Di-*tert*-butyl Dicarbonate and 4-(Dimethylamino)pyridine Revisited. Their Reactions with Amines and Alcohols[1]

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The reaction of BOC_2O in the presence and absence of DMAP was examined with some amines, alcohols, diols, amino alcohols, and aminothiols. Often, unusual products were observed depending on the ratio of reagents, reaction time, polarity of solvent, pK_a of alcohols, or type of amine (primary or secondary). In reactions of aliphatic alcohols with BOC_2O/DMAP, we isolated for the first time carbonic−carbonic anhydride intermediates; this helps explain the formation of symmetrical carbonates in addition to the *O*-BOC products. In the case of secondary amines, we succeeded to isolate unstable carbamic−carbonic anhydride intermediates that in the presence of DMAP led to the final *N*-BOC product. The effect of *N*-methylimidazole in place of DMAP was also examined.

Introduction

4-(Dimethylamino)pyridine (DMAP) and di-*tert*-butyl dicarbonate (BOC_2O) are two widely used and extremely efficient reagents in organic chemistry. DMAP is one of a few 4-dialkylaminopyridine derivatives that are known as super acylation catalysts and are used in cases of difficult acylations.[2] BOC_2O is widely applied to introduce the *tert*-butoxycarbonyl (BOC) protecting group.[3] In some cases BOC_2O is also used as an apparent dehydrating agent when it reacts with carboxylic acids,[4] certain hydroxyl groups[5] or with primary nitroalkanes.[6] In the conversion of nitroalkanes by BOC_2O to nitrile oxides, we have shown that the DMAP catalyst is essential and in its absence no reaction occurs.[6]

$$RCH_2NO_2 \xrightarrow{BOC_2O\text{-}DMAP} R\text{-}C{\equiv}\overset{+}{N}\text{-}\overset{-}{O}$$

The efficiency of the BOC_2O/DMAP couple in dehydrations of nitroalkanes prompted us to study reactions of other functional groups, like amines and alcohols, with BOC_2O in the presence of DMAP under different conditions from the point of view of synthetic applications as well as mechanism. Although reactions of amines as well as of alcohols with BOC_2O in the presence of DMAP are known, we recently found that in addition to the expected *N*-BOC and *O*-BOC derivatives other products were formed, sometimes in large amounts[7] (Scheme 1). For instance, cinnamyl alcohol **1a** reacted (in MeCN at room temperature) with BOC_2O/DMAP to give the expected *O*-BOC derivative **2a**, but unexpectedly a symmetrical carbonate **3a** was also isolated (ratio of **2a**:**3a** = 1:1).[8] Furthermore, reaction of cyclohexylamine **4a** with BOC_2O (1.5 equiv) and DMAP (0.1 equiv) led mainly to formation of urea **6a**. The same reaction at 0 °C gave 80% of isocyanate **7a**. Formation of isocyanates and ureas from reaction of primary amines with BOC_2O/DMAP was reported by Knölker and co-workers[9] but the proposed mechanism does not appear satisfactory. We believed that reaction of primary amines with BOC_2O/DMAP may involve carbamic−carbonic anhydride intermediates and set out to prove the formation of such species.

Since BOC_2O and DMAP are widely used for protection of substrates that contain amine and alcohol functional groups, we decided to establish the major products as well as side products that can be formed in such reactions and if possible to find reaction conditions that will reduce or totally prevent the formation of unwanted products.

We describe here the influence of catalyst, solvents and their polarity, reaction time, stoichiometry, and temperature on the products of reaction of some amines, alcohols, and amino alcohols with BOC_2O and DMAP. Often the mechanisms of these interesting transformations are not obvious, and an attempt to shed light on these questions was also made.

Results and Discussion

Reaction of Amines with BOC_2O/DMAP. Though amines are known to react with BOC_2O directly to give the *N*-BOC-protected amine in the absence of any cata-

(1) Synthetic methods. 51. For part 50, see: Patchornik, A.; Hassner, A.; Kramer, M.; Gottlieb, H. E.; Cojocaru, M. *Heterocycles* **1999**, *51*, 1243.

(2) (a) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569. (b) Hassner, A.; Alexanian, V. *Tetrahedron Lett* **1978**, 4475. (c) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129. (d) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069. (e) D'Sa, B. A.; Verkade, J. G. *J. Org. Chem.* **1996**, *61*, 2963. (f) Su, D.-W.; Wang, Y.-C.; Yan, T.-H. *Tetrahedron Lett.* **1999**, *40*, 4197. (g) Mohapatra, D. K.; Datta, A. *Synlett* **1996**, 1129.

(3) For *N*-BOC protection, see: Greene, T. W.; Wuts, P. G. M. *Protective Group in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp 518−525. For *O*-BOC protection, see: (a) Houlihan, F.; Bouchard, F.; Fréchet, J. M. J.; Willson, C. G. *Can. J. Chem.* **1985**, *63*, 153. (b) Losse, G.; Süptitz, G. *Synthesis* **1990**, 1035.

(4) (a) Pozdnev, V. F. *Tetrahedron Lett.* **1995** *36*, 7115. (b) Pozdnev, V. F. *Int. J. Peptide Protein Res.* **1994**, *44*, 36. (c) Takeda, K.; Akiyama, A.; Nakamura, H.; Takizawa, S.; Mizuno, Y.; Takayanagi, H.; Harigaya, Y. *Synthesis* **1994**, 1063.

(5) Mattern, R.-H *Tetrahedron Lett.* **1996**, *37*, 291.

(6) Basel, Y.; Hassner, A. *Synthesis* **1997**, 903.

(7) This differs from the reaction of amines and alcohols with simple carboxylic acid anhydrides (for alcohols, see, for instance, ref 2d).

(8) All ratios and yields in this work are based on NMR integration unless otherwise is mentioned.

(9) (a) Knölker, H.-J.; Braxmeier, T.; Schlechtingen, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2497. (b) Knölker, H.-J.; Braxmeier, T.; Schlechtingen, G. *Synlett* **1996**, 502. (c) Knölker, H.-J.; Braxmeier, T. *Tetrahedron Lett.* **1996**, *37*, 5861.

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Scheme 1. Reactions of Aliphatic Alcohols and Primary Amine with BOC_2O−DMAP

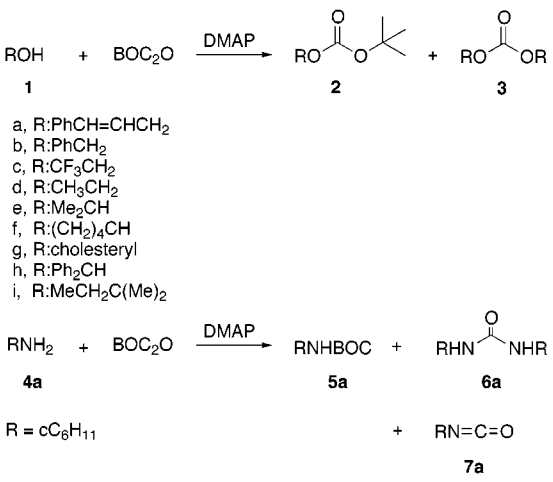


Table 1. Reaction of Amine 4a with BOC_2O−DMAP

	ratio[a] (%)		
catalyst/solvent/*T* °C	**5a** (*N*-BOC)	**6a** (urea)	**7a** (isocyanate)
no catalyst/MeCN/20	100		
DMAP/MeCN/20	5	95	
DMAP/CCl_4/20	80	20	
DMAP/MeCN/0	10	10	80
DMAP/$CDCl_3$/−30			100
MeIm/CCl_4/20	100		

[a] Ratios were calculated on the basis of the ^{1}H NMR spectra of the crude reaction mixture according to integration. Total yield 90−100%. The better conditions for isocyanate: low temperature, DMAP, polar solvent. For *N*-BOC: rt, MeIm, nonpolar solvent.

lyst, reaction of the primary amine, cyclohexylamine **4a**, with BOC_2O (1.5 equiv) in the presence of a catalytic amount of DMAP (0.1 equiv) in MeCN at room temperature gave the *N*-BOC derivative **5a** (5%) and the urea **6a** (95%). At 0 °C, isocyanate **7a** as well as **5a** and **6a** were found (80:10:10 ratio. See Table 1 and Scheme 1). As a substitute for DMAP, we also tested *N*-methylimidazole (MeIm), a known catalyst in acylation reactions.[10] Surprisingly, reaction of amine **4a** with BOC_2O in the presence of MeIm gave different result than with DMAP and the *N*-BOC derivative **5a** was obtained as the sole product.

While substituted electron-rich aniline **4b** reacted like the aliphatic amine,[9] anilines **4c** and **4d** gave totally different results and diBOC **8** and *N*-BOC urea **9** were also formed. The results of reactions of **4b**−**d** with BOC_2O in the presence of DMAP or MeIm catalysts in polar and nonpolar solvents are given in Table 2.[11] When MeIm was used as catalyst, reaction of **4b**−**d** with BOC_2O also afforded MeIm-anilide **10** (Scheme 2).

By contrast with aliphatic primary amines, reaction of aliphatic secondary amines with BOC_2O/DMAP led to isolation of the *N*-BOC as the sole product (no urea was formed). For example, *N*-ethylbenzylamine **11a** reacted with an excess of BOC_2O (2 equiv) in the presence of 0.5 equiv of DMAP in MeCN at room temperature to afford only the *N*-BOC derivative **12a** in quantitative yield and the reaction needed 4 h to be completed. On the other hand, **11a** reacted with 1 equiv of BOC_2O in the absence of catalyst in MeCN at room temperature to give also only the *N*-BOC protected amine **12a** but in less than 15 min. This apparent inconsistency in reaction rate was resolved by NMR analysis, which showed (e.g. two carbonyl in ^{13}C NMR) that in the presence of DMAP, an intermediate is involved during the formation of the *N*-BOC product. After several trials, isolation of this reactive intermediate became possible by stopping the reaction after 1 min by extraction of DMAP with 1% HCl. This led to isolation of the intermediate as a pure compound (in 70% isolated yield), which was identified as the carbamic−carbonic anhydride **13a** (Scheme 3). The assumption that **13a** reacts further to give the *N*-BOC protected amine was tested by addition of a catalytic amount of DMAP to a MeCN solution of isolated anhydride **13a** at room temperature. The *N*-BOC protected amine **12a** was formed after 3 h in 95% yield together with a small amount of starting amine (5%). Addition of starting amine **11a** to anhydride **13a** in MeCN at room temperature led also to **12a** after 0.5 h, and no urea was observed. The formation of anhydride **13** also explains the isolation of ureas **6** and **9** and isocyanate **7** in reaction of primary amines (see mechanistic aspects).

The reaction conditions for isolation of unstable carbamic−carbonic anhydride **13a** were optimized (Table 3). In all cases, the amine was added dropwise during 2 min to reduce formation of *N*-BOC **12a** (by direct reaction of amine **11a** with BOC_2O) and the reaction was stopped after 1−5 min. The use of 1.5 equiv of BOC_2O and 0.2 equiv of DMAP in MeCN at 0 °C was found to represent the optimum conditions leading to isolation of **13a** as a pure compound in 82% isolated yield (no **12a** observed by NMR). A reduced amount of BOC_2O or of DMAP led to isolation of *N*-BOC **12a** together with anhydride **13a**. Indeed, although the isolated yield of **13a** was higher (91%) when 2 equiv of BOC_2O and 0.1 equiv of DMAP were used, 4% of *N*-BOC **12a** was also formed. When MeIm (1 equiv) was used as catalyst instead of DMAP less anhydride **13a** was formed (Table 3, entry 8), while the same reaction in the nonpolar solvent toluene gave mainly **12a** and only 3% of anhydride **13a**.

Reaction of **11a** with BOC_2O/DMAP in an NMR tube in $CDCl_3$ showed that after a short time (5 min) all starting material had reacted to form anhydride **13a** together with 5% of *N*-BOC product **12a**. These observations testify to the fast formation of anhydride **13a** as an intermediate. The reactions of several other secondary aromatic and aliphatic amines with BOC_2O/DMAP in MeCN were also studied in order to obtain carbamic−carbonic anhydrides systematically (see Table 4). For example, *N*-methylaniline **11b** gave after 1 min, 99% of carbamic-carbonic anhydride[12] **13b**, while allowing the reaction to proceed 20 h afforded *N*-BOC **12b** in 98%. In $CDCl_3$, anhydride **13b** was formed in 60%, while in toluene only 40%. The more favorable formation of anhydride **13** in a polar solvent could be due to involvement of polar intermediates (see mechanistic aspects).

Since alkylamines reacted with BOC_2O/DMAP to form ureas we decided to examine under which conditions 1,2-diamines would lead to imidazolidinones. When 1,2-

(10) (a) Kamijo, T.; Yamamoto, R.; Harada, H.; Iizuka, K. *Chem. Pharm. Bull.* **1983**, *31*, 3724. In our work, MeIm reacted slower with BOC_2O to release carbon dioxide than DMAP. (b) Harváth, A. *Synthesis* **1994**, 102. (c) Pavlik, J. W.; Kurzweil, E. M. *J. Org. Chem.* **1991**, *56*, 6313. (d) Shapiro, G.; Gomez-Lor, B. *Heterocycles* **1995**, *41*, 215 and references therein.

(11) Details for best conditions to obtain various products are found in the footnotes of each table.

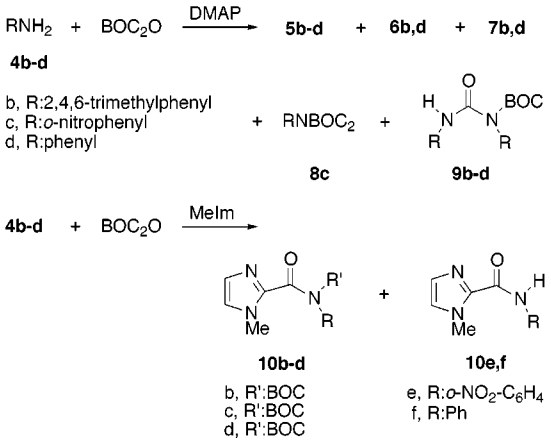
(12) Dean, C. S.; Tarbell, D. S. *J. Org. Chem.* **1971**, *36*, 1180.

Table 2. Reaction of Anilines 4b−d with BOC_2O−DMAP at Room Temperature

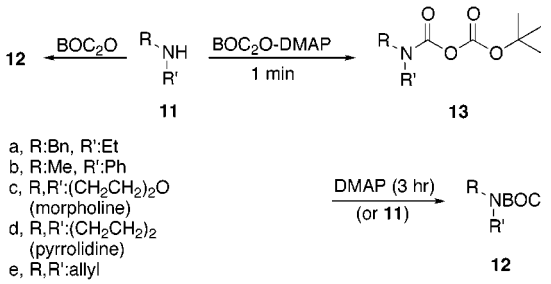
		ratio[a] (%)				
aniline	catalyst/solvent	*N*-BOC **5**	DiBOC **8**	*N*-BOC-urea **9**	MeIm anilide **10**	urea **6** or isocyanate **7**
2,4,6-trimethylaniline (**4b**)	no catalyst/MeCN	95				
	MeIm/CCl_4	80			15	5
	MeIm/PhMe	35			60	5
	DMAP/MeCN					100
o-nitroaniline (**4c**)	no catalyst/MeCN	*b*				
	MeIm/MeCN		20		80	
	DMAP/MeCN	60	20	20		
	DMAP/PhMe		100			
aniline (**4d**)	no catalyst/MeCN	100[c]				
	MeIm/MeCN	20		35	45	
	DMAP/MeCN	10		15		75

[a] Ratios were calculated on the basis of the ^{1}H NMR spectra of the crude reaction mixture according to integration. The conditions were not optimized for all cases. The best conditions (equiv BOC_2O/equiv DMAP, solvent, *T*, time, yield) for **5b**: 1/no catalyst, MeCN, rt, 1 week, 95%; for **5d**: 1.1/no catalyst, MeCN, rt, 48 h, 1 equiv of Et_3N, 100%; for **8b**: **5b**, 1.2/0.2, MeCN, rt, 1 h, 95%; for **8c**: 2.5/0.2, toluene, rt, 4 h, 100%; for **8d**: **5d**, 1.2/0.2, MeCN, rt, 1 h, 100%; for **9c**: 1.5/0.2, $CDCl_3$, rt, 20 min, 40%; for **9d**: 1.2/0.2, toluene, rt, 0.5 h, 65%; for **10b**: 2/1 equiv of MeIm, toluene, 0 °C, 2.5 h, 75%; for **10c,e**: 2/1.5 equiv of MeIm, MeCN, rt, 6 h, 65%; for **10d,f**: 1.5/0.5, MeCN, rt, 2 h, 35%; for **7b**: 1.2/0.2, MeCN, 0 °C, 0.5 h, 100% by NMR (90% isolated yield). [b] Starting material was recovered. [c] With 1 equiv of Et_3N.

Scheme 2. Reactions of Anilines with BOC_2O−DMAP



Scheme 3. Reactions of Secondary Amines with BOC_2O−DMAP. Carbamic−Carbonic Anhydrides



diaminoethane **14a** was added to a MeCN solution of 3.5 equiv BOC_2O and 0.5 equiv DMAP at room temperature, 1,3-diBOC-2-imidazolidinone **15a** was formed in 93% yield after 0.5 h. The use of only 1.2 equiv of BOC_2O gave rise to formation of **15a** in 25% yield together with imidazolidinone **15b** (50%) and mono *N*-BOC imidazolidinone **15c** (25%). This leads to the conclusion that 2-imidazolidinone is formed first and is followed by fast reaction with BOC_2O to give **15a**. Reaction of the diamine with 2 equiv of BOC_2O in the absence of DMAP in MeCN at room temperature led to immediate precipitation of the *N*,*N*′-diBOC **16a** (Scheme 4).

Reaction of 2-aminoaniline **14b** with 3.5 equiv of BOC_2O and 0.2 equiv of DMAP in MeCN at room temperature afforded 1,3-diBOC benzimidazolidinone **15d** in 98−100% yield after 5 min. The shorter reaction time in case of the aromatic diamine is presumably due to the more acidic imidazolidinone that reacted further with BOC_2O/DMAP to give **15d**. The use of less BOC_2O (1.5 equiv) in the presence of 0.5 equiv of DMAP afforded **15d** in 50% and no NH benzimidazolidinones (**15e**, **15f**) were formed (50% of **14b** was recovered). Treatment of the diamine **14b** with 2 equiv of BOC_2O in the absence of DMAP in $CDCl_3$ led to formation of *N*,*N*′-diBOC **16b** in 95% yield after 24 h. Addition of excess of BOC_2O to **16b** in the presence of DMAP led to formation of *N*,*N*,*N*′,*N*′-tetraBOC product **17b**.[13] Thus, **16** does not appear to be a precursor of **15**.

Reaction of Alcohols with BOC_2O/DMAP. Usually alcohols do not react with BOC_2O even in the presence of a base like Et_3N. The addition of a catalytic amount (0.1 equiv) of DMAP led to immediate reaction of alcohols with reported formation of *O*-BOC products.[14] Yet we found that reaction of several alcohols with BOC_2O/DMAP afforded the *O*-BOC derivative together with the symmetrical carbonate[15] (**3**), the later being the major product in many cases (Scheme 1). Reactions of several kinds of alcohols with BOC_2O in the presence of a DMAP catalyst (0.1−0.4 equiv) were examined, and the results are summarized in Table 5. In some reactions, an excess of BOC_2O (1.2−1.5) was used in order to ascertain that formation of the symmetric carbonates is not the result of lack of BOC_2O. The ratio of products **2** and **3** was not influenced by the amount of BOC_2O, and hence, 0.8 equiv was routinely used. Similarly, the amount of DMAP also did not effect the ratio of **2** and **3** in most cases. The use of dioxane[14] in place of MeCN in the reaction of aliphatic alcohols with BOC_2O/DMAP led to larger proportions of *O*-BOC products (compare with Table 5) from ethanol **1d** (60% of **2d**), from 2-propanol **1e** (40% **2e**), from cyclopentanol **1f** (60% **2f**), or from cholesterol **1g** (65% **2g**).

In the case of cinnamyl alcohol **1a** or benzyl alcohol **1b**, the amount of *O*-BOC product was drastically in-

(13) (a) Grehn, L.; Ragnarsson, U. *Synthesis* **1987**, 275. (b) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem* **1983**, *48*, 2424. (c) Burk, M. J.; Allen, J. G. *J. Org. Chem*. **1997**, *62*, 7054.

(14) Pozdnev, V. F. *Int. J. Peptide Protein Res.* **1992**, *40*, 407.

(15) For organic carbonates, see: Shaikh, A.-A. G.; Sivaram, S. *Chem. Rev.* **1996**, *96*, 951.

Table 3. Isolation of Anhydride 13a in Reaction of Secondary Amine 11a with BOC_2O−DMAP

entry	BOC_2O (equiv)	DMAP (equiv)	MeIm (equiv)	solvent and conditions	ratio[a](isolated yield, %) *N*-BOC **12a**	ratio[a](isolated yield, %) anhydride **13a**
1	2	0.5		MeCN, rt or 0 °C, 1 min		100 (70)
2	2	0.1		MeCN, rt or 0 °C, 5 min	4	96 (91)
3	2	0.1		MeCN, rt, 5 min, one portion	27	73
4	1.5	0.2		MeCN, 0 °C, 5 min		100 (82)
5	1.2	0.2		MeCN, 0 °C, 5 min	2	98
6	2	0.5		$CDCl_3$, rt, 10 min	5	95
7	2	0.5		toluene, 0 °C, 1 min−1.5 h	9	91
8	2		1	MeCN, 0 °C, 5 min	78	22
9	2		1	toluene, 0 °C, 1 min	97	3

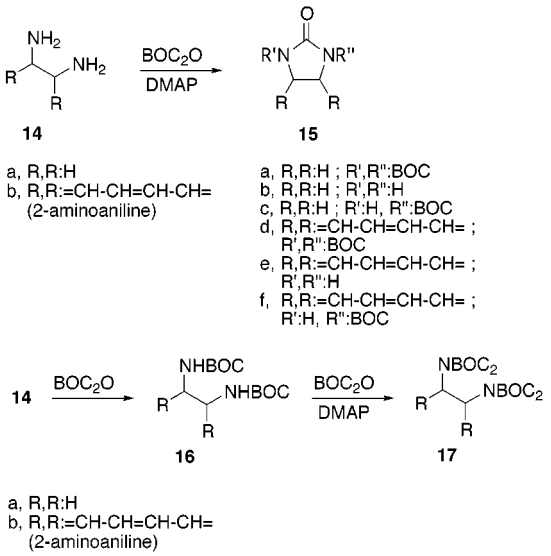
[a] Ratios were calculated on the basis of the ^{1}H NMR spectra of the crude reaction mixture. The best conditions for **13a** (isolated yield = 91%): 2 equiv of BOC_2O/0.1 equiv of DMAP, MeCN, rt, 5 min; (purity = 100%): 1.5 equiv of BOC_2O/0.2 equiv of DMAP, MeCN, 0 °C, 5 min.

Table 4. Reaction of Secondary Amines 11a−e with BOC_2O−DMAP in MeCN for 1 min To Form 13a−e

amine	ratio[a] (%) of *N*-BOC products **12** vs anhydride **13**	
N-ethylbenzylamine	**12a**:**13a**	0:100
N-methylaniline	**12b**:**13b**	1:99
morpholine	**12c**:**13c**	8:92
pyrrolidine	**12d**:**13d**	10:90
diallylamine	**12e**:**13e**	1:99

[a] Calculated by NMR. The best conditions (equiv BOC_2O/equiv DMAP, *T*) for 1 min in MeCN for **13a**: 1.5/0.2, 0 °C; for **13b**: 1.5/0.2, rt; for **13c**−**e**: 2/0.5, 0 °C.

Scheme 4. Reactions of 1,2-Diamines with BOC_2O−DMAP

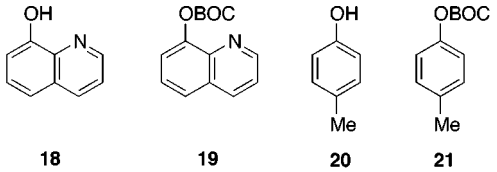


creased from 1:1 ratio of **2**:**3** to 9:1 ratio when *N*-methylimidazole (MeIm) was used as catalyst in nonpolar solvent toluene. Interestingly, while reaction of ethanol **1d** with BOC_2O/DMAP afforded diethyl carbonate **3d** as the major product, trifluoroethanol **1c** gave only the *O*-BOC derivative **2c.** Apparently, this is a function of the acidity of the alcohol; the more acidic alcohol produced less or no symmetrical carbonate. The pK_a effect was clearly demonstrated in a competition experiment using a 1:1 ratio of ethanol **1d** (pK_a 15.9) and trifluoroethanol **1e** (pK_a 12.4) with BOC_2O/DMAP in MeCN at room temperature, in which *O*-BOC protected trifluoroethanol was formed as the sole product and neither *O*-BOC ethanol nor diethyl carbonate were observed (by NMR). Reaction of CF_3CH_2OH with BOC_2O (1.2 equiv) and DMAP (0.2 equiv) in MeCN at room temperature afforded the *O*-BOC derivative within 5 min, while the reaction of CH_3CH_2OH under the same conditions required 1.5 h for completion.

Table 5. Reaction of Alcohols with BOC_2O−DMAP in MeCN at Room Temperature

alcohols **1a**−**i**, **18**, **20**	ratio[a] (%) of *O*-BOC products **2** (or **19**, **21**) vs symmetrical carbonate **3**	
cinnamyl alcohol	**2a**:**3a**	50:50
benzyl alcohol	**2b**:**3b**	50:50
trifluoroethanol	**2c**:**3c**	100:0
ethanol	**2d**:**3d**	30:70
2-propanol	**2e**:**3e**	20:80
cyclopentanol	**2f**:**3f**	10:90
cholesterol (in $CDCl_3$)	**2g**:**3g**	35:65
benzhydrol	**2h**:**3h**	100:0
8-hydroxyquinoline	**19**	100
p-cresol	**21**	100
tert-amyl alcohol	**2i**:**3i**	60:40

[a] Ratios of **2**:**3** were calculated on the basis of integration of the ^{1}H NMR spectra of the crude reaction mixture. Total yield: 100% for reaction of **1a**−**c**, **18**, **20**; 93−98% for **1d**−**h**; 15% for **1i**. The conditions were not optimized for all cases. The best conditions (equiv BOC_2O/equiv DMAP, solvent, time, yield) at room temperature for **2a**,**b**: 1.5/1 equiv of MeIm, toluene, 0.5 h; for **2c**: 1.2/0.1, MeCN, 5 min; for **2d**−**g**: 1.5/0.1, dioxane, 2 h; for **2h**: 1.2/0.1, toluene, 10 min; for **19**, **21**: 1.2/0.2, MeCN, 15 min; for **3a**,**b**: 1.5/0.1, MeCN, 1.5 h; for **3d**−**f**: 0.8/0.2−0.4, MeCN, 2.5 h; for **3g**: 1.2/0.4, $CDCl_3$, 3 h.

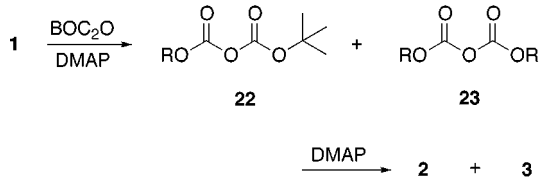


The more acidic phenols[16] reacted with BOC_2O in the absence of catalyst but the efficiency of the reaction is poor. For example, reaction of *p*-cresol **20** with BOC_2O in the absence of DMAP gave only 10% of *O*-BOC derivative **21** after 48 h. Addition of 1 equiv of Et_3N led to formation of **21** in 85% after 48 h and 96% after a week. The use of a catalytic amount of DMAP gave only **21** quantitatively after 15 min.

Benzhydrol **1h** reacted with BOC_2O/DMAP to afford the *O*-BOC product **2h** in quantitative yield (by NMR) in a nonpolar solvent like toluene or CCl_4 within 10 min, while in the polar solvent MeCN, reaction was slower and 10% of starting alcohol was recovered even after 30 min. This may reflect a preferred solubility of the *O*-BOC product compared to the alcohol in nonpolar solvent.

(16) Hansen, M. M.; Riggs, J. R. *Tetrahedron Lett.* **1998** *39*, 2705.

Scheme 5. Reactions of Aliphatic Alcohols Leading to Carbamic−Carbonic Anhydrides

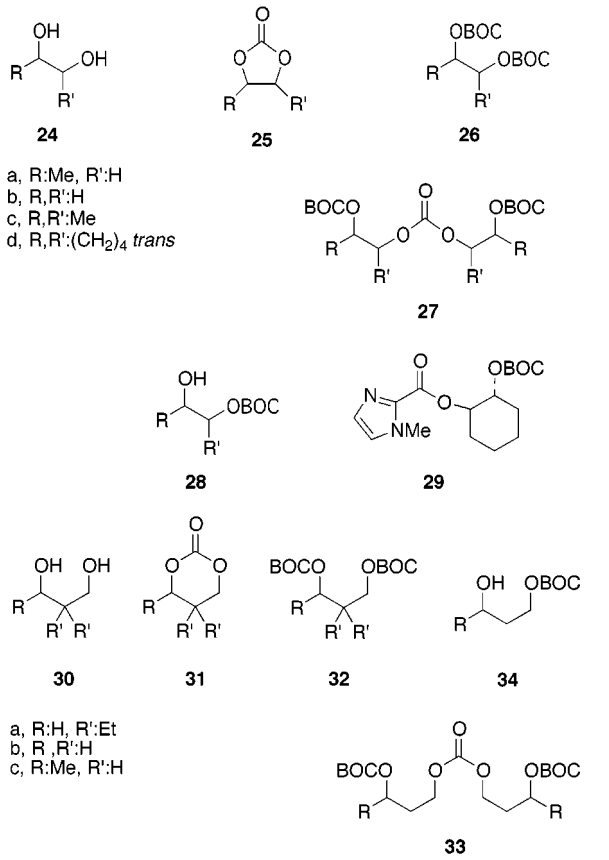


In the reactions of purely aliphatic alcohols with BOC_2O/DMAP, leading to *O*-BOC protected alcohols and symmetrical carbonates, two intermediates were detected by ^1H and ^{13}C NMR (new peaks at 1.53 ppm for *tert*-butyl protons and at 148 and 146 ppm for two carbonyls). These intermediates, which were identified as carbonic−carbonic anhydrides **22** and **23** (Scheme 5), can explain the formation of symmetrical carbonates in addition to the expected *O*-BOC-protected alcohols (see Mechanistic Aspects).

Attempts were made to find the optimum conditions for the isolation of these two dicarbonate intermediates as the major products. As in the case of secondary amines (see above), it was found that fast removal of DMAP catalyst (after 5−30 min) allowed the isolation of the dicarbonate intermediates as the major products (60−94%) in the mixture together with the two final monocarbonates products **2** and **3**. To get **22** and **23** as pure as possible the amount of BOC_2O was reduced to 0.8 equiv and not less than 0.4 equiv of DMAP was used. For instance, reaction of cyclopentanol with 0.8 equiv of BOC_2O and 0.4 equiv of DMAP in MeCN at room temperature afforded as final products symmetrical carbonate **3f** and *O*-BOC **2f** in a 9:1 ratio after 2.5 h, but when the reaction was stopped after 5 min by extraction with dilute HCl, unsymmetrical and symmetrical carbonic-carbonic anhydrides (dicarbonates) **22f** and **23f** were isolated together with **2f** and **3f** (ratio of **22f**+**23f**:**2f**+**3f** = 85:15). After 45 min, 55% of the dicarbonate intermediates were present and even after 2 h, 10% were still detected. The same reaction using 0.6 equiv BOC_2O and 0.2 equiv DMAP in MeCN at 0 °C led to an increased amount (94%) of dicarbonates **22f** and **23f** after 5 min but a large amount of BOC_2O was also present, due to the smaller amount of DMAP (0.2 equiv) employed (DMAP reacts fast with BOC_2O). The use of $CHCl_3$ as a solvent or of MeIm as a catalyst led to lower amounts of dicarbonates (ca. 60%). In the reaction of ethanol or of 2-propanol with BOC_2O/DMAP in MeCN at room temperature, carbonic−carbonic anhydrides **22d** and **23d** or **22e** and **23e**, as well as, **2d** and **3d** or **2e** and **3e** respectively were also detected.

The formation of carbonic−carbonic anhydrides (dicarbonates) in the reactions of primary and secondary aliphatic alcohols with BOC_2O/DMAP parallels the formation of carbamic−carbonic anhydrides in reactions of secondary amines with BOC_2O/DMAP.

It was of interest to see if 1,2-diols and 1,3-diols[17] in reaction with BOC_2O/DMAP lead to cyclic carbonates or to *O*,*O*′-diBOC derivatives. The results are summarized in Table 6. The effects of catalyst and solvent are given in Table 7. In the reaction of diols **24a**−**d** and **30a**−**c** with BOC_2O/DMAP, the cyclic carbonates[18] **25a**−**d** or **31a**−**c**, respectively, were formed together with *O*,*O*′-diBOC **26a**−**d** or **32a**−**c**. When an increased amount of DMAP was used the yield of **25** and **31** rose (Table 6). When 1 equiv of *N*-methylimidazole (MeIm) was used as catalyst instead of DMAP with toluene as the solvent at room temperature, less cyclic carbonate was observed and *O*,*O*′-diBOC was obtained as the major product (see Table 7). The use of MeIm instead of DMAP in toluene in the reaction of *trans*-1,2-cyclohexanediol **24d** with BOC_2O afforded in 30% yield *O*-BOC-2-(*N*-methylimidazole) ester **29**, in which MeIm had reacted not only as a catalyst but also as a reactant in the acylation reaction (compare anilines). Probably **29** was formed as a side product because the reaction is slower with the cyclic than with open chain 1,2-diols giving an opportunity for MeIm to act as a nucleophile. In reactions of diols **24** and **30** with BOC_2O/DMAP often *O*,*O*-diBOC symmetrical carbonate **27** or **33** respectively and mono *O*-BOC **28** or **34** were also isolated in addition to cyclic carbonates and *O*,*O*′-diBOC derivatives. In general, reaction of diols with BOC_2O/DMAP when the hydroxy is hindered gave less *O*,*O*′-diBOC symmetrical carbonate **27** or **33** while some mono *O*-BOC **28** or **34** was formed. For the formation of mono *O*-BOC **28** and **34**, polyDMAP was found to be the better choice. While reactions in which polyDMAP is used as a catalyst suffer from the limitation of slower rate, polyDMAP offers an advantage with reactions of diols leading to mono *O*-BOC as major products (see Table 6).



(17) For protection of diols, see: (a) De Angelis, F.; Marzi, M.; Minetti, P.; Misiti, D.; Muck, S. *J. Org. Chem* **1997**, *62*, 4159 and references therein. (b) Greene, T. W.; Wuts, P. G. M. *Protective Group in Organic Synthesis*; Wiley: New York; 3rd ed.; 1999; pp 201−245.

(18) For conversion of diols to cyclic carbonates by other methods see: (a) Burk, R. M.; Roof M. B. *Tetrahedron Lett.* **1993**, *34*, 395. (b) Cotarca. L.; Delogu, P.; Nardelli, A.; Sunjic′, V. *Synthesis* **1996**, 553. (c) Nicolaou, K. C.; Claiborne, C. F.; Nantermet, P. G.; Couladouros, E. A.; Sorensen E. J. *J. Am. Chem. Soc.* **1994**, *116*, 1591.

Table 6. Reaction of Diols 24a−d and 30a−c with BOC_2O−DMAP in MeCN

diol	cyclic carbonate	yield[a] (%) 0.5 equiv of DMAP	1 equiv of DMAP	1.5 equiv of DMAP
1,2-propandiol (**24a**)	**25a**	53	95	
ethylene glycol (**24b**)	**25b**	45	80	92
1,2-butanediol (**24c**)	**25c**	68	92	
1,2-*trans*-cyclohexandiol (**24d**)	**25d**	40	95	
2,2-diethyl-1,3-propanediol (**30a**)	**31a**	55	90	
1,3-propanediol (**30b**)	**31b**	68	88	
1,3-butanediol (**30c**)	**31c**	60	85	

[a] Calculated by NMR. The best conditions for **25a−c**, **31a−c**: 3 equiv of BOC_2O, 1 equiv of DMAP (1.5 eq for **25b**), MeCN, rt (0 °C for **25d**), 0.5 h. The best conditions (equiv BOC_2O/equiv DMAP, solvent, time, yield) at rt for **26a**: 2.5/0.1, toluene, 0.5 h, 95%; for **26b**: 2.5/0.1, toluene, 0.5 h, 85%; for **26c**: 2.5/0.2, toluene, 0.5 h, 93%; for **26d**: 2.5/0.5, toluene, 1 h, 60%; for **27b**: 3/1 equiv of MeIm, MeCN, rt, 2.5 h, 15%; for **28b**: 2/0.1 g of polyDMAP, MeCN, 1.5 h, 73%; for **28c** 2.5/1 equiv of MeIm, MeCN, rt, 1.5 h, 35%; for **28d**: 1.5/0.2, MeCN, 1 h, 60%; for **29**: 3/1 equiv of MeIm, toluene, 4 h, 30%; for **32a**: 2.5/0.1, toluene, 1 h, 77%; for **32b**: 2.5/1 equiv of MeIm, toluene, 2 h, 83%; for **32c**: 2.5/0.1, toluene, 1 h, 63%; for **33a**: 2.5/1 equiv of MeIm, toluene, 1.5 h, 30%; for **33b**: 2.5/1 equiv of MeIm, MeCN, 2 h, 20%; for **33c**: 2.5/1 equiv of MeIm, toluene, 1.5 h, 33%; for **34c**: 2.5/0.1 g of polyDMAP, toluene/MeCN (9:1), 3 h, 65% and also 3/1 equiv of MeIm, MeCN, rt, 1.5 h, 32%.

Table 7. Reaction of 1,2-diol 24a with BOC_2O−DMAP at Room Temperature

catalyst[b] (equiv)	solvent	ratio[a] (%) **25a**	**26a**
DMAP (1)	MeCN	96	4
DMAP (0.1)	PhMe	4	96
MeIm (1)	MeCN	38	62
MeIm (1)	PhMe	4	96

[a] Ratios were calculated by NMR. Total yield: 97−98% with DMAP; 80−85% with MeIm. [b] In the absence of catalyst no reaction occurred.

Table 8. Reaction of Amino Alcohol 35a with BOC_2O−DMAP

BOC_2O	catalyst	conditions	ratio[a] (%) **36a**	**37a**	**39a** or **40a**
1 equiv	no catalyst	MeCN, rt	100[b]		
3 equiv	DMAP (0.5 equiv)	MeCN, 0 °C		95[b]	
3 equiv	MeIM (1 equiv)	MeCN, rt		40[a]	**39a** (40), **40a** (20)
3 equiv	MeIm (1 equiv)	PhMe, rt		10[a]	**39a** (90)

[a] Ratios were calculated by NMR. [b] Actual yield. The best conditions for **37a** (95% yield): 3 equiv of BOC_2O/0.5 equiv of DMAP, MeCN, 0 °C, 1 h.

Reaction of 1,2-Amino Alcohols with BOC_2O/DMAP. With 1,2-amino alcohols it is often important to achieve transformation to oxazolidinones which normally requires reaction with phosgene. Hence, the reactions of BOC_2O/DMAP with several amino alcohols (primary amine) **35** were examined to determined if this transformation could be achieved. The results for phenylalaninol **35a** are shown in Table 8. BOC_2O alone afforded *N*-BOC phenylalaninol **36a** in quantitative yield and as expected no *O*-BOC derivative was observed (by NMR). When excess of BOC_2O (3 equiv) was used in the presence of 0.5 equiv of DMAP in MeCN at 0 °C for 1 h, *N*-BOC 2-oxazolidinone[19] **37a** was isolated in 95% yield (Scheme 6). Using less BOC_2O (1.5 equiv) with DMAP led to formation of 2-oxazolidinone **38a** (20%) together with (ca. 70%) *N*-BOC oxazolidinone **37a**. This led to the rationalization that first formation of oxazolidinone[20] **38a** had occurred and the latter reacted further with BOC_2O/DMAP, leading to *N*-BOC oxazolidinone **37a**, in analogy to reaction of amides.[13] MeIm led to a mixture of *N*-BOC 2-oxazolidinone **37a**, *N*,*O*-diBOC **39a** and *N*,*N*,*O*-triBOC

Scheme 6. Reaction of Amino Alcohols with BOC_2O−DMAP. *N*-BOC Oxazolidinones

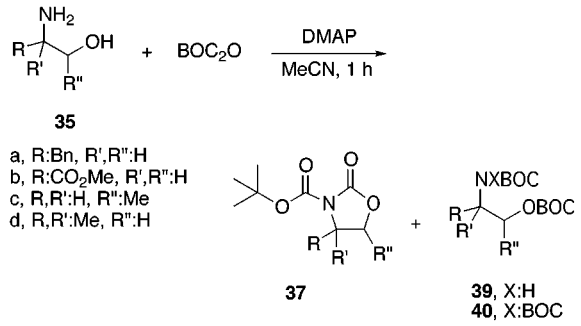
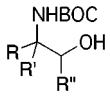


Table 9. Reaction of Amino alcohols 35a−d and Aminothiol 41 with BOC_2O−DMAP in MeCN at 0 °C

amino alcohol or aminothiol	*N*-BOC 2-oxazolidinone (or 2-thiazolidinone) product (yield %)[a]
phenylalaninol (**35a**)	**37a** (95)
serine methylester hydrochloride (**35b**)	**37b** (93)
3-amino-2-propanol (**35c**)	**37c** (95)
2,2-dimethylethanolamine (**35d**)	**37d** (98)
cysteine methylester hydrochloride (**41**)	**42** (75)

[a] Calculated by NMR. The best conditions (equiv BOC_2O/equiv DMAP, time) in MeCN at 0 °C for **37a−d**: 3/0.5, 1 h, (3 equiv of Et_3N for **37b**); for **42**: 3/1.5, 15 min (5 equiv of Et_3N).

derivative **40a** (Table 8 and Scheme 6). In analogy with **35a**, **35b−d** gave mainly *N*-BOC 2-oxazolidinones[21] **37b−d** (Table 9).



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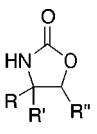

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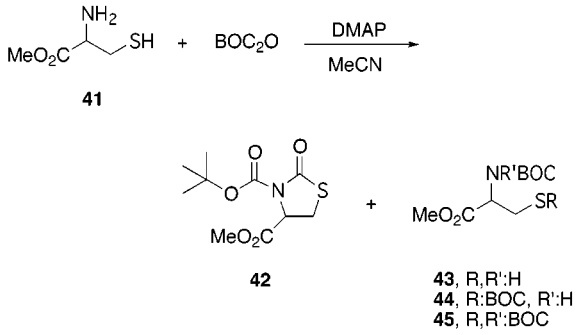
Formation of *N*-BOC 2-thiazolidinone **42** from a 1,2-aminothiol is less efficient than the formation of *N*-BOC

(19) Only one example and the mechanism remained in question: Sting, A. R.; Seebach, D. *Tetrahedron* **1996**, *52*, 279.

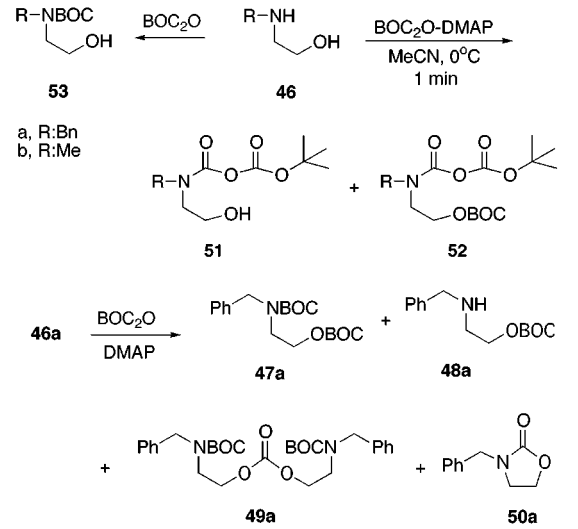
(20) For formation of 2-oxazolidinone by other methods see: (a) Dyen, M. E.; Swern, D. *Chem. Rev.* **1967**, *67*, 197. (b) Costa, M.; Chiusoli, G. P.; Rizzardi, M. *Chem. Commun.* **1996**, 1699. (c) Falb, E.; Nudelman, A.; Hassner, A. *Synth. Commun.* **1993**, 2839. (d) Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Laboroi, F.; Mazzanti, G.; Ricci, A.; Varchi, G. *J. Org. Chem.* **1999**, *64*, 8008. (e) Iwama, S.; Katsumura, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3363.

(21) Ishizuka, T.; Kunieda. T. *Tetrahedron Lett.* **1987**, *28*, 4185.

Scheme 7. Reaction of Aminothiol with BOC_2O–DMAP. *N*-BOC Thiazolidinone



Scheme 8. Reaction of Amino Alcohols with BOC_2O–DMAP. Carbamic–Carbonic Anhydrides 51 and 52



2-oxazolidinone **37** (Table 9 and Scheme 7). Reaction of the cysteine methyl ester **41** with BOC_2O in MeCN and 3 equiv of Et_3N in the absence of DMAP led to formation of *N*-BOC **43** (90%) together with 5% of *N*,*S*-diBOC **44**. **44** was produced in 90% yield from **43** by using BOC_2O (1.2 equiv) and DMAP (0.2 equiv) and when excess of BOC_2O was used *N*,*N*,*S*-triBOC **45** was formed in 85% yield.[13]

N-Benzylethanolamine **46a** possessing a secondary amine reacted with BOC_2O/DMAP with formation of *N*,*O*-diBOC derivative **47a** (70%), together with *O*-BOC amine **48a** (20%), *N*,*N*′-diBOC symmetrical carbonate **49a** (5%), and 2-oxazolidinone[22] (5%) **50a** (Scheme 8). The use of MeIm as catalyst also gave *N*,*O*-diBOC **47a** as the major product (75%), as well as carbonate **49a** (25%). Hence, MeIm offers only a small advantage here.

In the reaction of **46a** with BOC_2O/DMAP as mentioned above, two intermediates were detected by NMR. When the reaction was stopped after 1–10 min by extraction with 1% HCl (to remove DMAP) two compounds were isolated that were identified as carbamic-carbonic anhydrides **51a** and **52a**. One (**51a**) contained a free hydroxy group and the other (**52a**) an *O*-BOC protected alcohol. The formation of these two products is similar to the intermediates **13a–e** that were isolated in the reaction of the secondary amines **11a–e** with BOC_2O/DMAP (see above).

(22) Kubota, Y.; Kodaka, M.; Tomohiro, T.; Okuno, H. (Y.) *J. Chem. Soc., Perkin Trans 1* **1993**, 5.

Table 10. Reactivity of 51a and 52a

conditions	ratio[a] of products (%)	
51a in MeCN or in EtOH + Et_3N, 24 h, rt	**50a** (95)	**53a** (5)
51a in $CDCl_3$ + Et_3N, 24 h, rt	**50a** (17)	**53a** (83)
52a in EtOH, 1 h, 80 °C	**47a** (100)	
52a in MeCN + Et_3N, 48 h, rt	**47a** (100)	
52a in $CDCl_3$ + 1 equiv of MeIm, 18 h, rt	**47a** (100)	
52a in MeCN + 0.05 equiv of DMAP, 0.5 h, rt	**47a** (85)	**48a** (15)
52a in MeCN + 1 equiv of DMAP, 0.5 h, rt	**47a** (70)	**48a** (30)
52a in MeCN + **46a**, 1 h, rt	**53a** (50)	**48a** (50)

[a] Calculated by NMR. No other products were observed.

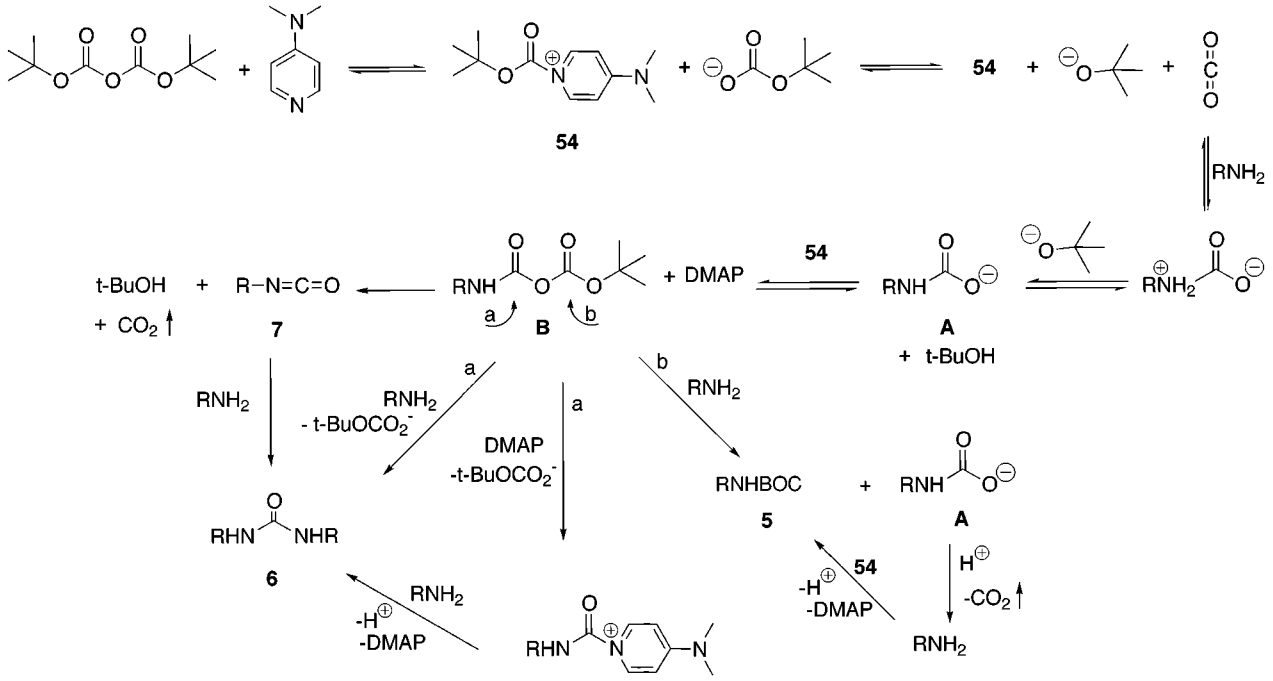
The reactivity and stability of anhydrides **51a** and **52a** were examined carefully under different conditions. Several attempts to isolate these unstable anhydrides by chromatography failed and only a trace of **52a** was collected. The best conditions leading to isolation of moderately pure anhydride **52a** were found to be chloroform as solvent and 2.5 equiv of BOC_2O and 0.5 equiv of DMAP at 0 °C. Washing the reaction mixture with 1% HCl after 5–10 min afforded 90% of **52a** (together with 10% **47a** in 92% total isolated yield) with no **51a** present. When the HCl extraction was carried out after 20 min, diBOC derivative **47a** was isolated and neither **52a** nor **51a** were found. This again indicates the intermediary of anhydrides **51** and **52** in the formation of **47**. Isolation of **51a** as the major anhydride (70%), but still containing some **52a**, was successful only when MeCN was used as solvent and the reaction was stopped after 1 min. The same reaction performed in toluene did not afford **51a** but mainly **52a**, even when the extraction was carried out after 1 min. These results are consistent with our observation that alcohols react with BOC_2O/DMAP fast in a nonpolar solvent like toluene to afford mainly *O*-BOC protected alcohols.

Carbamic–carbonic anhydrides **51a** and **52a** were stable for 1 month as neat compounds, but in solution decomposition to *N*-BOC derivatives occurred within less than 2 weeks. Heating a mixture of **51a** and **52a** in $CDCl_3$ at 60 °C for 1 h did not harm the anhydrides. When **51a** and **52a** were heated to 80 °C in EtOH, **52a** was completely decomposed to diBOC **47a** (Table 10), while 40% of **51a** cyclized to 2-oxazolidinone **50a** and the rest decomposed to *N*-BOC **53a**.

Addition of excess of Et_3N (3 equiv) to **51a** in a polar solvent like MeCN or EtOH afforded 2-oxazolidinone **50a** (95%) after 24 h (Et_3N as base), while in $CDCl_3$ only 17% of **50a** was formed together with the *N*-BOC derivative **53a**. Addition of DMAP to a solution of **52a** led to formation of **47a** together with *O*-BOC amine **48a** (Table 10; see Scheme 12). Using MeIm as the catalyst in $CDCl_3$ did not produce the *O*-BOC amine **48a** but only **47a**. Treatment of **52a** with an excess Et_3N (3 equiv) in MeCN gave only diBOC **47a** (Et_3N as catalyst). However, when starting amino alcohol **46a** was added to a MeCN solution of **52a** at room temperature, 50% of *O*-BOC amine **48a** was formed as well as *N*-BOC **53a**. This indicates that amine **46a** reacted with anhydride **52a** in a similar way to DMAP (Scheme 12) and hence no urea was formed.

N-Methylethanolamine **46b** reacted with BOC_2O/DMAP to give a mixture of products **47b** (major product), symmetrical carbonate **49b** and 2-oxazolidinone **50b**. Attempts to isolate intermediates **51b** and **52b** were

Scheme 9. Reaction of Primary Amines with BOC_2O−DMAP leading to *N*-BOC 5, Urea 6, and Isocyanate 7



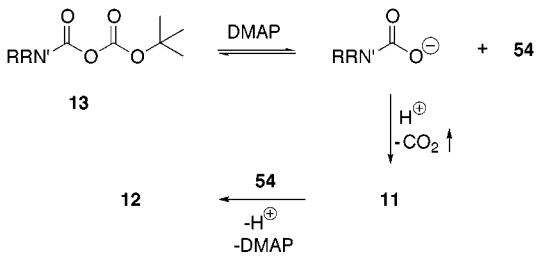
disappointing. After 1 min, **51b** (free OH) was found in 45% yield together with **52b** (*O*-BOC) and *N*,*O*-diBOC **47b**; after 5 h, NMR still indicated the presence of 50% of **52b** and 5% **51b**.

Mechanistic Aspects

The reaction of di-*tert*-butyl dicarbonate (BOC_2O) with amines or amino alcohols, in the absence of DMAP leads to *N*-BOC-protected amines, usually in high yield. In some cases, under the same conditions, the presence of DMAP totally changes the course of the reaction to give products that are coupling reaction (phosgene type addition) products such as ureas (e.g., **6**, **15**), 2-oxazolidinones (e.g., **37**, **50**) and carbonates (e.g., **3**, **49**). We succeeded in isolating unstable carbamic−carbonic anhydride intermediates (e.g., **13**, **51**, **52**) in these reactions by fast removal of DMAP. The formation of ureas or isocyanates from amines in the presence of DMAP has been observed before,[9] but only one example of formation of a carbamic−carbonic anhydride from the reaction of a pyrrolidine with BOC_2O/DMAP has been reported and a satisfactory mechanism was missing.[23]

To explain all the unusual products, among them formation of ureas and isocyanates from primary amines, and symmetrical carbonates from aliphatic alcohols, we suggest a comprehensive mechanistic pathway (Schemes 9−12). After initial reaction of BOC_2O with DMAP, which we observed to occur almost instantaneously to produce **54** and *tert*-butoxycarboxylate (the latter releases CO_2 and *tert*-butoxide), there takes place a preliminary reaction between the amine (or the alcohol) with carbon dioxide (CO_2) to form a carbamate as in Scheme 9 (or carbonate as in Scheme 11). The latter can react further with the BOC-pyridinium species[24] **54** to give a carbamic−carbonic anhydride (e.g., **13** or **B** in Scheme 9) in the case of amines, or a carbonic−carbonic anhydride (e.g., **22**) in the case of alcohols. These anhydrides are

Scheme 10. Decompostion of 13 to *N*-BOC 12 Catalyzed by DMAP



key intermediates and they can lead to coupling reaction products in addition to the *N*-BOC amine or *O*-BOC alcohol products. Isolation of carbamic-carbonic anhydrides **13**, **51**, **52** in reactions of secondary amines with BOC_2O/DMAP during our study, gives credence to the assumption that such intermediates are also formed in the case of primary amines.

Reaction of Amines. Amines are known to react with carbon dioxide under basic conditions to form carbamates.[25] The latter can react further with dehydrating agents such as DCC[26] and DEAD /PPh_3[27] to form an active intermediate that can lead to ureas or in case of amino alcohols, to 2-oxazolidinones. We propose that in reactions of amines or of alcohols with BOC_2O/DMAP, BOC_2O or its derivative **54** serves as the dehydrating agent by reacting with the carbamate (see **A** in Scheme 9) or with the carbonate (see **C** in Scheme 11) to form a carbamic-carbonic anhydride or carbonic-carbonic anhy-

(23) Kemp, D. S.; Curran, T. P. *J. Org. Chem.* **1988**, *53*, 5729.

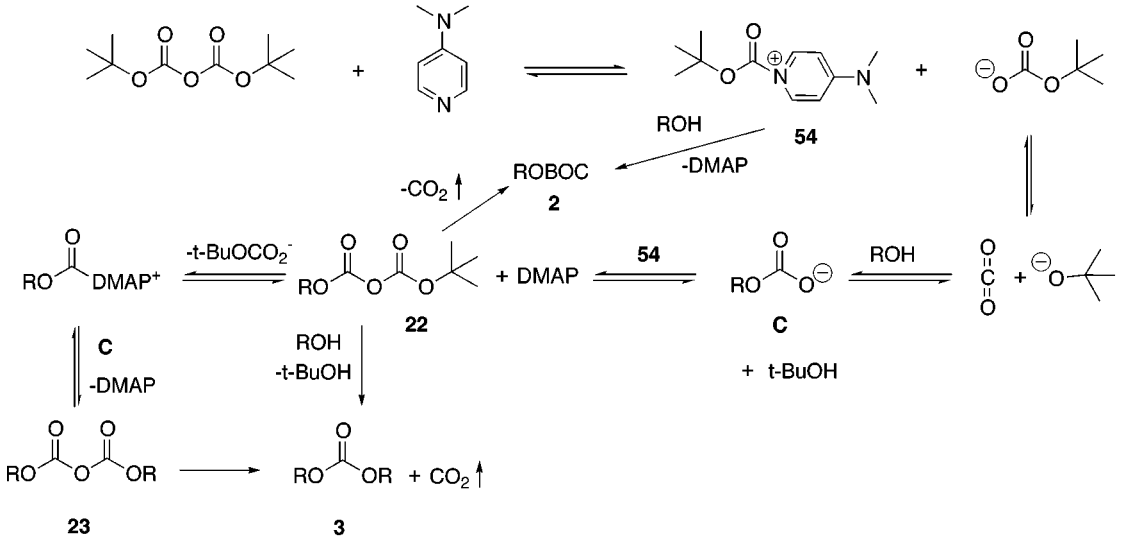
(24) Guibé-Jampel, E.; Wakselman, M. *Synthesis* **1977**, 772.

(25) (a) Aresta, M.; Quaranta, E. *Tetrahedron* **1992**, *48*, 1515. (b) McGhee, W., Riley, D. *J. Org. Chem.* **1995**, *60*, 6205. (c) Casadei, M. A.; Moracci, F. M.; Zappia, G.; Inesi, A.; Rossi, L. *J. Org. Chem.* **1997**, *62*, 6754 and references therein. (d) Cleland, W. W.; Andrews, J.; Guttridge, S.; Hartman, F. C.; Lorimer, G. H. *Chem. Rev.* **1998**. *98*, 549.

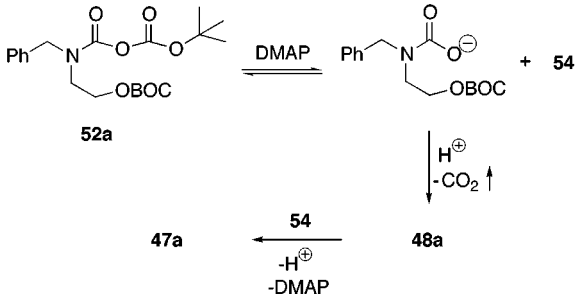
(26) Ogura, H.; Takeda, K.; Tokue, R.; Kobayashi, T. *Synthesis* **1978**, 394.

(27) Kodaka, M.; Tomohiro, T.; Okuno, H. (Y.) *J. Chem. Soc., Chem. Commun.* **1993**, 81.

Scheme 11. Reaction of Alcohols with BOC_2O−DMAP Leading to *O*-BOC 2 and Symmetrical Carbonate 3



Scheme 12. Reaction of 52a with DMAP Leading to *O*-BOC Amine 48a and DiBOC 47a



dride, respectively. The reaction is similar to that of carboxylates with alkyl chloroformates to give mixed anhydrides.[28]

The carbamic−carbonic anhydride of a primary amine may decompose by releasing CO_2 and *tert*-butyl alcohol and lead to isocyanate **7**. Formation of a urea product can occur either by reaction of the amine with the isocyanate or directly by attack of the amine on the carbamic carbonyl of **B** (see path a, Scheme 9). While the latter reaction leads to a urea, reaction at the carbonic carbonyl of **B** (see path b), which is expected to be more favorable, affords the *N*-BOC protected amine **5** and a carbamate ion **A**, that can reenter the cycle. Though we were successful in isolating carbamic-carbonic anhydrides **13** from secondary amines, attempts to isolate or to detect (by NMR) such intermediates from primary aliphatic amines as well as from primary anilines failed.

Carbamic−carbonic anhydrides of secondary amines cannot furnish isocyanates, and reaction with another molecule of amine to give a urea is difficult because of steric reasons. As a result, decomposition of the anhydride **13** to the *N*-BOC-protected amine **5** often can occur with release of CO_2 (possible via a 4-center transition state).[29] This decomposition is greatly accelerated by DMAP which can attack at the anhydride carbonyl in a reversible reaction leading to **54** and a carbamate anion **A** (see Scheme 10). Decomposition of the latter leads to an amine which reacts with **54** to afford the *N*-BOC product **5**. Hence, in most cases of reactions of secondary amines with BOC_2O/DMAP (conditions that are widely employed), formation of the carbamic-carbonic anhydride **B** is not observed and the *N*-BOC amines are isolated. It is likely that in many reactions of (secondary) amines with BOC_2O/DMAP, the *N*-BOC amine products are formed via carbamic−carbonic anhydrides. If the anhydride is stable enough (steric or electronic effects), its isolation becomes possible. Indeed, we found in this study that removal of DMAP, a short time (1−5 min) after the reaction was started, keeps the anhydride stable for a sufficient period of time to permit its isolation (see **13**, **51**, **52**). On the basis of this mechanism, DMAP plays the role not only as acyl (*tert*-butoxycarbonyl) transfer agent but also as producer of carbon dioxide.[30]

The first observation of a carbamic−carbonic anhydride from reaction of a secondary amine with BOC_2O/DMAP was reported by Kemp et al.;[23] however, their attempts to show the generality of this reaction with other secondary amines failed. Based on our results, this is probably attributable to the fact that DMAP was not removed as soon as possible after the reaction started. In fact we found that when an excess of BOC_2O was used, the anhydride **13a** survived for a longer period, probably due to the preferred reaction of DMAP with BOC_2O which prevented decomposition of **13a** by DMAP (Scheme 10). In case of less nucleophilic amines such as indoles or pyrroles reaction with BOC_2O/DMAP led to formation of *N*-BOC products. In these reactions, carbamic−carbonic anhydride intermediates were not isolated or detected. Apparently, the initial step involving reaction of the amine with carbon dioxide to form carbamate (see Scheme 9) is unfavorable.

Reaction of Alcohols. In the reaction of alcohols with BOC_2O/DMAP, after formation of the BOC-pyridinium species **54**, (the latter is much more reactive than BOC_2O with alcohols) *tert*-butoxycarboxylate is released and decomposed to carbon dioxide and the strong base *tert*-butoxide (Scheme 11). This decomposition should be an equilibrium reaction since alcoholates are known to react with carbon dioxide (in fact formation of BOC_2O involves reaction of *tert*-butoxide with carbon dioxide to give

(28) (a) Berkowitz, D. B.; Pedersen, M. L. *J. Org. Chem.* **1994**, *59*, 5476. (b) Kim, S.; Lee, J. I.; Kim, Y. C. *J. Org. Chem.* **1985**, *50*, 560.
(29) Tarbell, D. S. *Acc. Chem. Res.* **1969**, *2*, 296.
(30) Molina, P.; Alajarín, M.; Sánchez-Andrada, P.; Elguero, J.; Jimeno, M. L. *J. Org. Chem.* **1994**, *59*, 7306.

tert-butoxycarboxylate as the initial step).[31] After formation of **54**, the deprotonation step (by *tert*-butoxide) is essential to afford the alcoholate which can react further with carbon dioxide to give the monoalkyl carbonate anion **C**. This reaction also represents an equilibrium so that in case of more stable carbonates, further reaction with the BOC-pyridinium species **54** will afford carbonic−carbonic anhydride **22**. The latter can lead to formation of a symmetrical carbonate (see **3**). When diols are used, intramolecular reaction on the carbonic−carbonic anhydride occurs readily and leads to a high yield of cyclic carbonate (see **25** or **31**).

In case of relatively acidic alcohols, like trifluoroethanol, benzhydrol or phenols the alcoholate is more stable and the reaction with carbon dioxide is less favorable. Hence, reaction of the alcoholate with the BOC-pyridinium intermediate **54** takes place more rapidly affording only the *O*-BOC protected alcohol **2**, **19** or **21**. In general, more acidic alcohols gave more *O*-BOC products (e.g., **2**) and less of the symmetrical carbonate (e.g., **3**).

The pK_a of the alcohols strongly influences not only formation of products (symmetrical carbonate **3** or *O*-BOC alcohol **2**), but also the rate of reaction of alcohols with BOC_2O/DMAP. While reaction of ethanol with BOC_2O/DMAP is completed after 1.5 h, the same reaction of the more acidic trifluoroethanol is over after 5 min. The observation, that the more acidic alcohol reacts faster, is in agreement with reported reactions of amides or carbamates with BOC_2O/DMAP.[32] This leads to the conclusion that fast deprotonation is followed by reaction of the alcoholate with CO_2 and **54** (or only with **54**) affording products. The large difference in reaction time between ethanol and trifluoroethanol suggests that a strong base such as *tert*-butoxide rather than the weaker *tert*-butoxycarboxylate is involved in proton abstraction. Support for this conclusion is the observation that immediate evolution of carbon dioxide occurs when DMAP is added to a solution of BOC_2O. This indicates that the released *tert*-butoxycarboxylate *(tert*-butyl bicarbonate) is decomposed immediately to carbon dioxide and *tert*-butoxide; the latter then can serve as the strong base for removal of a proton from the alcohol.

Reactions of Amino Alcohols. In the reaction of 2-amino alcohol **46a** with BOC_2O/DMAP, when the amine is secondary, two carbamic−carbonic anhydride derivatives **51a** and **52a** were isolated. The fact that when the reaction was stopped after a short time, anhydride **51a** containing a free OH was isolated as the major product (70%) together with *O*-BOC anhydride **52a** is consistent with the amine reacting much faster than the alcohol function. **51a** can cyclize to 2-oxazolidinone **50a**, with release of carbon dioxide and *tert*-butyl alcohol, as was shown by treatment of **51a** with base (Et_3N). In the reaction of amino alcohols, where the amine is primary (e.g., **35a**), an anhydride similar to **51a** is probably formed and cyclization occurred readily to afford the 2-oxazolidinone **38a** in high yield. Further reaction of the NH oxazolidinone **38a** with BOC_2O/DMAP (in a reaction analogous to that of amides)[13] afforded *N*-BOC 2-oxazolidinone **42a**. Indeed, when less BOC_2O was used the NH oxazolidinone **38a** was also isolated together with the *N*-BOC derivative **37a**. In the case of 1,2-amines a similar pathway can lead to formation of 1,3-imidazolidinone **15**.

O-BOC amine **48a** is apparently the result of reaction of the *O*-BOC carbamic−carbonic anhydride **52a** with amino alcohol **46a** or with DMAP (see Scheme 12). In the event, addition of DMAP to a solution of isolated **52a** led to formation of *O*-BOC amine **48a** in 30% yield. Furthermore, when the reaction of **46a** with BOC_2O/DMAP was taking place in NMR tube ($CDCl_3$), anhydrides **51a** and **52a** were observed with a small amount of **47a** and **53a** but no *O*-BOC amine **48a** was detected. This leads to the conclusion that first reaction on the amine function takes place to produce the anhydride **52a** and then reverse reaction with DMAP gives back a free amine (**48a**).

***N*-Methylimidazole.** The use of *N*-methylimidazole (MeIm) as catalyst instead of DMAP in the reaction of amines and alcohols with BOC_2O led to formation of less coupling reaction products and more *N*- or *O*-BOC derivatives. In some cases, when the reaction with BOC_2O/MeIm was carried out in nonpolar solvents, formation of coupling reaction products (cf. **3**, **6**, **49**, **50**) was totally prevented. Isolation of compounds **10** and **29** indicate that sometimes MeIm reacted not only as a catalyst but also as a reactant. Although the big difference between MeIm and DMAP is as yet unclear it might be due to the fact that DMAP is a much more powerful acyl transfer catalyst than MeIm.[10a]

Conclusions

Reaction of BOC_2O in the presence and absence of DMAP was examined with primary aliphatic and aromatic amines, secondary amines, diamines, as well as with aliphatic and aromatic alcohols, amino alcohols, and an aminothiol. Different products were observed depending on the ratio of reagents and polarity of the solvent. From the synthetic point of view, the use of BOC_2O/DMAP was found to be useful for the synthesis of symmetrical carbonates, cyclic carbonates, *N*-BOC 2-oxazolidinones, *N*-BOC 2-thiazolidinone, and *N*,*N*′-diBOC 2-imidazolidinones.

Alcohols produced *O*-BOC derivatives as well as symmetrical carbonates. The effect of alcohol acidity and of replacement of DMAP by *N*-methylimidazole was also examined. More acidic alcohols afforded mainly *O*-BOC products and less or no carbonates. Secondary alcohols were more prone to formation of symmetrical carbonates than primary alcohols. In general the preferred conditions for formation of symmetrical carbonates were BOC_2O and 0.2−0.5 equiv DMAP in MeCN, whereas a high yield of *O*-BOC derivatives resulted when less than 0.1 equiv of DMAP was used in dioxane or with MeIm in toluene. Diols gave preferentially the cyclic carbonates (cf. **25**, **31**) using 1 equiv of DMAP in MeCN, whereas formation of *O*,*O*′-diBOC carbonates was favored with MeIm in toluene.

Conversion of primary aliphatic amines, e.g., **4a**, to its *N*-BOC derivative **5a** at room temperature occurs preferentially in the absence of DMAP but also in the presence of a MeIm catalyst in nonpolar solvent. By contrast, formation of isocyanate **7a** is favored at low temperature in polar MeCN in the presence of DMAP, while at room temperature urea **6a** is the major product. Similar behavior was observed with electron-rich aniline **4b** but electron-poor aromatic amines (e.g., **4c**) gave, in

(31) (a) Dean, C. S.; Tarbell, D. S *Chem. Commun*. **1969**, 728. (b) Könnecke, A.; Grehn, L.; Ragnarsson, U. *Tetrahedron Lett*. **1990** *31*, 2697 and references therein.

(32) Hansen, M. M.; Harkness, A. R.; Coffey, D. S.; Bordwell, F. G.; Zhao, Y. *Tetrahedron Lett*. **1995** *36*, 8949.

the presence of DMAP or MeIm, a mixture of products including *N*-BOC urea derivative **9c**. Secondary amines react readily with BOC_2O in MeCN at room temperature to produce *N*-BOC derivatives. The discrepancy that the reaction is slowed by DMAP was resolved by isolation and identification of carbamic-carbonic anhydride intermediates **13**. By removing DMAP within minutes in reactions of secondary amines with BOC_2O/DMAP, we showed that rapid formation of isolable carbamic−carbonic anhydride intermediates **13** had taken place. These react further with DMAP to form *N*-BOC products. The formation of isocyanates and ureas in reactions of primary amines with BOC_2O/DMAP also can be explained by such carbamic−carbonic anhydride intermediates. We suggest that such anhydrides can be formed by reaction of amines with CO_2 to produce a carbamate that reacts further with the *N*-acylpyridinium intermediate **54**. We also succeeded in isolating carbonic-carbonic anhydrides as fast formed intermediates in reactions of aliphatic alcohols with BOC_2O/DMAP. These can explain the formation of symmetrical (or cyclic) carbonates in addition to *O*-BOC protected alcohols (or diols).

1,2-Amines were converted to the diBOC derivative of the cyclic urea when an excess (3.5 equiv) of BOC_2O and 0.2−0.5 equiv of DMAP were used. To obtain the *N*,*N*′-diBOC diamine, 2 equiv of BOC_2O and no DMAP should be employed. 1,2-Amino alcohols as well as aminothiols (primary amine) behaved similarly to 1,2-diols and 1,2-diamines in as much as the cyclic carbamates **37** (or **42**) can be isolated in the presence of DMAP, but *N*-BOC amino alcohols **36** (or **43**) are formed in the absence of DMAP. By contrast, 1,2-amino alcohols (secondary amine) led to a mixture of products. However, if the reaction was stopped after 1−10 min, carbamic-carbonic anhydrides **51** and **52** were isolated and identified, as was the case with secondary amines. **51a** reacted further with base (Et_3N) to give cyclic carbamate **50a**, while **52a** reacted with DMAP to produce di-BOC amino alcohol **47a** in good yield.

Experimental Section

General Methods. For general experimental techniques and analytical measurements, see ref 6. Solvents $CHCl_3$ (AR), toluene (AR), dioxane (Analytical), and MeCN (HPLC) were used without additional purification. Starting materials were commercially available. All final compounds were purified by chromatography (petroleum ether/ether or ethyl acetate eluent) for ^1H and ^{13}C NMR analysis (except for unstable intermediates as crude product). Ratios and yields are calculated on the basis of the ^1H NMR spectra of the crude reaction mixture. Isolated yields for stable products are lower by 5−10% and for unstable intermediates by 5−30% than those observed in the crude NMR and this may be due to decomposition of products during purification.

General Procedure A for the Reaction of Aliphatic Alcohols with BOC_2O−DMAP. Formation of *O*-BOC Derivatives 2, 19, and 21 and Symmetrical Carbonates 3 (Scheme 1). To a solution of BOC_2O (0.8−1.2 equiv) and alcohol (0.5 mmol) in MeCN or toluene (5 mL) at room temperature was added DMAP (0.1−0.4 equiv) or MeIm (1 equiv). At the end of the reaction chloroform (10 mL) was added, and the solution was washed with 5% HCl (20 mL), dried with $MgSO_4$, and evaporated to give compound **2a**−**i**, **19**, **21**, and **3a**,**b**,**d**−**g**,**i** (see Table 5).

General Procedure B for the Reaction of Primary and Secondary Aliphatic Amines with BOC_2O. Formation of *N*-BOC Products 5 and 12 (Schemes 1 and 3). BOC_2O (1 equiv) was dissolved in 3 mL of MeCN at room temperature, and the amine (0.5 mmol) in 2 mL of MeCN was added in one portion. After 5−15 min, the reaction mixture was evaporated to give **5a** and **12a**,**c**−**e** quantitatively (by NMR).

General Procedure for the Reaction of Primary and Secondary Anilines with BOC_2O. Formation of *N*-BOC Products 5 and 12 (Schemes 2 and 3). General procedure B was repeated using BOC_2O (1−1.1 equiv), aniline **4b**, **4d** (0.5 mmol), and 1 equiv of Et_3N in case of **4b**. The mixture was stirred at room temperature for 2−7 days and evaporated to give **5b** or **5d** (see Table 2). In the case of **11b**, the procedure was carried out with 1 equiv of BOC_2O at $CHCl_3$ for 3 days to give **12b** in 90% yield (by NMR integration).

Reaction of Cyclohexylamine with BOC_2O−DMAP. Formation of Isocyanate 7a. BOC_2O (1.2 equiv) was dissolved in 3 mL of MeCN and placed in an ice bath, and DMAP (0.2 equiv) was added. After 5 min, cyclohexyl amine (0.5 mmol) in 2 mL of MeCN was added dropwise in 1 min, and the reaction was allowed to proceed for 10 min. The workup in procedure A was repeated to give **7a** in 80% yield (by NMR integration; see Table 1).

General Procedure C for the Reaction of Primary Anilines with BOC_2O−DMAP. Formation of *N*-BOC 5, Ureas 6, Isocyanates 7, DiBOC 8, *N*-BOC Ureas, and 9-MeIm Anilides 10 (Scheme 2). BOC_2O (1.2−2.5 equiv) was dissolved in 3 mL of MeCN (or toluene) at room temperature, and DMAP (or MeIm) was added. After 5 min, the aniline (0.5 mmol) in 2 mL of MeCN (or in toluene) was added dropwise during 1 min, and the reaction was allowed to proceed for 0.5−2 h. The workup in procedure A was followed to give **5b**,**d**, **6**, **7b**, **8b**−**d**, and **9c**,**d** (see Table 2; MeIm gave also **10b**−**f**).

General Procedure D for the Reaction of Secondary Amines with BOC_2O−DMAP. Formation of Carbamic−Carbonic Anhydrides 13 (Scheme 3). BOC_2O (2 equiv) was dissolved in 3 mL of MeCN and placed in an ice bath, and DMAP (0.5 equiv) was added. After 5 min, the amine (0.5 mmol) in 2 mL of MeCN was added dropwise during 2 min, and after an additional 1−5 min, chloroform (10 mL) was added and the solution was washed immediately with 1% HCl (2 × 50 mL) and water, dried with $MgSO_4$, and evaporated to give **13a**−**e** (see Tables 3 and 4).

Reaction of Diamines with BOC_2O−DMAP. Formation of *N*,*N*′-DiBOC Imidazolidinones 15 (Scheme 4). General procedure C was repeated using BOC_2O (3.5 equiv), DMAP (0.2 equiv for **b** or 0.5 equiv for **a**), and diamine (0.5 mmol), and the reaction was allowed to proceed for 10 min for **b** or 0.5 h for **a** to give **15a** in 93% yield and **15d** quantitatively (by NMR).

Reaction of Diamines with BOC_2O. Formation of *N*,*N*′-DiBOC Diamines 16 (Scheme 4). General procedure B was repeated using BOC_2O (2 equiv), MeCN for **a** or $CHCl_3$ for **b**, and diamine (0.5 mmol) and the reaction was allowed to proceed for 10 min for **a** or 24 h for **b** to give **16a** quantitatively and **16b** in 95% yield (by NMR).

Reaction of Phenols with BOC_2O−DMAP. Formation of *O*-BOC Phenols 19 and 21. General procedure A was repeated using BOC_2O (1.2 equiv), phenol (0.5 mmol), and DMAP (0.2 equiv) to give compounds **19** and **21** quantitatively (by NMR; see Table 5).

General Procedure E for Reaction of Aliphatic Alcohols with BOC_2O−DMAP. Formation of Mixed and Symmetrical Carbonic−Carbonic Anhydrides 22 and 23 (Scheme 5). BOC_2O (0.8 equiv) and alcohol (0.5 mmol) were dissolved in 5 mL of MeCN at room temperature, and DMAP (0.4 equiv) was added. The reaction was allowed to proceed for 10−20 min, and then chloroform (10 mL) was added. The solution was washed with 1% HCl (2 × 50 mL) and water, dried with $MgSO_4$, and evaporated to give inseparable **22d**−**f**,**i** and **23d**−**f** (as crude products together with **2** and **3**). Ratio of **22** + **23**:**2** + **3** (by NMR integration) and reaction time: for **d** 60:40, 5 min; for **e** 85:15, 10 min; for **f**: 85:15, 5 min; for **22i** 7% yield after 10 min.

General Procedure for the Reaction of Diols with BOC_2O−DMAP. Formation of Cyclic Carbonates 25 and 31, *O*,*O*′-DiBOC Products 26 and 32, *O*,*O*′-DiBOC Symmetrical Carbonates 27 and 33, and Mono *O*-BOC 28 and

34. General procedure A was repeated using BOC_2O (1.5−3 equiv), diol (**24** or **30**) (0.5 mmol), and DMAP (0.1−1.5 equiv) or MeIm (1 equiv), and the mixture was stirred for 0.5−2 h and then evaporated to give **25a**−**d** and **31a**−**c**. For the other compounds the workup in procedure A was repeated to give compounds **26a**−**d**, **27b**,**d**, **28c**,**d** and **29** for 1,2 diols and **32a**−**c**, **33a**−**c**, and **34c** for 1,3-diols (see Tables 6 and 7).

General Procedure for the Reaction of Amino Alcohols with BOC_2O. Formation of *N*-BOC 36 and 53. General procedure B was repeated using BOC_2O (1 equiv) and amino alcohol (**35** or **46**) (0.5 mmol) to give **36a**,**c**,**d**, or **53a**,**b** quantitatively (by NMR). In case of **36b**, 3 equiv of Et_3N was also added with the amino alcohol and after 1 h the workup in procedure A was repeated to give **36b** quantitatively.

General Procedure F for the Reaction of Amino Alcohols (Primary Amine) with BOC_2O−DMAP. Formation of *N*-BOC 2-Oxazolidinones 37, *N,O*-DiBOC Derivatives 39, and *N,N,O*-triBOC Derivatives 40 (Scheme 6). BOC_2O (3 equiv) was dissolved in 4 mL of MeCN (or toluene) and placed in an ice bath, and 0.5 equiv DMAP (or 1 equiv MeIm) and 3 equiv of Et_3N (for **37b**) were added. After 5 min, amino alcohol (0.5 mmol) in 1 mL of solvent was added dropwise (or as a solid in portions) during 2 min, and the reaction was allowed to run for 1 h more. The workup in procedure A was repeated to give **37a**−**d**, **39a**, and **40a** (see Tables 8 and 9).

Reaction of Aminothiol with BOC_2O−DMAP. Formation of 42 (Scheme 7). General procedure F was repeated using BOC_2O (3 equiv), DMAP (1.5 equiv), 5 equiv of Et_3N and cysteine methyl ester hydrochloride (0.5 mmol) to give **42** in 75% yield (by NMR integration).

Reaction of Aminothiol with BOC_2O. Formation of *N*-BOC Derivative 43, *N,S*-DiBOC Derivative 44, and *N,N,S*-triBOC Derivatives 45 (Scheme 7). BOC_2O (1 equiv) was dissolved in 5 mL of MeCN at room temperature, and the cysteine methyl ester hydrochloride (0.5 mmol) and Et_3N (3 equiv) were added in one portion. After 1 h, the workup in procedure A was followed to give **43** in 90% yield (by NMR integration). For **44**, the procedure for **43** was repeated, and BOC_2O (1.1 equiv) dissolved in 5 mL of MeCN was added to the crude mixture at room temperature. DMAP (0.2 equiv) was added, and the reaction was allowed to run for 1 h more. The workup in procedure A gave **44** in 90% yield (by NMR integration). For **45**, the procedure for **44** was repeated with 3 equiv of BOC_2O and 0.2 equiv of DMAP. After 2 h dichloromethane (10 mL) was added and the solution was washed with 2% HCl (20 mL) and water, dried with $MgSO_4$ and evaporated to give **45** in 85% yield (by NMR integration).

General Procedure for the Reaction of Amino Alcohols (Secondary Amine) with BOC_2O−DMAP. Formation of *N,O*-DiBOC Derivatives 47, *O*-BOC Amine 48, *N,N′*-DiBOC Symmetrical Carbonates 49, and 2-Oxazolidinones 50 (Scheme 8). General procedure F was repeated using BOC_2O (3 equiv), DMAP (0.5 equiv), or 1 equiv MeIm for **49** and amino alcohol (0.5 mmol), and the reaction was stirred for 1.5 h (for **46a**) or 10 h (for **46b**) more. The workup in procedure A was repeated to give (yield by NMR integration) for **46a**: 70% **47a**, 20% **48a**, 5% **49a**, and 5% **50a**. For **46b**: 65% **47b**, 33% **49b** and 2% **50b**.

General Procedure for the Reaction of Amino Alcohols (Secondary Amine) with BOC_2O−DMAP. Formation of Carbamic−Carbonic Anhydride 51 and 52 (Scheme 8). General procedure D was repeated using BOC_2O (3 equiv), MeCN for **51** or $CHCl_3$ for **52**, DMAP (0.5 equiv), and amino alcohol (0.5 mmol), and after an additional 1 min for **51a,b** (10 min for **52a** or 5 h for **52b**), the workup in procedure A was repeated to give (isolated yield) 63% **51a**, 40% **51b**, 82% **52a**, and 45% **52b**.

***tert*-Butyl 2-trifluoroethyl carbonate (2c):** colorless oil; bp 132 °C; ^{1}H NMR δ 4.44 (q, J_{HF} = 8 Hz, 2H), 1.51 (s, 9H); ^{13}C NMR δ 152.04, 122.78 ($^1J_{CF}$ = 280 Hz), 83.97, 62.52 ($^2J_{CF}$ = 37 Hz), 27.45; ^{19}F NMR δ −75.60 (t, J_{FH} = 8 Hz, 3 F); MS *m*/*z* (CI/NH_3) 218 (MNH_4^+, 100), 162 (30), 141 (46); HRMS calcd for $C_7H_{12}O_3F_3$ 201.0738, found 201.0753.

***tert*-Butyl cyclopentyl carbonate (2f):** colorless oil; ^{1}H NMR δ 5.06−4.99 (m, 1H), 1.93−1.71 (m, 8H), 1.49 (s, 9H); ^{13}C NMR δ 153.32, 81.47, 79.74, 32.54, 27.77, 23.59; MS *m*/*z* (dci/CH_4) 187 (MH^+, 2), 149 (92), 137 (100); HRMS calcd for $C_{10}H_{19}O_3$ 187.1334, found 187.1370.

***N,N*-Di(*tert*-butoxycarbonyl)-*o*-nitroaniline (8c):** white solid; mp 97−99 °C; ^{1}H NMR δ 8.07 (d, J = 8 Hz, 1H), 7.65 (t, J = 8 Hz, 1H), 7.51 (t, J = 8 Hz, 1H), 7.34 (d, J = 8 Hz, 1H), 1.40 (s, 18H); ^{13}C NMR δ 150.10, 145.57, 133.63, 133.15, 131.10, 128.71, 124.88, 83.56, 27.62; MS *m*/*z* (CI/NH_3) 356 (MNH_4^+, 42), 339 (MH^+, 95), 300 (10), 283 (20), 256 (100), 239 (10), 200 (28); HRMS calcd for $C_{16}H_{23}N_2O_6$ 339.1556, found 339.1960.

***N*-(*tert*-Butoxycarbonyl)di-*o*-nitrophenyl urea (9c):** yellow solid; mp 122−124 °C; ^{1}H NMR δ 12.62 (s br, 1H), 8.48 (dd, J = 1.5, 8.5 Hz, 1H), 8.19 (tm, 1H), 8.17 (tm, 1H), 7.72 (dd, J = 7.5, 1.5 Hz, 1H), 7.58 (tm, 2H), 7.40 (dd, J = 8, 1.5 Hz, 1H), 7.20 (tm, 1H), 1.38 (s, 9H); ^{13}C NMR δ 152.45, 151.55, 145.71, 138.38, 134.94, 133.99, 133.76, 131.98, 131.73, 129.33, 125.59, 125,29, 123.55, 123.43, 85.66, 27.59; MS *m*/*z* (CI/NH_3) 403 (MNH_4^+, 3), 320 (100), 303 (29); HRMS calcd for $C_{18}H_{18}N_4O_7$ 402.1175, found 402.1152.

2-(1-Methyl)imidazo-*o*-nitroanilide (10e): yellow solid; mp 183−185 °C; ^{1}H NMR δ 12.13 (s br, 1H), 8.84 (dd, J = 9, 1 Hz, 1H), 8.27 (dd, J = 8, 1 Hz, 1H), 7.68 (ddd, J = 9, 8, 1 Hz, 1H), 7.22 (dt, J = 8, 1 Hz, 1H), 7.20 (d, J = 1 Hz, 1H), 7.08 (d, J = 1 Hz, 1H), 4.12 (s, 3H); ^{13}C NMR δ 157.45, 138.51, 137.23, 135.51, 134.26, 128.35, 126.72, 125.96, 123.39, 122.01, 35.93; MS *m*/*z* (CI/NH_3) 247 (MH^+, 100), 217 (35), 199 (15); HRMS calcd for $C_{11}H_{11}N_4O_3$ 247.0831, found 247.0826.

***N*-(*tert*-Butoxycarbonyl)-*N*-benzylethylamine (12a):** colorless oil; ^{1}H NMR δ 7.38−7.18 (m, 5H), 4.24 (s, 2H), 3.21 (s br, 2H), 1.47 (s, 9H), 1.06 (s br, 3H); ^{13}C NMR δ 155.24, 138.52, 128.20, 127.41, 126.83, 79.19, 49.45, 41.08, 28.24, 12.98; MS *m*/*z* (CI/NH_3) 235 (M^+, 35), 197 (100), 180 (60), 136 (75); HRMS calcd for $C_{14}H_{22}NO_2$ 236.1650, found 236.1600.

***tert*-Butyl carbonic *N*-benzylethyl carbamic anhydride (13a):** colorless oil; ^{1}H NMR δ (two rotomers) (a) 7.39−7.23 (m, 5H), 4.53 (s, 2H), 3.34 (q, J = 7.5 Hz, 2H), 1.55 (s, 9H), 1.51 (s br, 3H); (b) 7.39−7.23 (m, 5H), 4.47 (s, 2H), 3.24 (q, J = 7.5 Hz, 2H), 1.55 (s, 9H), 1.51 (s br, 3H); ^{13}C NMR δ (two rotomers) 150.39, 149.49, 147.73, 147.60, 136.37, 136.28, 128.53, 128.48, 127.76, 127.52, 127.14, 84.53, 84.48, 50.63, 50.22, 42.14, 41.95, 27.29, 27.25, 13.24, 12.12; MS *m*/*z* (dci/CH_4) 280 (MH^+, 5), 180 (100); HRMS calcd for $C_{15}H_{22}NO_4$ 280.1548, found 280.1570.

***tert*-Butyl carbonic *N*-methylphenyl carbamic anhydride (13b):**[12] colorless oil; ^{1}H NMR δ 7.43−7.14 (m, 5H), 3.35 (s, 3H), 1.42 (s, 9H); ^{13}C NMR δ 148.16, 147.60, 141.67, 129.10, 127.38, 125.90, 84.48, 38.44, 27.19; MS *m*/*z* (EI) 251 (M^+, 31), 152 (100); HRMS calcd for (M^+ − BOC) $C_8H_{10}NO_2$ 152.0711, found 152.0750.

***tert*-Butyl carbonic morpholinyl carbamic anhydride (13c):** colorless oil; ^{1}H NMR δ 3.76−3.70 (m, 4H), 3.59−3.47 (m, 4H), 1.55 (s, 9H); ^{13}C NMR δ 148.72, 147.35, 84.98, 66.19, 45.26, 45.15, 27.35; MS *m*/*z* (CI/NH_3) 231 (M^+, 86), 188 (51), 149 (100), 132 (90); HRMS calcd for $C_{10}H_{18}NO_5$ 232.1184, found 232.1120.

***tert*-Butyl carbonic pyrrolidinyl carbamic anhydride (13d):** colorless oil; ^{1}H NMR δ 3.44 (m, 4H), 1.92 (m, 4H), 1.54 (s, 9H); ^{13}C NMR δ 148.01, 147.91, 84.44, 46.69, 46.58, 27.47, 25.49, 24.78; MS *m*/*z* (dci/CH_4) 215 (M^+, 1), 170 (67), 130 (100), 114 (94); HRMS calcd for $C_{10}H_{17}NO_4$ 215.1157, found 215.1161.

***tert*-Butyl carbonic diallyl carbamic anhydride (13e):** colorless oil; ^{1}H NMR δ 5.78 (m, 2H), 5.23 (m, 2H), 5.19 (m, 2H), 3.89 (dd, J = 3, 13 Hz, 4H), 1.53 (s, 9H); ^{13}C NMR δ 149.82, 147.66, 132.33, 131.97, 118.19, 117.68, 84.75, 49.48, 27.45; MS *m*/*z* (dci/CH_4) 242 (MH^+, 1), 186 (6), 142 (100); HRMS calcd for $C_{12}H_{20}NO_4$ 242.1392, found 242.1386.

1,3-Di(*tert*-butoxycarbonyl)imidazolidin-2-one (15a): white solid; mp 142−144 °C; ^{1}H NMR δ 3.73 (s, 4H), 1.53 (s, 18H); ^{13}C NMR δ 150.16, 148.70, 82.79, 39.38, 27.80; MS *m*/*z* (dci/CH_4) 215 (MH^+, 2), 231 (69), 203 (100); HRMS calcd for $C_{13}H_{23}N_2O_5$ 287.1606, found 287.1577.

1,3-Di-(*tert*-butoxycarbonyl)benzimidazolidin-2-one (15d): white solid; mp 142−144 °C; ^{1}H NMR δ 7.88 (m, 2H), 7.23 (m, 2H), 1.67 (s, 18H); ^{13}C NMR δ 148.32, 147.19, 125.99, 124.19, 113.87, 85.16, 27.91; MS *m*/*z* (CI/NH_3) 335 (MH^+, 6), 235 (8), 136 (100); HRMS calcd for $C_{17}H_{22}N_2O_5$ 344.1528, found 344.1516.

***tert*-Butyl cyclopentyl dicarbonate (22f):** colorless oil; ^{1}H NMR δ 5.25−5.15 (m, 1H), 1.92−1.83 (m, 4H), 1.82−1.71 (m, 2H), 1.69−1.58 (m, 2H), 1.53 (s, 9H); ^{13}C NMR δ 148.61, 146.41, 85,58, 83.23, 32.46, 27.41, 23.48; MS *m*/*z* (dci/CH_4) 231 (MH^+, 13), 131 (100); HRMS calcd for $C_{11}H_{19}O_5$ 231.1232, found 231.1190.

***tert*-Amyl *tert*-butyl dicarbonate (22i):** colorless oil; ^{1}H NMR δ 1.82 (q, J = 7.5 Hz, 2H), 1.52 (s, 9H), 1.49 (s, 6H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 146.76, 146.63, 87.72, 85.11, 32.95, 27.35, 24.76, 8.02; MS *m*/*z* (CI/NH_3) 250 (MNH_4^+, 100); HRMS calcd for $C_{11}H_{21}O_5$ 233.1389, found 233.1336.

***O*,*O*′-Di(*tert*-butoxycarbonyl)-1,2-*trans*-cyclohexanediol (26d):** white solid; mp 67−69 °C; ^{1}H NMR δ 4.66−4.54 (m, 2H), 2.18−2.07 (m, 2H), 1.80−1.66 (m, 2H), 1.48 (s, 18H), 1.47−1.37 (m, 4H); ^{13}C NMR δ 152.84, 81.92, 76.41, 29.91, 27.74, 23.25; MS *m*/*z* (dci/CH_4) 317 (MH^+, 2), 261 (27), 205 (61), 98 (100); HRMS calcd for $C_{16}H_{29}O_6$ 317.1964, found 317.1940.

Di(2-*trans*-*O*-(*tert*-butoxycarbonyl))cyclohexyl) carbonate (27d): white solid; mp 116−118 °C; ^{1}H NMR δ 4.62 (m, 4H), 2.15 (m, 4H), 1.71 (m, 4H), 1.48 (s, 9H), 1.47 (s, 9H), 1.48−1.26 (m, 8H); ^{13}C NMR δ 153 90, 153.45, 82.10, 77.29, 77.26, 76.14, 75.57, 29.84, 29.77, 29.63, 29.50, 27.77, 23.16, 23.13, 22.94, 22.91; MS *m*/*z* (dci/CH_4) 459 (MH^+, 1), 347 (23), 303 (15), 205 (33), 143 (61), 98 (100); HRMS calcd for $C_{23}H_{39}O_9$ 459.2594, found 459.2606.

***O*-(*tert*-Butoxycarbonyl)-1,2-*trans*-cyclohexanediol (28d):** colorless oil; ^{1}H NMR δ 4.36 (dtt, J = 15, 10, 4.5 Hz, 1H), 3.58 (dtt, J = 15, 10, 4.5 Hz, 1H), 2.17−2.08 (m, 2H), 1.78−1.65 (m, 2H), 1.50 (s, 9H), 1.39−1.21 (m, 4H); ^{13}C NMR δ 153.49, 82.32, 81.11, 72.65, 32.84, 29.95, 27.76, 23.93, 23.79; MS *m*/*z* (dci/CH_4) 217 (MH^+, 97), 161 (100); HRMS calcd for $C_{11}H_{21}O_4$ 217.1439, found 217.1431.

2-*trans*-(*O*-(*tert*-Butoxycarbonyl))cyclohexyl 2′-(1′-methyl)imidazole carboxylate (29): yellowish oil; ^{1}H NMR δ 7.14 (d, J = 1 Hz, 1H), 7.01 (d, J = 1 Hz, 1H), 5.08 (ddd, J = 15, 10, 4.5 Hz, 1H), 4.82 (ddd, J = 15, 10, 4.5 Hz, 1H), 3.99 (s, 3H), 2.17 (m, 2H), 1.77 (m, 2H), 1.70−1.40 (m, 4H), 1.39 (s, 9H); ^{13}C NMR δ 158.32, 152.80, 136.62, 129.41, 126 11, 82.10, 76.11, 74.65, 35.99, 30.01, 29.94, 27.66, 23.32, 23.22; MS *m*/*z* (dci/CH_4) 325 (MH^+, 100), 269 (15), 220 (27), 205 (37); HRMS calcd for $C_{16}H_{25}N_2O_5$ 325.1763, found 325.1779.

***O*,*O*′-Di(*tert*-butoxycarbonyl)-1,3-propanediol (32b):** colorless oil; ^{1}H NMR δ 4.16 (t, J = 6.5 Hz, 4H), 2.02 (pent, J = 6.5 Hz, 2H), 1.49 (s, 18H); ^{13}C NMR δ 153.41, 82.11, 63.44, 28.11, 27.75; MS *m*/*z* (CI/NH_3) 297 (MNH_4^+, 100), 238 (80), 182 (50); HRMS calcd for $C_{13}H_{25}O_6$ 277.1651, found 277.1653.

Di(3-(*tert*-butoxycarbonyloxy)propyl) carbonate (33b): colorless oil; ^{1}H NMR δ 4.24 (t, J = 7.5 Hz, 4H), 4.16 (t, J = 7.5 Hz, 4H), 2.04 (pent, J = 7.5 Hz, 4H), 1.49 (s, 18H); ^{13}C NMR δ 154.92, 153.34, 82.16, 64.43, 63.19, 28.05, 27.72; MS *m*/*z* (CI/NH_3) 396 (MNH_4^+, 74), 340 (18), 284 (100); HRMS calcd for $C_{17}H_{31}O_9$ 379.1968, found 379.1976.

3-(*tert*-Butoxycarbonyl)-5-methyloxazolidin-2-one (37c): white solid; mp 102−104 °C; ^{1}H NMR δ 4.64 (ddq, J = 8, 7.25, 6 Hz, 1H), 4.05 (dd, J = 10, 8 Hz, 1H), 3.50 (dd, J = 10, 7.25 Hz, 1H), 1.54 (s, 9H), 1.46 (d, J = 6 Hz, 3H); ^{13}C NMR δ 151.87, 149.53, 83.70, 69.70, 50.06, 27.92, 20.34; MS *m*/*z* (dci/CH_4) 202 (MH^+, 1), 146 (100), 102 (11); HRMS calcd for $C_9H_{16}NO_4$ 202.1079, found 202.1030.

3-(*tert*-Butoxycarbonyl)-4-(methoxycarbonyl)thiazolidin-2-one (42): yellow oil; ^{1}H NMR δ 4.99 (dd, J = 8.5, 2.25 Hz, 1H), 3.84 (s, 3H), 3.64 (dd, J = 11.75, 8.5 Hz, 1H), 3.32 (dd, J = 11.75, 2.25 Hz, 1H), 1.51 (s, 9H); ^{13}C NMR δ 169.74, 168.79, 148.48, 84.42, 59.37, 53.40, 27.75, 27.35; MS *m*/*z* (CI/NH_3) 279 (MNH_4^+, 7), 179 (100), 162 (42); HRMS calcd for $C_{10}H_{15}NO_5S$ 261.0670, found 261.0667.

***N*,*S*-Di(*tert*-butoxycarbonyl)cysteine methyl ester (44):** white solid; mp 52−54 °C; ^{1}H NMR δ 5.37 (s br, 1H), 4.55 (m, 1H), 3.75 (s, 3H), 3.31 (m, 1H), 3.21 (m, 1H), 1.49 (s, 9H), 1.44 (s, 9H); ^{13}C NMR δ 170.95, 168.34, 154.97, 85.43, 79.98, 52.53, 52.25, 33.08, 28.22, 28.06; MS *m*/*z* (CI/NH_3) 353 (MNH_4^+, 23), 336 (MH^+, 100), 297 (22), 280 (24), 236 (35); HRMS calcd for $C_{14}H_{26}NO_6S$ 336.1480, found 336.1515.

***N*,*O*-Di-(*tert*-butoxycarbonyl)-*N*-benzylethanolamine (47a):** colorless oil; ^{1}H NMR δ (two rotomers) (a) 7.35−7.14 (m, 5H), 4.50 (s br, 2H), 4.12 (s br, 2H), 3.38 (s br, 2H), 1.52−1.42 (m, 18H); (b) 7.35−7.14 (m, 5H), 4.50 (s br, 2H), 4.16 (s br, 2H), 3.48 (s br, 2H), 1.52−1.42 (m, 18H); ^{13}C NMR δ (two rotomers) 155.28, 153.05, 138.05, 138.82, 128.24, 127.50, 126.92, 81.66, 79.74, 64.47, 64.29, 51.37, 50.37, 45.20, 44.89, 28.08, 27.47; MS *m*/*z* (dci/CH_4) 352 (MH^+, 10), 296 (10), 240 (100); HRMS calcd for $C_{19}H_{30}NO_5$ 352.2123, found 352.2080.

***O*-(*tert*-Butoxycarbonyl)-*N*-benzylethanolamine (48a):** colorless oil; ^{1}H NMR δ 7.35−7.21 (m, 5H), 4.19 (t, J = 5.75 Hz, 2H), 3.82 (s, 2H), 2.90 (t, J = 5.75 Hz, 2H), 1.48 (s, 9H); ^{13}C 153.04, 139.42, 127.99, 127.74, 126.62, 81.74, 66.03, 53.16, 47.06, 27.32; MS *m*/*z* (dci/CH_4) 252 (MH^+, 100), 196 (93), 152 (17); HRMS calcd for $C_{14}H_{22}NO_3$ 252.1594, found 252.1577.

Di(*N*-(*tert*-butoxycarbonyl)-*N*-benzylaminoethyl) carbonate (49a): colorless oil; ^{1}H NMR δ (two rotomers) (a) 7.38−7.16 (m, 10H), 4.51 (s br, 4H), 4.23 (s br, 4H), 3.49 (s br, 4H), 1.50 (s, 18H); (b) 7.38−7.16 (m, 10H), 4.49 (s br, 4H), 4.16 (s br, 4H), 3.40 (s br, 4H), 1.44 (s, 18H); ^{13}C NMR δ (two rotomers) 155.57, 154.84, 138.16, 137.90, 128.53, 127.75, 127.27, 80.23, 66.06, 65.80, 51.68, 50.67, 45.35, 44.97, 28.33; MS *m*/*z* (dci/CH_4) 529 (MH^+, 1), 429 (55), 373 (100), 178 (90); HRMS calcd for $C_{29}H_{41}N_2O_7$ 529.2913, found 529.2915;

***tert*-Butyl carbonic *N*-benzyl-(*N*-hydroxylethyl) carbamic anhydride (51a):** colorless oil; ^{1}H NMR δ (two rotomers) (a) 7.40−7.22 (m, 5H), 4.63 (s, 2H), 3.71 (t, J = 5.75 Hz, 2H), 3.36 (t, J = 5.75 Hz, 2H), 1.54 (s, 9H); (b) 7.40−7.22 (m, 5H), 4.58 (s, 2H), 3.78 (t, J = 5.75 Hz, 2H), 3.44 (t, J = 5.75 Hz, 2H), 1.51 (s, 9H); ^{13}C NMR δ (two rotomers) 150.94, 150.76, 147.71, 147.45, 136.34, 136.13, 128.74, 128.00, 127.78, 85.05, 60.50, 60.43, 52.56, 51.57, 49.79, 49.12, 27.35; MS *m*/*z* (CI/NH_3) 313 (MNH_4^+, 12), 296 (MH^+, 5), 252 (78), 196 (62), 152 (100); HRMS calcd for $C_{15}H_{22}NO_5$ 296.1497, found 296.1507.

***tert*-Butyl carbonic *N*-benzyl-*N*-(2-(*tert*-butoxycarbonyloxy)ethyl) carbamic anhydride (52a):** colorless oil; ^{1}H NMR δ (two rotomers) (a) 7.39−7.23 (m, 5H), 4.60 (s, 2H), 4.14 (t, J = 5.75 Hz, 2H), 3.45 (t, J = 5.75 Hz, 2H), 1.51 (s, 9H), 1.48 (s, 9H); (b) 7.39−7.23 (m, 5H), 4.57 (s, 2H), 4.23 (t, J = 5.75 Hz, 2H), 3.53 (t, J = 5.75 Hz, 2H), 1.55 (s, 9H), 1.49 (s, 9H); ^{13}C NMR δ (two rotomers) 153.00, 150.48, 150.10, 147.20, 147.16, 135.94, 128.79, 128.76, 128.07, 127.88, 127.85, 127.40, 84.94, 84.87, 82.37, 82,24, 63.96, 52.22, 51.30, 45.89, 45.36, 27.56, 27.32, 27.27; MS *m*/*z* (CI/NH_3) 413 (MNH_4^+, 100), 352 (22), 313 (56), 252 (75); HRMS calcd for $C_{20}H_{29}N_2O_7$ 395.2022, found 396.2050.

***tert*-Butyl carbonic *N*-methyl-*N*-(2-(*tert*-butoxycarbonyloxy)ethyl) carbamic anhydride (52b):** colorless oil; ^{1}H NMR δ (two rotomers) (a) 4.25 (t, J = 5.5 Hz, 2H), 3.58 (t, J = 5.5 Hz, 2H), 3.03 (s, 3H), 1.54 (s, 9H), 1.49 (s, 9H); (b) 4.19 (t, J = 5.5 Hz, 2H), 3.54 (t, J = 5.5 Hz, 2H), 3.04 (s, 3H), 1.53 (s, 9H), 1.49 s, 9H); ^{13}C NMR δ (two rotomers) 153.18, 150.19, 149.95, 147.41, 84.92, 82.60, 82.46, 64.22, 64.13, 48.61, 48.45, 36.41, 35.88, 27.69, 27.45; MS *m*/*z* (CI/NH_3) 320 (MH^+, 5), 237 (77), 220 (31), 176 (32), 137 (38), 120 (100); HRMS calcd for $C_{14}H_{26}NO_7$ 320.1709, found 320.1726.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of new compounds and a copy of ^{19}F NMR spectrum for **2c**. Characterization data for compounds **2h**, **5b**,**c**, **8b**,**d**, **9d**, **10b**,**f**, **12b**−**d**, **16a**,**b**, **26b**,**c**, **27b**, **28c**, **36d**, **37a,d**, **43**, **45**, **49b**, and **53a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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