Synthetic Methods

1,3-Dipolar Cycloadditions of Carbonyl Ylides to Aldimines: A Three-Component Approach to *syn*-α-Hydroxy-β-amino Esters**

*Staffan Torssell, Marcel Kienle, and Peter Somfai**

The β-amino alcohol and α-hydroxy-β-amino acid moieties are found in a large variety of biologically important compounds and natural products[1] as well as in a growing number of ligands and chiral auxiliaries for asymmetric synthesis.[2] 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.[3] Considerable efforts have been made in developing asymmetric routes to β-amino alcohols to circumvent these drawbacks; these can be divided into two strategically different approaches.[4] Most commonly, the amino alcohol functionality is introduced into a pre-existing carbon skeleton, and this can be accomplished by Sharpless aminohydroxylation[5] or by ring opening of epoxides[4,6,7] or aziridines[4,7,8] 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*-β-amino alcohols[1b,9] or by addition of α-alkoxy enolates to aldimines in a Mannich-type reaction.[1a,10] 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).[11] 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*-α-hydroxy-β-amino esters and its application to the asymmetric synthesis of the C13 taxol side chain.

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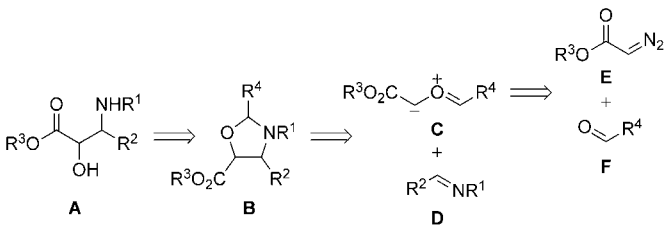
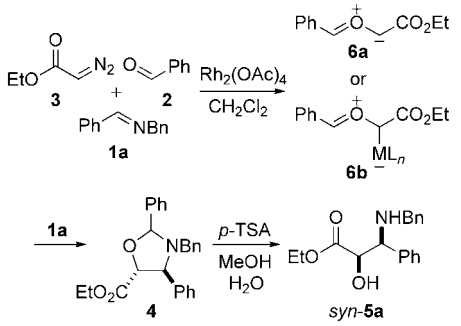


Scheme 1. Retrosynthetic analysis of the α-hydroxy-β-amino ester synthesis.

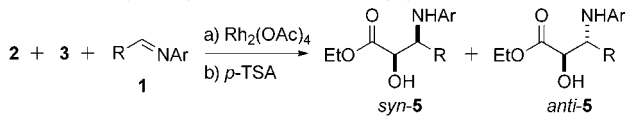
Initially, a mixture of benzylidenebenzylamine (**1a**), benzaldehyde (**2**), and $Rh_2(OAc)_4$ in CH_2Cl_2 was stirred at room temperature (Scheme 2). Addition of ethyl diazoacetate (EDA; **3**) over 1 h at room temperature afforded the desired cycloadduct **4**, which yielded *vic*-amino alcohol **5a** (*syn*/*anti* 93:7) in 82% yield (*syn*; Table 1, entry 1) on hydrolysis.[12] The relative stereochemistry of **5a** was verified by its conversion into the corresponding oxazolidinone by ^{1}H NMR spectroscopic analysis of the relevant coupling constants.[13]



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

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. $Cu(OTf)_2$ 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.[11c,d,14] 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*-α-hydroxy-β-amino ester in high yield and excellent diastereoselectivity.[15] Several benzylidenebenzylamine derivatives 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*-β-hydroxyaspartate (**5l**), a potent blocker of glutamate transporters,[16] 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.

Table 1: 1,3-Dipolar cycloaddition of carbonyl ylides to aldimines.[a]



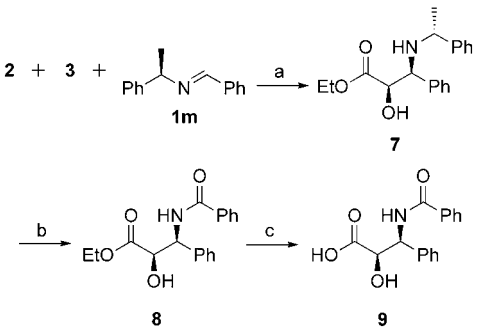
Entry	**1** (R/Ar)	d.r. (*syn*/*anti*)[b]	Yield of *syn*-**5** [%][c]
1	**a** (Ph/Bn)	93:7	**a** (82)
2[d]	**a** (Ph/Bn)	N.A.	**a** (0)[e]
3	**b** (Ph/Ph)	N.A.	**b** (0)[f]
4	**c** (Ph/4-MeOC$_6$H$_4$)	N.A.	**c** (0)[e]
5[g]	**d** (4-NO$_2$C$_6$H$_4$/Bn)	91:9	**d** (61)
6	**e** (4-ClC$_6$H$_4$/Bn)	98:2	**e** (75)
7	**f** (4-FC$_6$H$_4$/Bn)	97:3	**f** (78)
8	**g** (4-MeOC$_6$H$_4$/Bn)	98:2	**g** (77)
9	**h** (4-MeC$_6$H$_4$/Bn)	97:3	**h** (87)
10[g]	**i** (4-MeOC$_6$H$_4$/Bn)	94:6	**i** (78)
11	**j** (2-naphthyl/Bn)	98:2	**j** (83)
12[g,h]	**k** (2-furyl/Bn)	92:8	**k** (75)
13[g,h]	**l** (CO$_2$Et/Bn)	83:17	**l** (64)

[a] The reaction was carried out with imine **1** (1.0 equiv), benzaldehyde (1.5 equiv), $Rh_2(OAc)_4$ (2.0 mol%), and powdered 4-Å molecular sieves in CH_2Cl_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_2O (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] $Cu(OTf)_2$ (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.

The mechanism of the reaction proceeds through a chemoselective insertion of the metallocarbene into benzaldehyde to form either a metal-free[11a,17a] **6a** or a metal-associated ylide[17] **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*-α-hydroxy-β-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 $[Rh_2(hfb)_4]$ (hfb = heptafluorobutyrate) and $[Rh_2\{(S)\text{-dosp}\}_4]$ ((*S*)-dosp = (*S*)-*N*-dodecylbenzenesulfonyl prolinate), respectively. When $[Rh_2(hfb)_4]$ was used, **5a** was obtained in only 13% yield with lower diastereoselectivity (*syn*/*anti* = 88:12 compared to entry 1, Table 1), whereas with $[Rh_2\{(S)\text{-dosp}\}_4]$ **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.[11c,d]

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



Scheme 3. Asymmetric synthesis of the C13 side chain of taxol. Reagents and conditions: a) 1) $Rh_2(OAc)_4$ (2 mol%), 4-Å molecular sieves, CH_2Cl_2, 0°C; 2) *p*-TSA, MeOH/H_2O (95:5), RT (77%, 2 steps, d.r. 8:1:1); b) 1) H_2, [$Pd(OH)_2$], EtOH, 3 M HCl, RT; 2) PhCOCl, $NaHCO_3$, EtOAc, 0°C (77% over 2 steps); c) LiOH·H_2O, THF/MeOH/H_2O (10:5:4), RT (89%).

for the antitumor activity of taxol.[18] Initial attempts with (−)-8-phenylmenthyl diazoacetate[19] 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 (+)-α-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.[5,18]

In conclusion, we have developed an efficient protocol for the synthesis of *syn*-β-amino alcohols and *syn*-α-hydroxy-β-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.

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