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One-Pot Stereoselective Synthesis of 1,2-Amino Alcohol Derivatives

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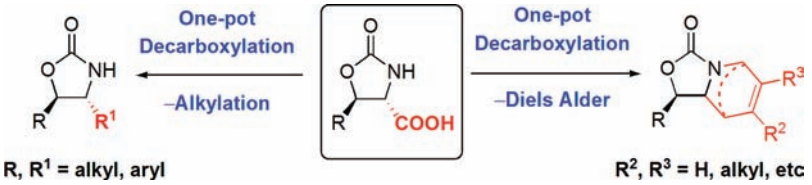
ABSTRACT

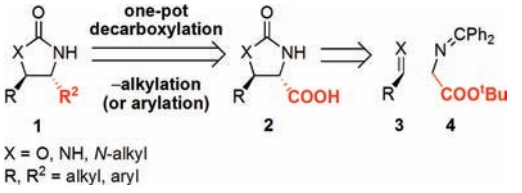


Common β-hydroxy amino acids (such as threonine) can be readily transformed into 1,2-amino alcohols with excellent stereoselectivity. This one-pot decarboxylation–alkylation process allows the replacement of the carboxyl group by alkyl, allyl, or aryl groups, generally in high yields. A variation of the process (decarboxylation–Diels–Alder) allows the formation of bi- and polycyclic systems, which are useful precursors of alkaloid cores or iminosugars.

The synthesis of chiral 1,2-amino alcohols and 1,2-diamines has elicited much interest, since these compounds are present in chiral ligand or catalysts[1] and also in bioactive products, such as alkaloids,[2] iminosugars,[3] and synthetic drugs.[4]

We reasoned that a diversity of these compounds could be built in two steps from simple glycine derivatives (Scheme 1). Thus, the desired amino alcohol or diamine compounds **1** could be formed from the amino acids **2** by one-pot decarboxylation–alkylation (or arylation).[5]

Scheme 1



The amino acids **2** can be formed in good yields and high stereoselectivities by different methodologies,[6,7] such as the reaction of aldehydes (X = O) or imines **3** (X = *N*-alkyl) with glycine enolates, generated from glycine derivatives **4** under phase-transfer conditions.[6]

With these two processes, a variety of alkyl or aryl groups R and R^2 could be introduced. This communication describes the preliminary studies of this strategy, which allowed the conversion of threonine derivative **2a**[8] (R = Me, X = O, Scheme 2) into 1,2-amino alcohols **1a** (R^2 = alkyl, aryl) in good yields and high optical purity.

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(3) (a) Davis, B. G. *Tetrahedron: Asymmetry* **2009**, *20*, 652–671. (b) Pearson, M. S. M.; Mathé-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159–2191. (c) Afarinkia, K.; Bahar, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1239–1297. (d) Lillelund, V. H.; Jensen, H. H.; Laing, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–553. (e) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680. (f) See also: Kumar, A.; Rawal, G. K.; Vankar, Y. D. *Tetrahedron* **2008**, *64*, 2379–2390.

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(6) (a) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656–5682. (b) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222–4266. (c) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518–525.

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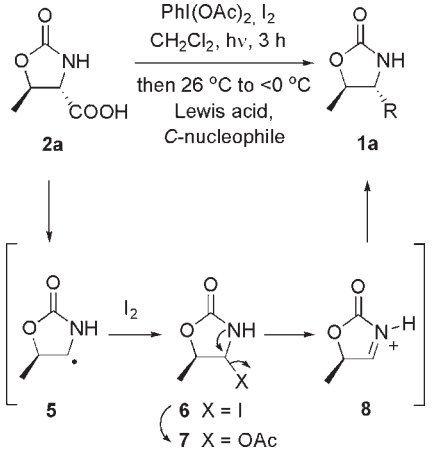
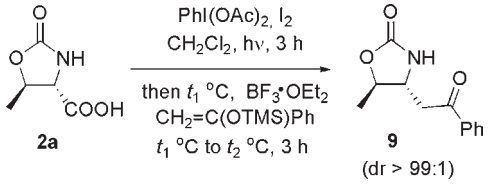
Scheme 2



Moreover, the choice of compound **2a** as the substrate would highlight whether a small-sized R group can induce good stereoselectivities in the alkylation step.

The one-pot decarboxylation–alkylation couples radical and ionic processes and takes place under mild conditions. Thus, when compound **2a** (Scheme 2) is treated with (diacetoxyiodo)benzene (DIB) and iodine, in the presence of visible light (sunlight or 80 W tungsten-filament lamps), a carboxyl radical is formed which undergoes scission to give a *C*-radical **5**.[9] The radical reacts with iodine, to give the unstable α-iodoamide **6**, which reacts with acetate ions from DIB to give the *N,O*-acetal **7**. In the presence of a Lewis acid, the acyliminium ion **8** is formed, which can be trapped by carbon nucleophiles,[10] affording the aminoalcohols **1a**.

Table 1. One-Pot Scission–Alkylation



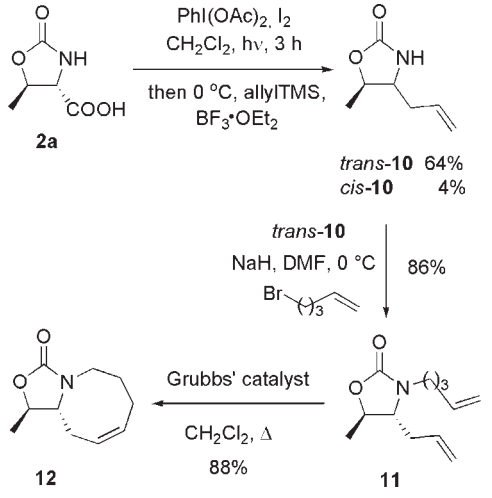
entry	I_2 (equiv)[a]	t_1 °C → t_2 °C	Nu (equiv)	yield (%)[b]
1	1.0	0→25	3	35
2	1.0	−78→−10	3	36
3	0.5	0→25	3	51
4	0.5	0→25	3[c]	42
5	0.5	0→25	5	78

[a] DIB (2 equiv), I_2, *hν*, 25 °C, 3 h; then t_1 °C, CH_2=C(OTMS)Ph and BF_3•OEt_2 (2 equiv), t_1 °C → t_2 °C, 3 h. [b] The yields are given for products purified by chromatography on silica gel. [c] Boron trifluoride was added before the nucleophile.

The best conditions for the one-pot scission–alkylation process were studied using the conversion **2a**→**9** (Table 1). The different temperatures tried (entries 1 and 2) gave similar results. However, the amount of iodine was important (entries 1 and 3), and the best yields were obtained with substoichiometric amounts. The order of addition was studied as well (entries 3 and 4) and the amount of nucleophile (entries 3 and 5). The optimized conditions are given in entry 5. Remarkably, an excellent stereoselectivity was obtained (dr > 99:1).

The application of this reaction to the synthesis of chiral nitrogen heterocycles is shown in Scheme 3. Thus, the scission–allylation reaction gave the allyl derivatives

Scheme 3



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(8) Although substrate **2a** can be prepared from glycine enolates, it was prepared from commercial L-threonine, following standard procedures: Zietlow, A.; Steckhan, E. *J. Org. Chem.* **1994**, *59*, 5658–5661.

(9) (a) The decarboxylation of amino acids can also be induced electrochemically: Renaud, P.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 843–844. (b) Seebach, D.; Charczuk, R.; Gerber, C.; Renaud, P.; Berner, H.; Schneider, H. *Helv. Chim. Acta* **1989**, *72*, 401–425. (c) Herborn, C.; Zietlow, A.; Steckhan, E. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1399–1401. (d) Matsumura, Y.; Shirakawa, Y.; Satoh, Y.; Umino, M.; Tanaka, T.; Maki, T.; Onomura, O. *Org. Lett.* **2000**, *2*, 1689–1691. (e) For reviews on the subject, see: Utley, J. *Chem. Soc. Rev.* **1997**, *26*, 157–167. (f) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527–9554.

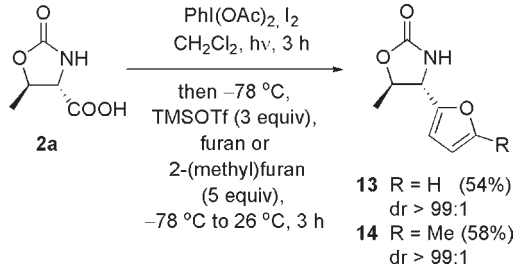
(10) (a) For the addition of nucleophiles to iminium ions, see: Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 339–368 (part I). (b) Yazici, A.; Pyne, S. G. *Synthesis* **2009**, 513–541 (part 2). (c) Ferraris, D. *Tetrahedron* **2007**, *63*, 9581–9597. (d) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541–2569. (e) Schaus, S. E.; Ting, A. *Eur. J. Org. Chem.* **2007**, 5797–5815. (f) Petrini, M.; Torregiani, E. *Synthesis* **2007**, 159–186. (g) Petrini, M. *Chem. Rev.* **2005**, *105*, 3949–3977. (h) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352. (i) Maryanoff, B. E.; Zhang, H. C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628.

trans-**10** and *cis*-**10**[9c] in good overall yield, with a dr of 16:1. Both isomers could be readily separated.

The lower stereoselectivity with respect to the previous process was probably due to the smaller size of the nucleophile, which allowed its addition to the acyliminium ion **8** from the most hindered face. The product *trans*-**10** was *N*-alkylated, and the resultant diolefin **11** underwent a metathesis reaction to give compound **12** in very good yield.

The process can be also applied to electron-rich aromatic rings, such as furan derivatives (Scheme 4). In this case, a lower temperature (−78 °C) and a different Lewis acid (TMSOTf) were required to obtain the furan derivatives **13**[9c] or **14** in good yields. The furan ring can be easily derivatized (reduction, Achmatowitz oxidation, ozonolysis, Diels−Alder, etc.),[11] allowing the formation of many different 1,2-amino alcohols.

Scheme 4

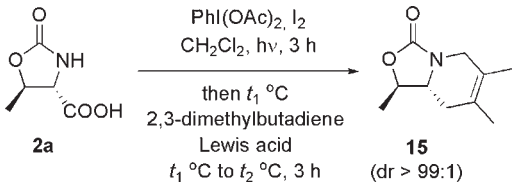


A variation of the scission−alkylation process allowed us to obtain chiral bicyclic and polycyclic systems. In this variation, the decarboxylation was coupled to an aza-Diels−Alder cyclization.[12] The optimization of the reaction conditions is shown in Table 2, using 2,3-dimethyl-1,3-butadiene as the diene, to give the bicyclic product **15**. The best conditions were obtained with t_1 = −78 °C and TMSOTf as the Lewis acid (entry 3, 71% yield). Product **15** was formed with excellent stereoselectivity (dr > 99:1).

Using the same conditions, 1,3-cyclohexadiene afforded the tricyclic product **16** (Scheme 5), also in good yield (70%) and excellent dr (> 99:1).

With 1,3-cyclooctadiene, however, the Diels−Alder reaction was replaced by an alkylation reaction, giving the diene **17** as the major product. Although only the *trans* isomer was formed, it was isolated as a mixture of epimers at 1′-C.[13]

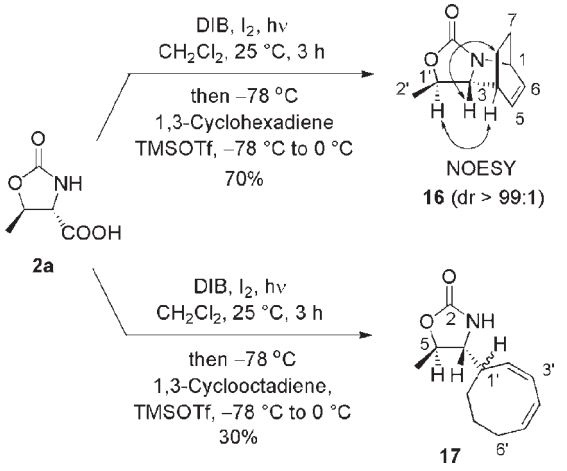
Table 2. One-Pot Scission−aza-Diels−Alder



entry	t_1 °C → t_2 °C	Lewis acid (equiv)[a]	yield (%)[b]
1	−78 → −10	BF_3•OEt_2 (2)	49
2	0 → 25	BF_3•OEt_2 (2)	31
3	−78 → −10	TMSOTf (4)	71
4	0 → 25	TMSOTf (4)	51
5	−78 → −10	$Cu(OTf)_2$ (2)	21
6	0 → 25	$Cu(OTf)_2$ (2)	36
7	−78 → −10	$TiCl_4$ (2)	20

[a] DIB (2 equiv), I_2 (0.5 equiv), *hν*, 25 °C, 3 h; then t_1 °C, 2,3-dimethylbutadiene and the Lewis acid, t_1 °C → t_2 °C, 3 h. [b] The yields are given for products purified by chromatography on silica gel.

Scheme 5



The best conditions could vary according to the diene. In the case of electron-rich dienes such as Danishefsky's diene or 1-trimethylsilyloxy-1,3-butadiene (Scheme 6), the best results were obtained with ZnI_2 at 0 °C.

When Danishefsky's diene was used, the piperidinone **18** was obtained in good yield as the exclusive product. In the case of 1-trimethylsilyloxy-1,3-butadiene, the initially formed cycloaddition product **19** underwent elimination to the acyliminium ion **20**, which was trapped by an excess of nucleophile, to give the addition compound **21**. Considering the number of steps involved in the addition, each step has proceeded in

(11) Boto, A.; Alvarez, L. Furan and its derivatives. In *Heterocycles in Natural Product Synthesis*; Majumdar, K. C., Chattopadhyay, S. K., Eds.; Wiley-VCH: 2011; Chapter 4, ISBN: 978-3-527-32706-5.

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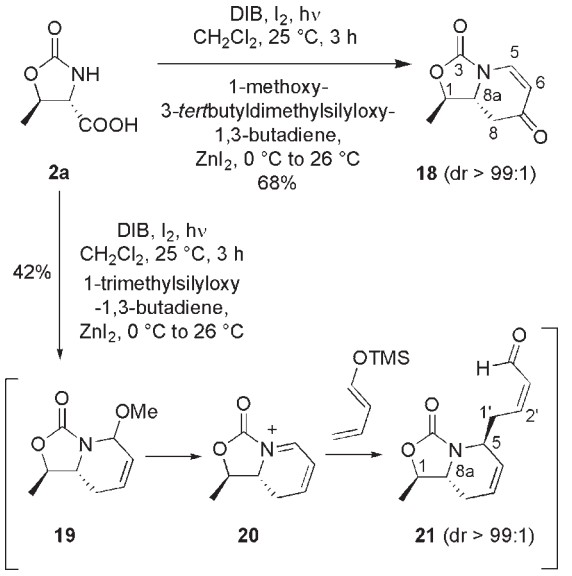
(13) Compound **17** was probably formed from a 1′-oxazolidinyl-4′-halo (or acyl)-2′-cyclooctene, by elimination of the leaving group. This intermediate, in turn, was formed by addition of the cyclooctadiene to the acyliminium ion **8**, followed by addition of a heteroatomic nucleophile at the 4′-position.

Scheme 6



high yield to account for the final result. These bicyclic products obtained during the scission–aza-Diels–Alder process can be further functionalized to give iminosugars and polycyclic systems, among others.

Since the *trans* isomers can be easily transformed into the *cis* diastereomers using Mitsunobo[14] or other related methodologies, this process could allow the preparation of a variety of chiral amino alcohols.

In summary, the one-pot decarboxylation–alkylation process and its variation, the decarboxylation–aza-Diels–Alder reaction, allow the efficient conversion of cyclic carbamates of β-hydroxy amino acids into chiral 1,2-disubstituted-1,2-amino alcohols. The process takes place under mild conditions, generally in good yields and high stereoselectivities. The application of this process to the syntheses of other amino alcohols and chiral diamines will be reported in due course.

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Supporting Information Available. Procedures for the synthesis of compounds **9**–**18** and **21**, and their ^{1}H and ^{13}C NMR spectra; COSY or/and NOESY experiments for compounds **9** and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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