.; Tokuyama, H.; Ihara, M. *Tetrahedron Lett.* **2007**, *48*, 8678–8682; (b) Garcia-Egido, E.; Fernandez, I.; Munoz, L. *Synth. Commun.* **2006**, *36*, 3029–3042; (c) Toda, T.; Kitagawa, Y. *Angew. Chem.* **1987**, *99*, 366–367. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 334–335; (d) Takeda, Y.; Okumura, S.; Tone, S.; Sasaki, I.; Minakata, S. *Org. Lett.* **2012**, *14*, 4874–4877; (e) Fernandez, I.; Munoz, L. *Tetrahedron: Asymmetry* **2006**, *17*, 2548–2557.

14. *General procedure for the cyclocarboxylation reaction of allylamines **1a–i** under gaseous CO_2 in MeCN/MeOH mixture (Table 1 and 2):* The substituted allylamine, (2.0 mmol) was transferred to a 45-mL stainless steel autoclave together with 4 mL of a MeCN/MeOH mixture. The autoclave was then sealed, purged at room temperature several times with CO_2 (10 bar) with stirring, and eventually was pressurized with 40 bar of gaseous CO_2 at room temperature. After stirring of the mixture at 90–110 °C for 24 h, the autoclave was cooled, degassed and opened. The products were recovered using 15 mL of CH_2Cl_2 and then purified by column chromatography on silica gel, using hexane–acetone or hexane–ethyl acetate as the eluent.
15. Belli Dell'Amico, D.; Calderazzo, F.; Labella, L.; Marchetti, F.; Pampaloni, G. *Chem. Rev.* **2003**, *103*, 3857–3897.
16. (a) Jessop, P. G.; Ikariya, T.; Noyori, R. *Chem. Rev.* **1999**, *99*, 475–494; (b)*Green Chemistry Using Liquid and Supercritical Carbon Dioxide*; De Simone, J. M., Tumas, W., Eds.; Oxford University Press: New York, 2003; (c)*Chemical Synthesis Using Supercritical Fluids*; Jessop, P. G., Leitner, W., Eds.; Wiley-VCH: Weinheim, 1999; (d) Beckmann, E. J. *J. Supercrit. Fluids* **2004**, *28*, 121–191.
17. (a) Yoshida, M.; Hara, N.; Okuyama, S. *Chem. Commun.* **2000**, 151–152; (b) Abla, M.; Choi, J.-C.; Sakakura, T. *Chem. Commun.* **2001**, 2238–2239; (c) Selva, M.; Tundo, P.; Perosa, A. *Tetrahedron Lett.* **2002**, *43*, 1217–1219; (d) Ihata, O.; Kayaki, Y.; Ikariya, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 717–719.
18. For the formation mechanism of carbamate derivatives see: (a) Aresta, M.; Quaranta, E. *J. Org. Chem.* **1988**, *53*, 4153–4154; (b) Aresta, M.; Quaranta, E. *J. Chem. Soc., Dalton Trans.* **1992**, 1893–1899; (c) Aresta, M.; Quaranta, E. *Tetrahedron* **1992**, *48*, 1515–1530; (d) Inesi, A.; Mucciante, V.; Rossi, L. *J. Org. Chem.* **1998**, *63*, 1337–1338; (e) Belforte, A.; Calderazzo, F. *J. Chem. Soc., Dalton Trans.* **1989**, 1007–1009.
19. Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Tetrahedron* **1987**, *43*, 4377–4383.