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Practical Modifications and Applications of the Sharpless Asymmetric Aminohydroxylation in the One-Pot Preparation of Chiral Oxazolidin-2-ones

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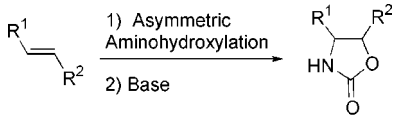
ABSTRACT



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Chiral oxazolidin-2-ones are synthetically valuable as chiral auxiliaries, and many have pharmaceutically interesting biological activity. This communication focuses on a convenient, practical one-pot preparation of chiral 4,5-disubstituted oxazolidan-2-ones in good yield with high enantioselectivities, using a modified Sharpless asymmetric aminohydroxylation of β-substituted styrene derivatives followed by base-mediated ring closure. This procedure has been demonstrated on both small and large scale, utilizing 1,3-dichloro-5,5-dimethyl hydantoin as an easily handled, commercially available substitute for *tert*-butyl hypochlorite.

Since its introduction as a chiral auxiliary in 1981, the oxazolidin-2-one moiety has emerged as a useful tool in asymmetric synthesis.[1] The oxazolidinone is also a common heterocyclic motif in a variety of biologically active and pharmaceutically interesting molecules.[2] A survey of the literature reveals a variety of both natural[3] and unnatural[4] starting points for the preparation of oxazolidinones including the reaction of diols with isocyanates, epoxide openings, amino acids, aziridines, oxetanes, 2-oxazolones, hydroxy acids or esters, and perhaps the most common, amino alcohols.[5] The chiral oxazolidin-2-ones employed in the chemistry of Evans are typically prepared from the amino alcohol reduction products of naturally occurring α-amino acids.[6] Recently, Takacs has reported the preparation of 4-substituted oxazolidin-2-ones.[7] In this procedure, a chiral *N*-acyloxazolidinone titanium enolate is condensed with formaldehyde or acetone followed by hydrolysis to the β-hydroxy acid. Curtius rearrangement then allows access to a variety of chiral oxazolidin-2-ones not available from natural α-amino acids.

During the development of a novel drug candidate containing the oxazolidin-2-one moiety, we required access to asymmetric 4-aryl-5-alkyl oxazolidin-2-ones. After ex-

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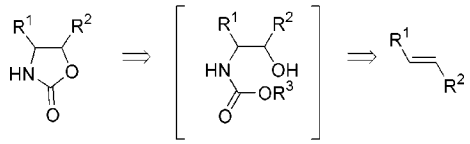
amination of the known asymmetric oxazolidinone preparation methods, we envisioned an additional approach using the Sharpless asymmetric aminohydroxylation[8] of a styrene derivative followed by base-mediated selective ring closure of the carbamate to afford oxazolidinones in a single step (Scheme 1). During the development of this procedure, Li

Scheme 1

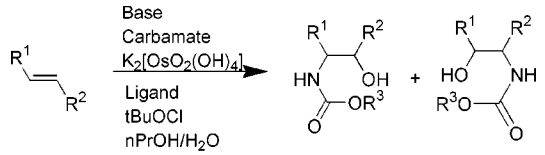


2 **3** **1**

reported a two-step process for the conversion of unsubstituted styrene derivatives to chiral oxazolidin-2-ones using a potassium carbonate mediated ring closure.[9] Herein, we wish to report preliminary examples of a practical, one-pot conversion of disubstituted styrene derivatives to chiral oxazolidin-2-ones using a modified Sharpless carbamate-based asymmetric aminohydroxylation that has been demonstrated on both small (mg) and large (kg) scale.[10]

Of the many aminohydroxylation procedures reported by Sharpless, only those utilizing a carbamate as the nitrogen source were suitable for use in the direct conversion to oxazolidinones (Scheme 2).[8e,f,h,k] According to Sharpless, the

Scheme 2



1 **3** **4**

chemo-, regio-, and enantioselectivity of the aminohydroxylation reaction can be readily controlled by small variations in the reaction parameters. In addition, these previous reports support a suprafacial addition of nitrogen and oxygen to the olefin, wherein asymmetric aminohydroxylation of *trans*-olefins would afford *trans*-oxazolidinones.[8e] The most favorable conditions for carbamate-based aminohydroxylation of styrenes resulting in benzylic amination are given as urethane with PHAL ligands in *n*-PrOH/water solvent systems using *tert*-butyl hypochlorite as the co-oxidant, so this was our starting point.

The requirement for 3 equiv of freshly prepared *tert*-butyl hypochlorite was untenable for large scale development of an aminohydroxylation-based process. Therefore, alternative co-oxidants/chlorine sources were examined for utility in the asymmetric aminohydroxylation reaction. Despite the fact that NCS, cyanuric chloride, and trichloroisocyanuric acid were unsuccessful substitutes for *tert*-butyl hypochlorite, either 1,3-dichloro-5,5-dimethyl hydantoin or dichloroiso-

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(10) (a) **Typical Experimental Procedure. 4(*S*)-(3,4-Difluorophenyl)-5(*S*)-methyloxazolidin-2-one.** Sodium hydroxide (1.57 g, 39.3 mmol) was dissolved in 50 mL of H_2O. A 1-mL aliquot of the NaOH solution was used to dissolve $K_2OsO_2(OH)_4$ (0.048 g, 0.13 mmol) in a separate vial. 1-Propanol (25 mL) and ethyl carbamate (3.56 g, 40.0 mmol) were added to the reaction flask at 20 °C, followed by 1,3-dichloro-5,5-dimethylhydantoin (3.89 g, 19.7 mmol); the solids dissolved in approximately 5 min. A solution of $(DHQ)_2PHAL$ (0.125 g) and *trans*-1-(3,4-difluorophenyl)-1-propene (2.0 g, 12.97 mmol) in 25 mL of 1-propanol was added, followed by addition of the potassium osmate solution. The reaction was monitored for the disappearance of olefin using HPLC. A mixture of the hydroxy carbamates was obtained in a 4:1 ratio, as determined by NMR or by HPLC. Sodium hydroxide (2 g) was added to the flask at 20 °C. After 30 min, the reaction mixture was diluted with H_2O (50 mL) and extracted with 2 × 50 mL of EtOAc. The organic layers were combined and concentrated, and the oxazolidinone products were purified by column chromatography. The product was isolated as a pale yellow oil and was determined to have 90% ee by SFC: ^1H NMR ($CDCl_3$) δ 7.19 (m, 2H), 7.08 (m, 1H), 5.58 (s, 1H), 4.41 (m, 2H), 1.51 (d, J = 5.9 Hz, 3H). (b) Satisfactory analytical data (IR, H NMR, C NMR, and elemental analysis) was obtained for all new products.

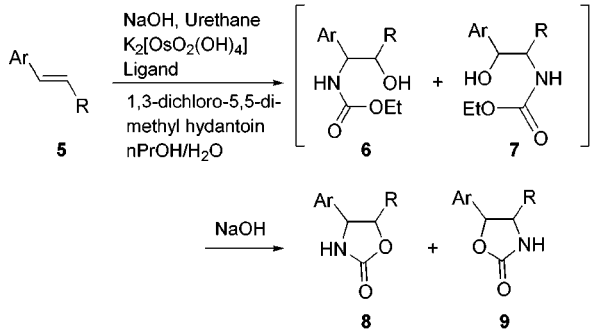
cyanuric acid sodium salt proved to be convenient, inexpensive, readily available alternatives that could be employed without decreasing regio- or enantioselectivity or reaction yield. This discovery is of particular utility because both of these reagents are stable, commercially available solids, obviating the need for large volumes of freshly prepared *tert*-butyl hypochlorite. Interestingly, both chlorines on either 1,3-dichloro-5,5-dimethyl hydantoin or dichloroisocyanuric acid sodium salt are available for reaction, maximizing efficiency.

Using our optimized aminohydroxylation conditions [NaOH (3.05 equiv), urethane (3.08 equiv), 1,3-dichloro-5,5-dimethyl hydantoin (1.53 equiv), $(DHQD)_2$- or $(DHQ)_2$PHAL ligand (0.025 equiv), and potassium osmate (0.02 equiv) in *n*-PrOH/water (1:1)] several β-substituted styrene derivatives (1.0 equiv) were subjected to aminohydroxylation. Upon completion of the aminohydroxylation reaction, the acyclic carbamate could be isolated by standard techniques. These products could be converted to the corresponding amino alcohol if desired. Alternatively, a second charge of base (NaOH, NaOMe, K_2CO_3, Cs_2CO_3, or Na_2CO_3 all afforded comparable results) added directly to the reaction mixture converted the acyclic carbamates to the oxazolidin-2-ones in most cases. While this afforded a rapid, highly selective route to substituted oxazolidinones, chromatographic separation of the regioisomers was required.

As expected, the regioselectivity of the aminohydroxylation reaction varied with the reaction conditions (Table 1). The regioselectivities obtained using the modified conditions are consistent with the results reported by Sharpless for the aminohydroxylation of styrene derivatives using benzyl carbamate and $(DHQ)_2$PHAL, which range from 1:1 to 10:1. Isolated yields of the oxazolidinones ranged from poor (28%, *trans* stilbene) to good (81%, *p*-methoxy β-methyl styrene). Using the DHQ ligand series, the enantiomeric excess of the resultant oxazolidinones was very good for the benzylamine regioisomer (**8**) and low to moderate for the benzyl alcohol isomer (**9**) without recrystallization. Interestingly, aminohydroxylation of ethyl *p*-nitrocinnamate using these modified conditions gave good yields and high regio- and enantioselectivity, but the acyclic intermediates could not be forced to cyclize even with excess base and prolonged heating. Identical to the results with 1,3-dichloro-5,5-dimethyl hydantoin (Table 1), the use of dichloroisocyanuric acid sodium salt in the aminohydroxylation of *trans*-β-methyl styrene afforded a 3:1 ratio of **8**:**9** in 65% yield. The Sharpless AQN ligand series also works with the 1,3-dichloro-5,5-dimethyl hydantoin or dichloroisocyanuric acid oxidants, but the regio- and enantioselectivities are low to moderate for **9** as the major product.

During the course of these studies, the separations of regioisomers **8** and **9** were accomplished via column chromatography. During optimization of the reaction conditions, closer examination of the acyclic carbamate reaction mixtures immediately following aminohydroxylation showed that in the presence of base the desired benzylic amine derivative cyclized much more rapidly than the benzylic alcohol derivative. This difference in cyclization rate for the regioisomers allowed for differentiation through careful base selection, charge, and timing of an acidic reaction quench (Scheme 3).

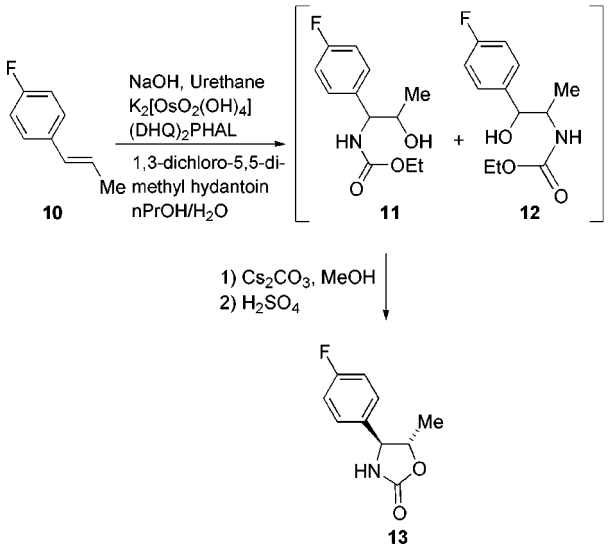
Table 1. Aminohydroxylation with 1,3-Dichloro-5,5-dimethylhydantoin as the Co-oxidant



Ar	R	ligand[a]	yield[b]	**8**:**9**	% ee **8**, **9**[c]
Ph	Me	B	65	2:1	88.1[e], 73.4[f]
4-OMe-Ph	Me	A	81	5:1	98.0[g], 70.5[h]
4-OMe-Ph	Me	B	42	4:1	98.0[i], 99.4
Ph	Ph	A	28		87.4[j]
Ph	Ph	B	72		80.7[k]
4-NO_2-Ph	CO_2Et	A	76	4:1[d]	90.0, 30.7[d]
4-NO_2-Ph	CO_2Et	B	73	8:1[d]	90.6, 19.7[d]

[a] Ligand A = $(DHQ)_2$PHAL, major isomer is 4(*S*),5(*S*)-**8**, B = $(DHQD)_2$PHAL, major isomer is 4(*R*),5(*R*)-**8**. [b] Combined yield of **8** + **9**. [c] Enantioselectivity of the crude product as determined by SFC. [d] Open chain products only (**6** and **7**). [e] $[\alpha]^{25}_D = 25.3°$. [f] $[\alpha]^{25}_D = -7.4°$. [g] $[\alpha]^{25}_D = 1.1°$. [h] $[\alpha]^{25}_D = -20.7°$. [i] $[\alpha]^{25}_D = -1.0°$. [j] $[\alpha]^{25}_D = -90.6°$. [k] $[\alpha]^{25}_D = 93.7°$.

Scheme 3



The addition of sulfuric acid transformed the uncyclized benzylic alcohol isomer **12** to the corresponding amino alcohol, leaving the desired oxazolidinone **13** untouched. A simple extraction sequence could then be used to separate **13** from the amino alcohol. Typically, the aminohydroxylation reactions were monitored for consumption of styrene,

then 1 equiv of additional base was added, and the reaction was monitored for cyclization of the benzylic carbamate. This procedure was used to convert β-methyl styrene **10** to oxazolidinone **13** in 71% yield and 90−93% ee. The present method for the one-step preparation of chiral oxazolidin-2-ones from β-substituted styrenes demonstrates that the Sharpless asymmetric aminohydroxylation can be successfully employed in a practical and economical procedure using 1,3-dichloro-5,5-dimethyl hydantoin or dichloroisocyanuric acid sodium salt in good yield and high regio- and enantioselectivity.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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