Highly Stereoselective Intramolecular S_N2' Cyclization Yielding Chiral Oxazolidin-2-ones: General Route to α-Hydroxy-β-amino Acids

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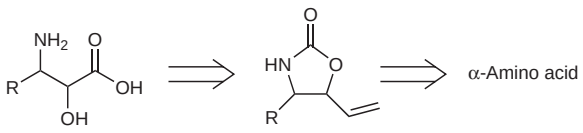
Abstract: Intramolecular nucleophilic attack onto allylsulfonates promoted by silica gel acting as an acid catalyst provides expedient stereoselective access to 4,5-difunctionalized oxazolidin-2-ones. Precursors were prepared efficiently from enantiopure α-amino acids and subsequent manipulation of the oxazolidin-2-ones yielded enantiopure α-hydroxy-β-amino acids.

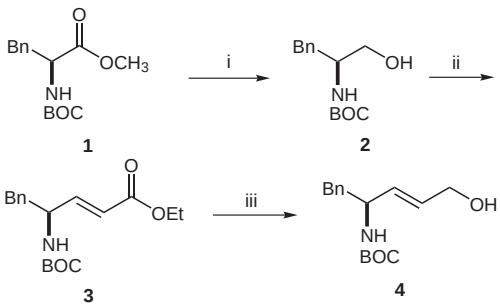
Key words: oxazolidin-2-one, intramolecular S_N2' cyclization, AHPBA, silica gel, α-hydroxy-β-amino acids

The stereoselective transformation of homochiral α-amino acids remains an active area of research on account of their high optical purity giving scope for further manipulation into other useful compounds in high enantiomeric excesses.[1] In amino acid chemistry, many efforts focus on generating enantiomerically pure amino alcohols, many of which are considered biologically active, which also can be converted to biologically important compounds.[2] Thus, the transformation of α-amino acids to oxazolidin-2-ones is also attractive because oxazolidin-2-ones are amino alcohol equivalents and show potent bioactivity as well.[3] Despite the various practical transformations of oxazolidin-2-ones from amino alcohols,[4] aziridines,[5] allyl alcohols,[6] and allyl amines,[7] there are but a few synthetic routes involving a direct chiral induction step.[8] We found that a chiral oxazolidin-2-one possessing a vinyl group on the 5 position could be generated by internal cyclization of chiral carbamate onto an allylic cation (Scheme 1).



Scheme 1

This methodology is appealing not only because it derives from chiral amino alcohols, an ideal basis for an asymmetric synthetic scheme, but also because the products are protected α-hydroxy-β-amino acid derivatives, which are highly useful in their own right. In this way, such a methodology constitutes a transformation for the synthesis of enantioenriched α-hydroxy-β-amino acids. The synthesis of the carbamate began with N-Boc-protected α-amino ester **1**. Reduction by $LiAlH_4$ of **2**, followed by Swern oxidation furnished an aldehyde intermediate, which was set up for a Horner–Wadsworth–Emmons reaction to install the allylic carbamate **3** required for the cyclization step. Regioselective DIBAL reduction afforded allylic alcohol **4**, which was activated for the final ring forming step using a range of different activating groups and conditions (Scheme 2).



Scheme 2 *Reagents and conditions*: i) $LiAlH_4$ (2.0 equiv), anhyd THF, 0 °C, 1 h, 90%; ii) (a) $(COCl)_2$ (2.8 equiv), DMSO (4 equiv), Et_3N (8 equiv), anhyd CH_2Cl_2, –78 °C; (b) triethylphosphonoacetate (2 equiv), NaH (2 equiv), anhyd THF, 0 °C to r.t., 80%; iii) DIBAL (3.0 equiv), THF, –78 °C, 81%.

Initially, the hydroxyl group was activated by mesylation. In the first set of conditions, a thermal induced cyclization was tested, and whilst the desired product formed, the selectivity for *trans* versus *cis* was low (2:1) and the yield was less than optimal.

Assuming a polar transition state, where the mesylate is effectively partially bonded to an allylic cation, it was decided that formation of an ion pair could assist the departure of the nucleofuge, while giving some bias for the elimination; accordingly, trichloroacetimidate was screened.[9] In the standard thermal cyclization, the de was slightly more favorable than with the tosylate, however, copper was used to augment the leaving group capacity of the Schiff base which was unable to increase the level of

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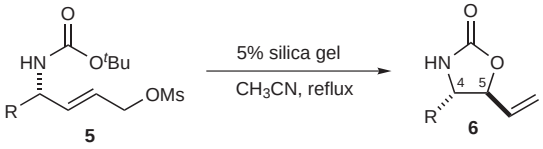
selectivity to the required level, even though the dr increased.

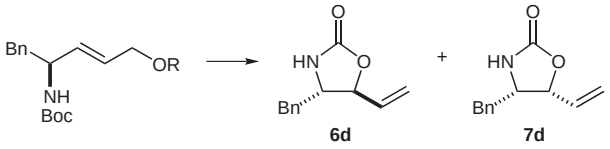
Therefore, two enantiomers of a chiral organocatalyst were screened separately.[10] Although the dr was independent of the organocatalyst used, it none the less increased, which we believe is due to stablization of the nascent mesylate in the transition state, silica gel was screened, and it was found that the dr increased to 9:1 in favor of the *trans* product (Scheme 3). This highly selectivity is believed to be due to bounded protons and the steric effect of the heterogeneous catalyst (amorphous silica gel). Changing the nucleofuge to the tosylate, lowered the yield and dr, the former at least probably being due to the lower stability of the tosylate compared to the mesylate.



Scheme 3

Finally, this trend was extended when the triflate, a compound of low stability, gave only a trace of the desired product (Table 1). The optimized protocol was then extended by repetition to a range of substrates derived from naturally occurring α-amino acids. In the case of substituents containing more bulky side chains, Bn and Ph, the drs were good to excellent, however, as the size decreased to Me, the dr decreased rapidly. For the smallest group, Me, the dr was of no great significance (Table 2).

Table 1 Intramolecular Hydroxylation of Amino Allylic Alcohols[a]



Entry	R	Conditions	Yield (%)[b]	Ratio[c]
1	Ms	Silica gel, reflux, 5 h	79	9:1
2	Ms	Reflux, 24 h	70	2:1
3	Ms	Organocatalyst,[e] 2 h	60	4:1
4	Ts	Silica gel, reflux, 5 h	45	6:1
5	Tf[f]	CH_2Cl_2, –78 °C	trace	–[d]
6	TCA[g]	DMSO, reflux, 2 h	68	3:1
7	TCA	$(CF_3SO_3Cu)_2$, 3 h	70	6:1

[a] All reactions were carried out in CH_3CN.
[b] Isolated yield.
[c] Determined by ^1H NMR integration.
[d] Not determined.
[e] (+)-Cinchonine or (–)-cinchonidine.
[f] Trifluoromethanesulfonyl.
[g] Trichloroacetimidate.

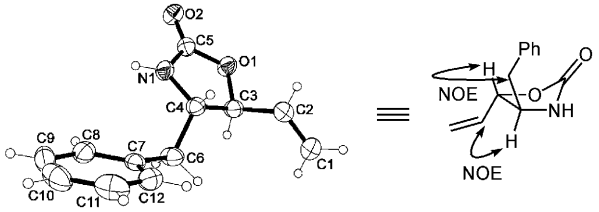
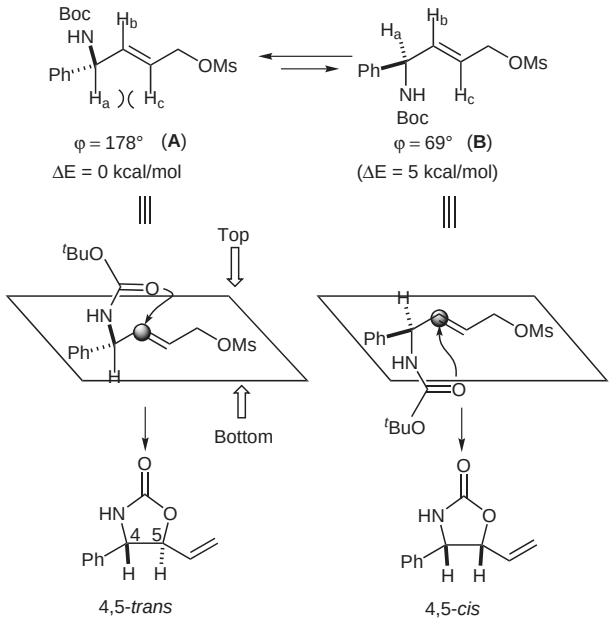


Figure 1

The *cis/trans* stereostructures of oxazolidin-2-ones were determined by NOESY experiments and with the aid of the X-ray crystal structure of **6d** (Figure 1).[11] Comparison of coupling constants of $J_{4,5}$ clearly indicates the difference between *cis*-4,5-disubstituted ($J_{4,5}$ = 4.7–7.7 Hz) and *trans*-4,5-disubstituted oxazolidin-2-one ($J_{4,5}$ = 4.2–7.3 Hz).



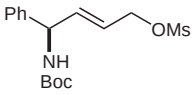
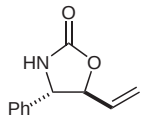
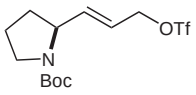
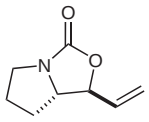
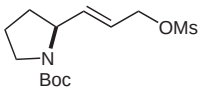
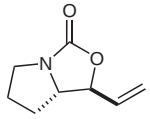
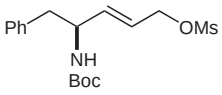
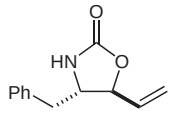
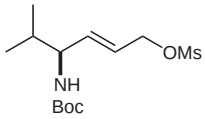
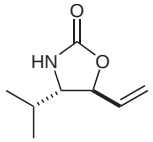
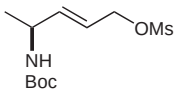
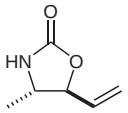
φ : Dihedral angle of H_a and H_b

ΔE: Relative energy of φ = 178° and φ = 69° in **5a**

Figure 2

It is generally accepted that *cis*-oxazolidin-2-ones have larger coupling constants than *trans*.[12] The stereoselectivity in the case of the formation of the 4,5-*trans* systems arises from attack of the carbonyl oxygen of the Boc group from the top (*Si*) face of the prochiral center of the allylsulfonate group. Thus, an S_N2' reaction resulted in the highly stereoselective intramolecular cyclization. The geometric structures of compound **5a** were theoretically optimized by Hartree–Fock/6-31G* level.[13] The energy of the *trans*-conformer **A** (φ = 178°) was 5 kcal/mol lower compared with that of the *cis*-conformer **B** (φ = 69°; Figure 2). Whilst there seems to be some theoretical basis for a bias for the ground state to adopt the preferred reac-

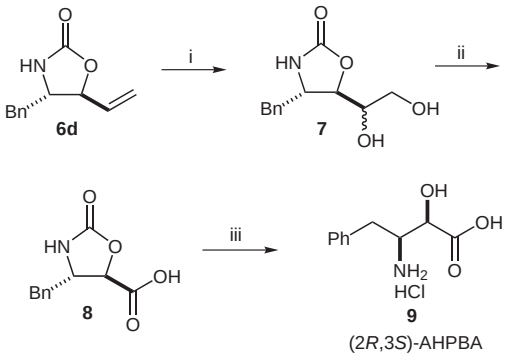
Table 2 Silica Gel Promoted Oxazolidinonation of Amino Allyl Mesylate[a]

Entry	Allyl alcohol adduct	Oxazolidin-2-one	Ratio[b]	Yield[c]
1	 **5a**	 **6a**	99:1	85%
2	 **5b**	 **6b**	99:1	65%
3	 **5c**	 **6b**	6:1	65%
4	 **5d**	 **6d**	9:1	79%
5	 **5e**	 **6e**	6:1	70%
6	 **5f**	 **6f**	2:1	75%

[a] All reactions were refluxed in anhyd CH_3CN.
[b] Determined by integration of the ^1H NMR spectroscopy.
[c] Isolated yield.

tive conformation, the standard A1,3 strain model is in general applicable to *Z* double bonds.[14] In this way, it seems that there may be some steric effect in the transition state, which retard the formation of the *syn* product as R increases in size.

The utility of this methodology can be shown by the use of the oxazolidin-2-one as a protecting group of the amino alcohol functionality. Oxidation of the vinyl group using OsO_4, followed by periodate cleavage, in the presence of $KMnO_4$ yielded acid **8**. Oxazolidin-2-one ring was easily cleaved by refluxing with KOH to give (2*R*,3*S*)-3-amino-2-hydroxy-4-phenyl butanoic acid (AHPBA; **9**) in 86% yield (Scheme 4). The spectroscopic data and optical rotation for **9** are consistent with those reported.[15] In conclusion, an expedient route to enantiomerically pure oxazolidin-2-ones has been developed using non-toxic conditions in a short number of steps, with excellent selectivity when strain is maximized. The potential for derivatization of the oxazolidin-2-one has also been demonstrated in the synthesis of α-hydroxy-β-amino acid, (2*R*,3*S*)-AHPBA **9**.



Scheme 4 *Reagents and conditions*: i) OsO_4 (10%), NMO (2 equiv), acetone, r.t, 24 h; ii) (a) $NaIO_4$ (1.5 equiv), EtOH–H_2O 2:1, r.t., 2 h; (b) $KMnO_4$ (1.2 equiv), K_2CO_3 (2.1 equiv), THF–H_2O 2:1, r.t., 1 h, 80%; iii) 4 N KOH, EtOH, reflux to r.t., 24 h, 86%

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References

(1) (a) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825. (b) Abell, A. D.; Taylor, J. M. *J. Org. Chem.* **1993**, *58*, 14. (c) Davies, S. B.; McKervey, M. A. *Tetrahedron Lett.* **1999**, *40*, 1229. (d) Boto, A.; Hernandez, R.; Leon, Y.; Suarez, E. *J. Org. Chem.* **2001**, *66*, 7796. (e) Boto, A.; Hernandez, R.; Leon, Y.; Murguia, J. R.; Rodriguez-Afonso, A. *Tetrahedron Lett.* **2004**, *45*, 6841.

(2) (a) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141. (b) Lee, B. W.; Lee, J. H.; Jang, K. C.; Kang, J. E.; Kim, J. H.; Park, K. M.; Park, K. H. *Tetrahedron Lett.* **2003**, *44*, 5905. (c) Back, T. G.; Parvez, M.; Zhai, H. *J. Org. Chem.* **2003**, *68*, 9389. (d) Vuljanic, T.; Kihlberg, J.; Somfai, P. *J. Org. Chem.* **1998**, *63*, 279. (e) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.

(3) (a) Barbachyn, M. R.; Ford, C. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 2010. (b) Diekema, D. J.; Jones, R. N. *Lancet* **2001**, *358*, 1975. (c) Xu, J.; Golshani, A.; Aoki, H.; Remme, J.; Chosay, J.; Shinabarger, D. L.; Ganoza, M. C. *Biochem. Biophys. Res. Commun.* **2005**, *328*, 471.

(4) (a) Feroci, M.; Inesi, A.; Mucciante, V.; Rossi, L. *Tetrahedron Lett.* **1999**, *40*, 6059. (b) Chiarotto, I.; Feroci, M. *Tetrahedron Lett.* **2001**, *42*, 3451. (c) Madhusudhan, G.; Reddy, G. O.; Ramanatham, J.; Dubey, P. K. *Tetrahedron Lett.* **2003**, *44*, 6323. (d) Gabriele, B.; Salerno, G.; Brindisi, D.; Costa, M.; Chiusoli, G. P. *Org. Lett.* **2000**, *2*, 625.

(5) (a) Lucarini, S.; Tomasini, C. *J. Org. Chem.* **2001**, *66*, 727. (b) Park, C. S.; Kim, M. S.; Sim, T. B.; Pyun, D. K.; Lee, C. H.; Choi, D.; Lee, W. K.; Chang, J. M.; Ha, H. J. *J. Org. Chem.* **2003**, *68*, 43. (c) Sim, T. B.; Kang, S. H.; Lee, K. S.; Lee, W. K.; Yun, H.; Dong, Y.; Ha, H. J. *J. Org. Chem.* **2003**, *68*, 104.

(6) (a) Coelho, F.; Rossi, R. C. *Tetrahedron Lett.* **2002**, *43*, 2797. (b) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1997**, *62*, 4449.

(7) Cardillo, G.; Orena, M.; Sandri, S. *J. Org. Chem.* **1986**, *51*, 713.

(8) (a) Overman, L. E.; Remarchuk, T. P. *J. Am. Chem. Soc.* **2002**, *124*, 12. (b) Lei, A.; Liu, G.; Lu, X. *J. Org. Chem.* **2002**, *67*, 974. (c) Kawano, T.; Negoro, K.; Ueda, I. *Tetrahedron Lett.* **1997**, *38*, 8219.

(9) (a) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412. (b) Patil, V. J. *Tetrahedron Lett.* **1996**, *37*, 1481. (c) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *23*, 212.

(10) (a) Loh, T. P.; Zhou, J. R.; Yin, Z. *Org. Lett.* **1999**, *1*, 1855. (b) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.

(11) The structure was solved by direct methods and refined by full matrix least-squares against F^2 for all data using the SHELXTL program package. CCDC reference number 275654. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre.

(12) Miyata, O.; Koizumi, T.; Asai, H.; Iba, R.; Naito, T. *Tetrahedron* **2004**, *60*, 3893.

(13) Frish, M. J.; Trucks, G. W.; Head-Gordon, M. H.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C. R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. *Gaussian 03*; Gaussian Inc.: Pittsburgh PA, **2003**.

(14) Tamaru, Y.; Mountain, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079.

(15) Andres, J. M.; Martinez, M. A.; Pedrosa, R.; Perez-Encabo, A. *Tetrahedron: Asymmetry* **2001**, *12*, 347.