

**1,3-Dipolar Cycloadditions of Carbonyl Ylides to Aldimines: A Three-Component Approach to *syn*- $\alpha$ -Hydroxy- $\beta$ -amino Esters\*\***

Staffan Torssell, Marcel Kienle, and Peter Somfai\*

The  $\beta$ -amino alcohol and  $\alpha$ -hydroxy- $\beta$ -amino acid moieties are found in a large variety of biologically important compounds and natural products<sup>[1]</sup> as well as in a growing number of ligands and chiral auxiliaries for asymmetric synthesis.<sup>[2]</sup> Existing synthetic routes towards enantiopure *vic*-amino alcohols have traditionally relied on derivatization of the chiral pool of amino acids for the most part; however, there is an inherent limitation of accessible targets.<sup>[3]</sup> Considerable efforts have been made in developing asymmetric routes to  $\beta$ -amino alcohols to circumvent these drawbacks; these can be divided into two strategically different approaches.<sup>[4]</sup> Most commonly, the amino alcohol functionality is introduced into a pre-existing carbon skeleton, and this can be accomplished by Sharpless aminohydroxylation<sup>[5]</sup> or by ring opening of epoxides<sup>[4,6,7]</sup> or aziridines<sup>[4,7,8]</sup> with appropriate nucleophiles. More effectively, the amino alcohol moiety can be constructed by concomitant formation of a new carbon–carbon bond and two vicinal stereogenic centers in a single step. This approach has been realized by addition of glycine-derived enolates to aldehydes to yield *anti*- $\beta$ -amino alcohols<sup>[1b,9]</sup> or by addition of  $\alpha$ -alkoxy enolates to aldimines in a Mannich-type reaction.<sup>[1a,10]</sup> Although several methods are currently available for the stereo- and enantioselective formation of *vic*-amino alcohols, there is clearly a demand for simple and efficient entries to this interesting class of substance.

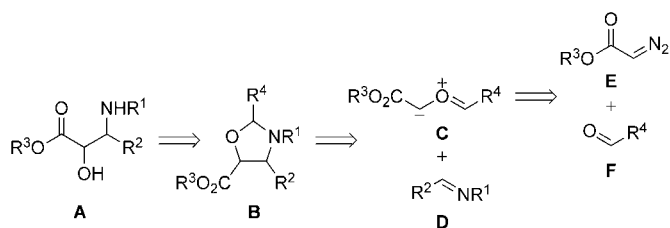
It was envisioned that *vic*-amino alcohols **A** could be obtained by hydrolysis of the corresponding oxazolidines **B**, and that these heterocycles could be prepared from the 1,3-dipolar cycloaddition of a carbonyl ylide **C** to an imine **D** (Scheme 1).<sup>[11]</sup> The carbonyl ylide **C**, in turn, could be prepared from insertion of the carbene derived from **E** into aldehyde **F**. Herein, we report the realization of this strategy by detailing the first example of such a three-component protocol for the synthesis of *syn*- $\alpha$ -hydroxy- $\beta$ -amino esters and its application to the asymmetric synthesis of the C13 taxol side chain.

[\*] S. Torssell, M. Kienle, Prof. P. Somfai  
Organic Chemistry  
KTH Chemistry, Royal Institute of Technology  
10044 Stockholm (Sweden)  
Fax: (+46) 8791-2333  
E-mail: somfai@kth.se

[\*\*] This work was supported financially by AstraZeneca Södertälje, the Swedish Research Council, and the Knut and Alice Wallenberg Foundation.

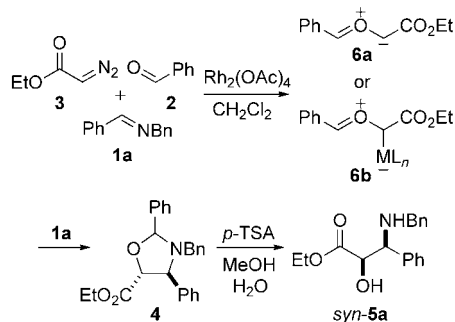


Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.



**Scheme 1.** Retrosynthetic analysis of the  $\alpha$ -hydroxy- $\beta$ -amino ester synthesis.

Initially, a mixture of benzylidenebenzylamine (**1a**), benzaldehyde (**2**), and  $\text{Rh}_2(\text{OAc})_4$  in  $\text{CH}_2\text{Cl}_2$  was stirred at room temperature (Scheme 2). Addition of ethyl diazoacetate



**Scheme 2.** 1,3-Dipolar cycloaddition to benzylidenebenzylamine. *p*-TSA = *para*-toluenesulfonic acid, Bn = benzyl.

tate (EDA; **3**) over 1 h at room temperature afforded the desired cycloadduct **4**, which yielded *vic*-amino alcohol **5a** (*syn/anti* 93:7) in 82% yield (*syn*; Table 1, entry 1) on hydrolysis.<sup>[12]</sup> The relative stereochemistry of **5a** was verified by its conversion into the corresponding oxazolidinone by  $^1\text{H}$  NMR spectroscopic analysis of the relevant coupling constants.<sup>[13]</sup>

With the reaction conditions established, it was of interest to optimize the key components of the reaction. First, the choice of metal catalyst was examined.  $\text{Cu}(\text{OTf})_2$  is known to be a suitable catalyst for the decomposition of **3**, but unfortunately this only led to recovery of **1a** (entry 2), probably because of coordination of the metal to the basic imine nitrogen atom with concomitant inhibition of the carbenoid formation.<sup>[11c,d,14]</sup> Next, the substituent on the imine was varied to investigate if this would influence the reaction outcome. When using imine **1b**, which was derived from aniline and **2**, a complex reaction mixture was obtained with no trace of the desired product (entry 3), whereas attempts with **1c** gave only recovered starting material (entry 4). Aldehyde **2** could be exchanged for other aromatic aldehydes, but this did not improve the reaction outcome so the remaining experiments were performed with **2**. The performances of other aldimines under the optimized reaction conditions are summarized in Table 1. In all cases, the reaction proceeded cleanly to provide the desired *syn*- $\alpha$ -hydroxy- $\beta$ -amino ester in high yield and excellent diastereoselectivity.<sup>[15]</sup> Several benzylidenebenzylamine derivatives

**Table 1.** 1,3-Dipolar cycloaddition of carbonyl ylides to aldimines.<sup>[a]</sup>

$2 + 3 + \text{R}^2\text{CH=NAr} \xrightarrow[\text{b) } p\text{-TSA}]{\text{a) } \text{Rh}_2(\text{OAc})_4} \text{EtO} \begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\   \\ \text{OH} \end{array} \begin{array}{c} \text{NHAr} \\   \\ \text{R} \end{array} + \text{EtO} \begin{array}{c} \text{O} \\ \parallel \\ \text{C} \\   \\ \text{OH} \end{array} \begin{array}{c} \text{NHAr} \\   \\ \text{R} \end{array}$			
Entry	1 (R/Ar)	d.r. ( <i>syn/anti</i> ) <sup>[b]</sup>	Yield of <i>syn</i> - <b>5</b> [%] <sup>[c]</sup>
1	<b>a</b> (Ph/Bn)	93:7	<b>a</b> (82)
2 <sup>[d]</sup>	<b>a</b> (Ph/Bn)	N.A.	<b>a</b> (0) <sup>[e]</sup>
3	<b>b</b> (Ph/Ph)	N.A.	<b>b</b> (0) <sup>[f]</sup>
4	<b>c</b> (Ph/4-MeOC <sub>6</sub> H <sub>4</sub> )	N.A.	<b>c</b> (0) <sup>[e]</sup>
5 <sup>[g]</sup>	<b>d</b> (4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> /Bn)	91:9	<b>d</b> (61)
6	<b>e</b> (4-ClC <sub>6</sub> H <sub>4</sub> /Bn)	98:2	<b>e</b> (75)
7	<b>f</b> (4-FC <sub>6</sub> H <sub>4</sub> /Bn)	97:3	<b>f</b> (78)
8	<b>g</b> (4-MeOC <sub>6</sub> H <sub>4</sub> /Bn)	98:2	<b>g</b> (77)
9	<b>h</b> (4-MeC <sub>6</sub> H <sub>4</sub> /Bn)	97:3	<b>h</b> (87)
10 <sup>[g]</sup>	<b>i</b> (4-MeOC <sub>6</sub> H <sub>4</sub> /Bn)	94:6	<b>i</b> (78)
11	<b>j</b> (2-naphthyl/Bn)	98:2	<b>j</b> (83)
12 <sup>[g,h]</sup>	<b>k</b> (2-furyl/Bn)	92:8	<b>k</b> (75)
13 <sup>[g,h]</sup>	<b>l</b> (CO <sub>2</sub> Et/Bn)	83:17	<b>l</b> (64)

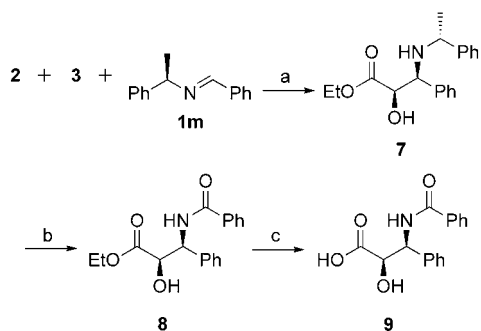
[a] The reaction was carried out with imine **1** (1.0 equiv), benzaldehyde (1.5 equiv),  $\text{Rh}_2(\text{OAc})_4$  (2.0 mol %), and powdered 4-Å molecular sieves in  $\text{CH}_2\text{Cl}_2$  at RT with addition of ethyl diazoacetate (1.5 equiv) over 1 h. Hydrolysis was performed with *p*-TSA (2 equiv) in MeOH/H<sub>2</sub>O (95:5). [b] Determined by NMR spectroscopic analysis of the crude product; *syn* and *anti* diastereoisomers were separated with flash chromatography. [c] Yield of isolated product. [d]  $\text{Cu}(\text{OTf})_2$  (5 mol %) in THF. [e] Only imine and hydrolyzed imine. [f] Complex mixture of by-products. [g] Addition time = 10 h. [h] 0 °C. N.A. = not available.

containing electron-withdrawing (entries 5–8) or electron-donating substituents (entries 9–11) in the *meta* or *para*-positions gave comparable yields and diastereoselectivities irrespective of the steric or electronic properties of the aryl substituent. The furfural-derived imine **1k** afforded the corresponding product **5k** in high yield and diastereoselectivity (entry 12), which is of interest as the furan moiety can be readily derivatized into several useful functional groups. The reaction of ethyl glyoxalate imine (**1l**) gave *syn*- $\beta$ -hydroxyaspartate (**5l**), a potent blocker of glutamate transporters,<sup>[16]</sup> in high yield and good diastereoselectivity (entry 13), thus indicating that the reaction is not only restricted to aromatic imines and the scope of the transformation can be widened.

The mechanism of the reaction proceeds through a chemoselective insertion of the metalcarbene into benzaldehyde to form either a metal-free<sup>[11a,17a]</sup> **6a** or a metal-associated ylide<sup>[17]</sup> **6b**, both of which can then undergo a 1,3-dipolar cycloaddition with the aldimine yielding the *trans*-substituted oxazolidine **4**, which can then be hydrolyzed to the corresponding *syn*- $\alpha$ -hydroxy- $\beta$ -amino ester **5** (Scheme 2). To ascertain if ylide **6** is metal-associated, the generation of the ylide and its subsequent reaction with imine **1a** was performed with  $[\text{Rh}_2(\text{hfb})_4]$  (hfb = heptafluorobutyrate) and  $[\text{Rh}_2\{(S)\text{-dosp}\}_4]$  ((*S*)-dosp = (*S*)-*N*-dodecylbenzenesulfonyl proline), respectively. When  $[\text{Rh}_2(\text{hfb})_4]$  was used, **5a** was obtained in only 13% yield with lower diastereoselectivity (*syn/anti* = 88:12 compared to entry 1, Table 1), whereas with  $[\text{Rh}_2\{(S)\text{-dosp}\}_4]$  **5a** was obtained in 62% yield with excellent diastereoselectivity (*syn/anti* = 94:6) and modest enantiose-

lectivity (24% *ee*). These preliminary results support the formation of a metal-associated ylide in this case. It is interesting to note that no products derived from the formation of azomethine ylides, by combination of **1** with **3**, was observed in these reactions.<sup>[11c,d]</sup>

It was also of interest to develop an asymmetric protocol for the synthesis of enantiomerically enriched *syn*- $\alpha$ -hydroxy- $\beta$ -amino esters and to apply it to the synthesis of the taxol C13 side chain **9** (Scheme 3),<sup>[5,18]</sup> which is known to be important



**Scheme 3.** Asymmetric synthesis of the C13 side chain of taxol. Reagents and conditions: a) 1)  $\text{Rh}_2(\text{OAc})_4$  (2 mol%), 4-Å molecular sieves,  $\text{CH}_2\text{Cl}_2$ , 0°C; 2) *p*-TSA, MeOH/ $\text{H}_2\text{O}$  (95:5), RT (77%, 2 steps, d.r. 8:1:1); b) 1)  $\text{H}_2$ ,  $[\text{Pd}(\text{OH})_2]$ , EtOH, 3 M HCl, RT; 2)  $\text{PhCOCl}$ ,  $\text{NaHCO}_3$ , EtOAc, 0°C (77% over 2 steps); c)  $\text{LiOH}\cdot\text{H}_2\text{O}$ , THF/MeOH/ $\text{H}_2\text{O}$  (10:5:4), RT (89%).

for the antitumor activity of taxol.<sup>[18]</sup> Initial attempts with (–)-8-phenylmenthyl diazoacetate<sup>[19]</sup> as the carbene source with **1a** and **2** gave none of the desired product. Gratifyingly, however, reaction of the enantiomerically pure imine **1m**, derived from (+)- $\alpha$ -methylbenzylamine, with **2** and **3** gave the desired *syn*-amino alcohol **7** in good yield (77%) and selectivity (*syn/syn/anti* = 8:1:1) after hydrolysis (Scheme 3). Compound **7** was readily isolated from the two minor isomers by flash chromatography, and subsequent catalytic hydrogenolysis of this compound followed by benzoylation under Schotten–Baumann conditions afforded amide **8** (77% yield, two steps). Finally, hydrolysis of **8** using LiOH yielded the taxol side chain **9** as a white solid in five steps and an overall yield of 42%. Analytical data of **9** were in good agreement with previously reported data.<sup>[5,18]</sup>

In conclusion, we have developed an efficient protocol for the synthesis of *syn*- $\beta$ -amino alcohols and *syn*- $\alpha$ -hydroxy- $\beta$ -amino acid derivatives based on a highly diastereoselective three-component coupling of imines, benzaldehyde, and EDA. The methodology was applied to a short enantioselective synthesis of the C13 side chain of taxol.

Received: January 26, 2005  
Published online: April 12, 2005

**Keywords:** amino alcohols · carbenoids · cycloaddition · multicomponent reactions · ylides

- [1] a) S. Kobayashi, H. Ishitani, M. Ueno, *J. Am. Chem. Soc.* **1998**, *120*, 431–432; b) J. Kobayashi, M. Nakamura, Y. Mori, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2004**, *126*, 9192–9193; c) H.-S. Lee, S. H. Kang, *Synlett* **2004**, 1673–1685, and references therein.
- [2] D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835–875.
- [3] M. T. Reetz, *Angew. Chem.* **1991**, *103*, 1559–1573; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531–1546.
- [4] S. C. Bergmeier, *Tetrahedron* **2000**, *56*, 2561–2576.
- [5] G. Li, H.-T. Chang, K. B. Sharpless, *Angew. Chem.* **1996**, *108*, 449–452; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451–454.
- [6] J. F. Larrow, S. E. Schaus, E. N. Jacobsen, *J. Am. Chem. Soc.* **1996**, *118*, 7420–7421.
- [7] B. Olofsson, U. Khamrai, P. Somfai, *J. Org. Chem.* **2002**, *67*, 8574–8583.
- [8] a) G.-I. Hwang, J.-H. Chung, W. K. Lee, *J. Org. Chem.* **1996**, *61*, 6183–6188; b) X. E. Hu, *Tetrahedron* **2004**, *60*, 2701–2743.
- [9] With glycine derived enolates: a) M. Horikawa, J. Busch-Petersen, E. J. Corey, *Tetrahedron Lett.* **1999**, *40*, 3843–3846; b) N. Yoshikawa, M. Shibasaki, *Tetrahedron* **2002**, *58*, 8289–8298; c) T. Ooi, M. Taniguchi, M. Kameda, K. Maruoka, *Angew. Chem.* **2002**, *114*, 4724–4726; *Angew. Chem. Int. Ed.* **2002**, *41*, 4542–4544.
- [10] Mannich-type reaction: a) B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827–833; b) A. Córdova, W. Notz, G. Zhong, J. M. Betancort, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1842–1843; c) B. M. Trost, L. R. Terrell, *J. Am. Chem. Soc.* **2003**, *125*, 338–339; d) S. Matsunaga, N. Kumagai, S. Harada, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 4712–4713.
- [11] For three-component reactions using diazo compounds for carbonyl ylides, see: a) C.-D. Lu, Z.-Y. Chen, H. Liu, W.-H. Hu, A.-Q. Mi, *Org. Lett.* **2004**, *6*, 3071–3074; b) A. E. Russell, J. Brekan, L. Gronenberg, M. P. Doyle, *J. Org. Chem.* **2004**, *69*, 5269–5274; for azomethine ylides, see: c) K. B. Hansen, N. S. Finney, E. N. Jacobsen, *Angew. Chem.* **1995**, *107*, 750–752; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 676–678; d) C. V. Galliford, M. A. Beenen, S. T. Nguyen, K. A. Scheidt, *Org. Lett.* **2003**, *5*, 3487–3490; e) M. Yan, N. Jacobsen, W. Hu, L. S. Gronenberg, M. P. Doyle, J. T. Colyer, D. Bykowski, *Angew. Chem.* **2004**, *116*, 6881–6884; *Angew. Chem. Int. Ed.* **2004**, *43*, 6713–6716; for oxonium ylides, see: f) C.-D. Lu, H. Liu, Z.-Y. Chen, W.-H. Hu, A.-Q. Mi, *Org. Lett.* **2005**, *7*, 83–86; for ammonium ylides, see: g) Y. Wang, Y. Zhu, Z. Chen, A. Mi, W. Hu, M. P. Doyle, *Org. Lett.* **2003**, *5*, 3923–3926.
- [12] Addition of powdered activated 4-Å molecular sieves gave higher yields and more reproducible results, see: C.-D. Lu, Z.-Y. Chen, H. Liu, W.-H. Hu, A.-Q. Mi, M. P. Doyle, *J. Org. Chem.* **2004**, *69*, 4856–4859.
- [13] The  $J(4,5) = 5.1$  Hz coupling constant is consistent with 4,5-*trans* relative stereochemistry, see: C. H. Heathcock, T. A. Blumenkopf, K. M. Smith, *J. Org. Chem.* **1989**, *54*, 1548–1562.
- [14] M. P. Doyle, M. Yan, W. Hu, L. S. Gronenberg, *J. Am. Chem. Soc.* **2003**, *125*, 4692–4693.
- [15] The *syn* and *anti* diastereoisomers were readily separated by flash chromatography for all substrates.
- [16] K. Shimamoto, Y. Shigeri, Y. Yasuda-Kamatani, B. Lebrun, N. Yumoto, T. Nakajima, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2407–2410.
- [17] For discussions about metal-associated ylides, see: a) M. P. Doyle, D. C. Forbes, M. N. Protopopova, S. A. Stanley, M. M. Vasbinder, K. R. Xavier, *J. Org. Chem.* **1997**, *62*, 7210–7215; b) S. Kitagaki, M. Anada, O. Kataoka, K. Matsuno, C. Umeda, N. Watanabe, S.-I. Hashimoto, *J. Am. Chem. Soc.* **1999**, *121*, 1417–1418; c) D. M. Hodgson, A. H. Labande, F. Y. T. M.

- Pierard, M. Á. Expósito Castro, *J. Org. Chem.* **2003**, 68, 6153–6159.
- [18] For the shortest synthesis of the C13 side chain of taxol, see Ref. [5] a) L. Deng, E. N. Jacobsen, *J. Org. Chem.* **1992**, 57, 4320–4323; b) D.-M. Gou, Y.-C. Liu, C.-S. Chen, *J. Org. Chem.* **1993**, 58, 1287–1289; c) V. K. Aggarwal, J.-L. Vasse, *Org. Lett.* **2003**, 5, 3987–3990.
- [19] For the synthesis of (–)-8-phenylmenthyl diazoacetate, see: A. V. Bedekar, E. B. Koroleva, P. G. Andersson, *J. Org. Chem.* **1997**, 62, 2518–2526.