Expanding Synthetic Utilities of Asymmetric Dihydroxylation Reaction: Conversion of *syn*-Diols to *syn*-Amino Alcohols

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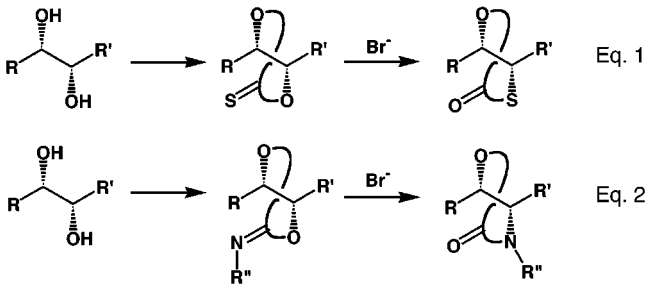
Sharpless's asymmetric dihydroxylation (AD) is among the most efficient asymmetric transformations available to synthetic chemists.[1] Its rapid acceptance to the synthetic arsenal testifies the power of the process: high enantioselectivities, substrate generality, easy operation, etc. Equally important is the rich chemistry that one can do with the initial products of the process. Selective transformations of *vicinal* diols further expand the synthetic utility of the AD process. Their discoveries, therefore, have been much sought after. Toward this end, conversions of *vicinal* diols to cyclic sulfates, halohydrin esters, and epoxides and subsequent transformations have been reported.[2]

Our interest in this area has been mainly centered on the inability of the AD process to produce *anti*(*erythro*)-diols in high enantioselectivity. This inherent weakness of the AD process, which results from the fact that disubstituted (*Z*)-olefins are poor substrates for AD, has limited the synthetic utilities to only half of the all the possible stereoisomers as far as disubstituted *vicinal* diols and derivatives thereof are concerned.[3] As a solution to this, we have reported a "cyclic sulfate rearrangement−opening process" and shown that *anti*-diols as well as *cis*-epoxides are now accessible via the AD process.[4] We have also reported a rearrangement process of *vicinal*-diol cyclic thionocarbonates, which proceeds with *net retention* of stereochemistry (eq 1, Scheme 1). This process provides an access to *syn*(*threo*)-hydroxy thiols from AD products, *syn*-diols, not a straightforward transformation otherwise.[5] Expanding on this cyclic thionocarbonate rearrangement chemistry, we envisaged that cyclic iminocarbonates would undergo a similar tandem displacement (rearrangement) with net retention of stereochemistry (eq 2).[6] The overall process, after necessary protective and deprotective steps, would be a conversion of *syn*-diols (AD products) to *syn*-amino alcohols. As most of the presently known protocols (e.g., via cyclic sulfates or epoxides) convert the AD products to *anti*-amino alcohols, the iminocarbonate rearrangement process, if successful, would complement the current methodology and greatly expand the synthetic utility of the AD process. Amino alcohol functional groups are often found in many bioactive compounds, and their stereoselective synthesis is of interest.[7]

Scheme 1



Results and Discussion

Using a tartrate ester as our model *syn*-diol and following the literature procedure, we prepared the cyclic iminocarbonate.[8] Thus, the starting diol was activated via tin ketal and then, without the isolation of the tin intermediate, treated with an isothiocyanate.[8d] An electron-withdrawing substituent (R″) on the nitrogen was expected to facilitate the subsequent tandem displacement step. Also the lability of the group in the final deprotection step was taken into consideration; the commercially available benzoyl isothiocyanate was used throughout this initial study. The cyclic *N*-benzoyl iminocarbonate thus prepared proved too unstable to be chromatographed; therefore, it was treated directly with a bromide nucleophile (Bu_4NBr). Following reflux for 2 h, the desired *N*-benzoyloxazolidin-2-one (cyclic *N*-benzoylcarbamate) was obtained in 81% overall yield. The three-step sequence from the starting diol to the rearranged product (*N*-benzoyloxazolidin-2-one)—tin ketalization, iminocarbonate formation, and rearrangement—was conducted in a single reaction vessel.

The same three-step sequence was tried on a variety of diol substrates. As the significance of this transformation is the retention of configuration of *both* carbinol carbons, and as this process would, in practice, often be utilized following an AD reaction, only *syn*-diols, i.e., the AD products of (*E*)-disubstituted olefins, were chosen as the substrates. All the diol substrates tried provided the desired *N*-benzoyloxazolidin-2-ones in good yields, although certain substrates required minor modifications from the standard reaction conditions described above. The results are summarized in Table 1.

The rearrangement proceeded in a regioselective manner. The nitrogen functionality was incorporated either at the α to carbonyl or benzylic sites. When there is a competition between these two activating groups, a mixture of regioisomers was obtained as determined by

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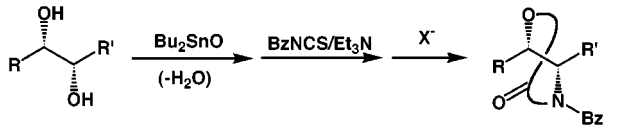
Table 1. Conversion of *syn*-Diols to Protected *syn*-Amino Alcohols via Cyclic Iminocarbonates[a]



entry	diol (R,R′)	M−X	yield[b]
1	$CO_2{}^iPr$, $CO_2{}^iPr$	Bu_4NBr	81
2	CH_3, CO_2Et[c]	Bu_4NBr[d]	74
3	Ph, CO_2Et[c]	Bu_4NBr	77[e]
4	CO_2Et, *p*-$MeOC_6H_4$ [c]	Bu_4NBr	83[f]
5	Ph, Ph[g]	LiI	73
6	CH_3, *p*-$MeOC_6H_4$ [g]	LiI	58

[a] Refer to the Experimental Section for details. [b] Overall yield from the diol. [c] Racemic diol was used. [d] The BzNCS step and the Bu_4NBr step were conducted concurrently. [e] A mixture of the regiosiomers (2.7:1) was obtained. The major isomer was the one shown above. [f] A mixture of the regiosiomers (1.4:1) was obtained. The major isomer was the one shown above. [g] The enantiomer antipodal to the structure given was used.

NMR (entries 3 and 4). In general, the rearrangement proceeded more smoothly with the diol substrates containing a carbonyl activating group than with aryl-activated diols. Thus, poor yields were initially observed with stilbenediol and anetholediol following the standard procedure. When the halide nucleophile was changed from bromide to iodide (LiI), however, satisfactory yields were obtained from these aryl diols (entries 5 and 6). Although the halide nucleophile is thought to be regenerated at the end of the tandem displacement and therefore should be required in a catalytic amount, less than 1 equiv of Br^- or I^- has so far resulted in lower yields. The iminocarbonate formation step and the tandem displacement may be conducted in situ. Thus, the diol prepared from a crotonate ester was activated via tin ketal and it was treated with BzNCS and Bu_4NBr in the presence of Et_3N to yield the desired *N*-benzoyloxazolidin-2-one in overall 74% (enty 2). With some diols (for example, stilbenediol and tartrate), however, the in situ procedure resulted in lower yields of the products, a concurrent monobenzoylation of the diols being a major side reaction under these conditions. Dichloroethane is in general preferred to toluene as the reaction solvent.

The *N*-benzoyloxazolidin-2-ones thus obtained may be deprotected to amino alcohols in the following manner. Basic or acidic solvolysis (Cs_2CO_3, LiOH, DBU, or Ti($O^iPr)_4$ in alcoholic solvents) removes the benzoyl group first (an ester functional group present in the product may undergo a transesterification). The remaining oxazolidin-2-one ring (cyclic carbamate) may be most conveniently cleaved in a three-step sequence of *N*-Boc protection [$(Boc)_2O$, DMAP], basic solvolysis cleaving the carbamate ring (Cs_2CO_3), and Boc-deprotection (TFA).[9]

The nature of the stereochemistry during the rearrangement step has been confirmed to be net retention (double-inversion) by a chemical correlation. Thus, a threonine ester was converted first to the oxazolidin-2-one (phosgene), which was then *N*-benzoylated (BzCl, DMAP). The *N*-benzoylated product as well as the intermediate oxazolidin-2-one each proved identical to those derived from the crotonate diol as described above.

Combining with the AD process, the present methodology, therefore, introduces a *syn*-amino alcohol functionality in two steps from (*E*)-disubstituted olefins in a stereoselective manner. In this regard, it is interesting to compare the present chemistry with the latest asymmetric process from Sharpless group, namely the asymmetric aminohydroxylation (AA) process.[10] The AA process provides protected amino alcohols from olefins in a single step. Perhaps as it is relatively new and still to be further developed, the enantioselectivities are not yet invariably high.[11] The present methodology owes the absolute stereocontrol to the AD, so it enjoys generally higher enantioselectivities, albeit in two separate operations. More importantly, the two processes complement each other in terms of the regioselection. In crotonate- and cinnamate-type substrates, the AA process preferentially introduces a nitrogen function at β to the carbonyl and an oxygen at the α site, while the present chemistry yields regioisomeric α-amino-β-hydroxy derivatives.[12]

In conclusion, the chemistry described in this paper allows one to convert *syn*-diols to *syn*-amino alcohols. As most of the previously known diols transformations are usually accompanied by an inversion of a stereocenter, the iminocarbonate rearrangement process described herein is unique in retaining the diol configurations. Also, it effects the regioselection opposite to what the AA brings about. Therefore, the present chemistry complements the existing methodologies for amino alcohol synthesis.

Experimental Section

Rearrangement of a Tartrate Ester to the Corresponding *N*-Benzoyloxazolidin-2-one. Diisopropyl L-tartrate (242 mg, 1.03 mmol) was dissolved in dichloroethane (15 mL). Dibutyltin oxide was added and the mixture heated to reflux for 4 h under nitrogen with a concomitant removal of water (Dean−Stark trap). Benzoyl isothiocyanate (0.228 mL, 1.73 mmol) and triethylamine (0.167 mL, 1.2 mmol) were added, and the mixture was heated to reflux. After 1 h, tetrabutylammonium bromide (332 mg, 1.03 mmol) was added and heating was continued for a further 2 h. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was separated, washed with brine, and dried (Na_2SO_4). The concentrated crude product was chromatographed on a silica column (hexane:EtOAc = 2.2:1) to yield the pure product (304 mg, 81%): $[\alpha]_D$ −47.7 (*c* 0.80, EtOH); mp 115−116 °C; ^1H NMR ($CDCl_3$) δ 7.70 (2H, d, J = 7.0 Hz), 7.58 (1H, m), 7.45 (2H, m), 5.23−5.12 (2H, m), 5.02 (1H, d, J = 3.7 Hz), 4.87 (1H, d, J = 3.6 Hz), 1.55−1.30 (12H, m); IR 2993 (m), 1809 (b), 1741 (s), 1688 (s), 1387 (m) cm^{-1}; MS *m/e* 364 (MH^+). Anal. Calcd for $C_{18}H_{21}NO_7$: C, 59.50; H, 5.83; N, 3.85. Found: C, 59.71; H, 5.85; N, 3.80.

Rearrangement of a Crotonate Diol to the Corresponding *N*-Benzoyloxazolidin-2-one. Ethyl crotonate diol (racemic, 92.9 mg, 0.63 mmol) was activated via tin ketal as described above. Benzoyl isothiocyanate (0.116 mL, 0.88 mmol), triethyl-

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(11) Enantioselectivities of the AA process range typically 80−90% ee for disubstituted (*E*)-olefins,[10g] while anything below 90% ee would be a rare exception for the AD process.

(12) Cf.: Tao, B.; Schlingloff, G.; Sharpless, K. B. *Tetrahedron Lett.* **1998**, *39*, 2507.

amine (0.104 mL, 0.75 mmol) and tetrabutylammonium bromide (203 mg, 0.63 mmol) were added, and the mixture was heated to reflux overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was separated, washed with brine, and dried (Na_2SO_4). The concentrated crude product was chromatographed on a silica column (hexane:EtOAc = 2.2:1) to yield the pure product (166 mg, 74%): mp 95−97 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (2H, d, J = 7.7 Hz), 7.58 (1H, m), 7.45 (2H, m), 4.71−4.64 (2H, m), 4.30 (2H, q, J = 7.1 Hz), 1.65 (3H, d, J = 5.9 Hz), 1.31 (3H, t, J = 7.2 Hz); IR 2989 (m), 2940 (m), 1802 (s), 1753 (s), 1686 (s) cm^{-1}; MS *m/e* 278 (MH^+). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.67; H, 5.37; N, 4.94.

Rearrangement of a Cinnamate Diol to the Corresponding *N*-Benzoyloxazolidin-2-one. Ethyl cinnamate diol (racemic, 167 mg, 0.79 mmol) was converted to the corresponding cyclic *N*-benzoyliminocarbonate (the benzoyl isothiocyanate step took 2 h), which was then treated with tetrabutylammonium bromide (274 mg, 0.85 mmol) as described above for the reaction with a tartrate ester (reflux overnight). The reaction mixture was partitioned between ethyl acetate and water. The organic phase was separated, washed with brine, and dried (Na_2SO_4). The concentrated crude product was chromatographed on a silica column (hexane:EtOAc = 2.5:1) to yield the product as a 2.7:1 mixture of regioisomers (205.5 mg, 77%). The regioisomers were separated by crystallization (hexanes−EtOAc). α-*N*-isomer (major): mp 95−96 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (2H, d, J = 7.7 Hz), 7.59 (1H, m), 7.49−7.44 (7H, m), 5.55 (1H, d, J = 5.2 Hz), 5.01 (1H, d, J = 5.1 Hz), 4.36 (2H, q, J = 7.0 Hz), 1.34 (3H, t, J = 7.1 Hz); IR 2993 (m), 1787 (s), 1751 (s) cm^{-1}; MS *m/e* 340 (MH^+). Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.20; H, 5.05; N, 4.13. Found: C, 66.86; H, 5.06; N, 4.01. β-*N*-isomer (minor): mp 165−167 °C; ^{1}H NMR ($CDCl_3$) δ 7.68 (2H, d, J = 7.8 Hz), 7.55 (1H, m), 7.47−7.38 (7H, m), 5.63 (1H, d, J = 4.6 Hz), 4.87 (1H, d, J = 4.6 Hz), 4.38 (2H, q, J = 7.1 Hz), 1.38 (3H, t, J = 7.1 Hz); IR 3058 (m), 1800 (s), 1768 (s) cm^{-1}; MS *m/e* 340 (MH^+). Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.20; H, 5.05; N, 4.13. Found: C, 67.13; H, 4.73; N, 3.96.

Rearrangement of a *p*-Methoxycinnamate Diol to the Corresponding *N*-Benzoyloxazolidin-2-one. Ethyl *p*-methoxycinnamate diol (racemic, 214 mg, 0.89 mmol) was converted to the corresponding cyclic *N*-benzoyliminocarbonate (the benzoyl isothiocyanate step took 1 h), which was then treated with tetrabutylammonium bromide (370 mg, 1.15 mmol) as described above for the reaction with a tartrate ester (reflux for 9 h). The reaction mixture was partitioned between ethyl acetate and water. The organic phase was separated, washed with brine, and dried (Na_2SO_4). The concentrated crude product was chromatographed on a silica column (hexane:EtOAc = 2:1) to yield the product as a 1.4:1 mixture of regioisomers (271 mg, 83%). The regioisomers were partially separated by column chromatography (hexane:EtOAc = 2:1). α-*N*-isomer (minor): ^{1}H NMR ($CDCl_3$) δ 7.74 (2H, d, J = 7.1 Hz), 7.59 (1H, t, J = 7.4 Hz), 7.46 (2H, t, J = 7.4 Hz), 7.36 (2H, d, J = 8.7 Hz), 6.98 (2H, d, J = 8.7 Hz), 5.49 (1H, d, J = 5.5 Hz), 5.01 (1H, d, J = 5.5 Hz), 4.33 (2H, q, J = 7.1 Hz), 3.85 (3H, s), 1.31 (3H, t, J = 7.1 Hz). β-*N*-isomer (major): ^{1}H NMR ($CDCl_3$) δ 7.67 (2H, d, J = 7.2 Hz), 7.55 (1H, t, J = 7.4 Hz), 7.42 (2H, t, J = 7.8 Hz), 7.38 (2H, d, J = 8.7 Hz), 6.94 (2H, d, J = 8.7 Hz), 5.58 (1H, d, J = 4.7 Hz), 4.87 (1H, d, J = 4.7 Hz), 4.36 (2H, q, J = 7.1 Hz), 3.80 (3H, s), 1.35 (3H, t, J = 7.1 Hz).

Rearrangement of Stilbenediol to the Corresponding *N*-Benzoyloxazolidin-2-one. (*R*,*R*)-Stilbenediol (208 mg, 0.97 mmol) was converted to the corresponding cyclic *N*-benzoyliminocarbonate as described above (the benzoyl isothiocyanate step took 1 h). Lithum iodide (160 mg, 1.2 mmol) was added and the entire mixture heated to reflux overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was separated, washed with brine, and dried (Na_2SO_4). The concentrated crude product was chromatographed on a silica column (hexane:EtOAc = 3:1) to yield the pure product (243.4 mg, 73%): $[\alpha]_D$ 13.1 (*c* 0.82, $CHCl_3$); mp 168−170 °C; ^{1}H NMR ($CDCl_3$) δ 7.8 (2H, d, J = 7.8 Hz), 7.58 (1H, m), 7.49−7.29 (12H, m), 5.46 (1H, d, J = 8.0 Hz), 5.42 (1H, d, J = 7.9 Hz); IR 3068 (m), 3035 (m), 1793 (s), 1681 (s) cm^{-1}; MS *m/e* 344 (MH^+). Anal. Calcd for $C_{22}H_{17}NO_3$: C, 76.95; H, 4.99; N, 4.08. Found: C, 76.91; H, 5.00; N, 4.00.

Rearrangement of Anetholediol to the Corresponding *N*-Benzoyloxazolidin-2-one. (*R*,*R*)-Anetholediol (210 mg, 1.15 mmol) was converted to the corresponding cyclic *N*-benzoyliminocarbonate (the benzoyl isothiocyanate step took 2 h), which was then treated with lithium iodide (140 mg, 1.0 mmol) as described above for the reaction with stilbenediol (reflux for 2 h). The reaction mixture was partitioned between ethyl acetate and water. The organic phase was separated, washed with brine, and dried (Na_2SO_4). The concentrated crude product was chromatographed on a silica column (hexane:EtOAc = 2.2:1) to yield the pure product (206.4 mg, 58%): $[\alpha]_D$ −61.2 (*c* 0.69, $CHCl_3$); mp 155−156 °C; ^{1}H NMR ($CDCl_3$) δ 7.72 (2H, d, J = 7.9 Hz), 7.55 (1H, m), 7.42 (2H, m), 7.36 (2H, d, J = 8.6 Hz), 6.92 (2H, d, J = 8.6 Hz), 5.06 (1H, d, J = 7.8 Hz), 4.62−4.53 (1H, m), 3.79 (3H, s), 1.53 (3H, d, J = 6.2 Hz); IR 2839 (b), 1798 (s), 1681 (s), 1517 (s) cm^{-1}; MS *m/e* 312 (MH^+). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.28; H, 5.55; N, 4.49.

Deprotection of the *N*-Benzoyloxazolidin-2-ones to the Corresponding Amino Alcohols: Representative Procedure. The *N*-benzoyloxazolidin-2-one derived from (*S*,*S*)-stilbenediol (70 mg, 0.2 mmol) was dissolved in absolute ethanol (7 mL), and Cs_2CO_3 (84 mg, 0.25 mmol) was added. The mixture was stirred at room temperature for 2 h. It was concentrated, and the residue was chromatographed on a silica column (3:2 hexanes−EtOAc) to yield the debenzoylated product (48 mg, 99%) as a white solid: mp 127−130 °C; ^{1}H NMR ($CDCl_3$) δ 7.40 (6H, m), 7.32 (4H, m), 5.42 (1H, brs), 5.31 (1H, d, J = 7.4 Hz), 4.75 (1H, d, J = 7.4 Hz); IR 3264 (b), 1754 (s), 1723 (s) cm^{-1}; MS *m/e* 239 (MH^+).

The oxazolidin-2-one obtained as above (48 mg, 0,2 mmol) was dissolved in THF (6 mL) and treated with $(Boc)_2O$ (90 mg, 0.41 mmol) and DMAP (12 mg, 0.2 mmol) at room temperature for 1.5 h. Aqueous workup (water−EtOAc) was followed by a column chromatography (7:2 hexanes−EtOAc) to yield the *N*-Boc-oxazolidin-2-one (53 mg, 78%) as a white solid: mp 78∼80 °C; ^{1}H NMR ($CDCl_3$) δ 7.42 (6H, m), 7.29 (4H, m), 5.26 (1H, d, J = 5.9 Hz), 4.98 (1H, d, J = 5.8 Hz), 1.25 (9H, s); IR 2981 (m), 2931 (m), 1826 (s), 1735 (s) cm^{-1}.

The *N*-Boc-oxazolidin-2-one (163 mg, 0.48 mmol) was then treated with Cs_2CO_3 (163 mg, 0.5 mmol) in absolute ethanol (10 mL) at room temperature. The mixture was concentrated and the residue chromatographed on a silica column (2:1 hexanes−EtOAc) to yield the *N*-Boc-amino alcohol (117 mg, 78%): mp 112−113 °C; ^{1}H NMR ($CDCl_3$) δ 7.29 (10H, m), 5.40 (1H, d, J = 7.5 Hz), 4.82 (2H, m), 2.72 (1H, brs); IR 3317 (b), 2981 (m), 1672 (s), 1521 (s) cm^{-1}.

The final *N*-Boc deprotection was performed with the *N*-Boc-amino alcohol (117 mg, 0.37 mmol) in a 1:1 mixture (v/v) of trifluoroacetic acid−dichloromethane (10 mL). After being stirred at room temperature for 1 h, the mixture was concentrated and the residue partitioned between 10% aqueous Na_2CO_3 and EtOAc. The organic phase was separated, dried (Na_2SO_4), and chromatographed on a silica column (EtOAc) to yield (*S*,*S*)-2-amino-1,2-diphenylethan-1-ol (60 mg, 77%) as a white solid: $[\alpha]_D$ −99.7 (*c* 0.8, EtOH);[13] mp 104−108 °C; ^{1}H NMR ($CDCl_3$) δ 7.26 (10H, m), 4.67 (1H, d, J = 6.5 Hz), 3.99 (1H, d, J = 6.5 Hz), 1.85 (3H, br); IR 3367 (s), 3086 (b), 1448 (s) cm^{-1}.

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(13) (a) The observed optical rotation of this compound is comparable to the literature value ($[\alpha]_D$ −106.7 (*c* 0.72, EtOH)),[13b] confirming that little, if any, racemization has taken place during the entire transformations and the course of the stereochemistry is indeed retention at both carbinol carbons. (b) Shimizu, M.; Tsukamoto, K.; Matsutani, T.; Fujisawa, T. *Tetrahedron* **1998**, *54*, 10265.