Communications

Highly Diastereoselective Epoxidation of Ketene Dithioacetal Dioxides: A New Approach to the Asymmetric Synthesis of α-Amino Amides

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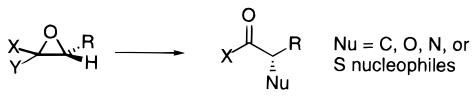
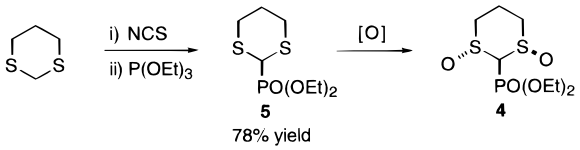
A variety of methods are available for the preparation of α-heterosubstituted carbonyl compounds in enantiomerically enriched form.[1−3] Excellent levels of stereocontrol have been achieved in the reaction of chiral enolates with heteroatomic electrophiles[4−6] and in the addition of carbonyl anion equivalents to aldehydes or imines.[7−11] However, a common feature of these strategies is that the choice of heteroatomic functional group affects both reactivity and selectivity in the asymmetric induction event. Such substrate dependence could be avoided by the enantioselective preparation of a general chiral precursor that could be *stereospecifically* transformed into a variety of α-heterosubstituted carbonyl compounds (Scheme 1). This strategy is exemplified by Corey's one-pot conversion of (trichloromethyl)carbinols, generated by oxazaborolidine-catalyzed asymmetric reduction of trichloromethyl ketones, into α-azido and α-hydroxy acids.[12,13] The chiral precursor in this case is a reactive *gem*-dichlorooxirane formed upon deprotonation of the carbinol (X = Y = Cl in Scheme 1), while an *in situ* nucleophile provides the heteroatomic functional group. An alternative, auxiliary-based approach in which the chiral precursor could be isolated as a single diastereoisomer would provide additional opportunities for stereochemical control. This paper reports such an approach to the stereospecific formation of α-heterosubstituted carbonyl compounds, in which the chiral precursor is a crystalline spirocyclic bis-sulfinyl oxirane (X = Y = SOR), isolable in greater than 98% diastereomeric and enantiomeric excess.

The preparation of spirocyclic epoxides such as **1**/**2** has previously been attempted *via* the corresponding halohydrins, themselves formed by condensation of 2-halogeno-1,3-dithiane 1,3-dioxide with aldehydes.[14] This route was abandoned due to the inefficiency of the ring-closure step, which was attributed to the deactivating effect of the two sulfoxides. It was decided, as an alternative, to attempt the diastereoselective epoxidation of ketene thioacetals **3**, which could potentially be accessed by a Wadsworth−Emmons reaction using phosphonate **4**. Phosphonate **4** was prepared in racemic form by sodium periodate oxidation of the known phosphonate **5**.[15] Asymmetric oxidation of **5** was achieved in excellent enantiomeric excess using the Modena protocol (Scheme 2),[16] which has previously been successfully applied by ourselves to the oxidation of 2-carbethoxy-1,3-dithiane[17] and by Page to the oxidation of other 2-substituted 1,3-dithianes.[18] The enantiomeric excess of **4** was determined as >98% by chiral shift ^{31}P NMR using the Pirkle shift reagent.[19] The absolute configuration of **4** was assigned by analogy with previous results.[20]

Scheme 1



Scheme 2[a]



[a] Racemic oxidation: $NaIO_4$, 30% H_2O/MeOH, 53% yield. Asymmetric oxidation: $PhC(CH_3)_2OOH$ (4 equiv), $Ti(O^iPr)_4$ (0.5 equiv), (+)-DET (2 equiv), CH_2Cl_2, 43% yield, >98% ee.

Wadsworth−Emmons-type olefination of α-phosphoryl sulfones[21] and sulfoxides[22,23] with aldehydes are precedented; however, the same conditions were unsuccessful when applied to the bis-sulfoxide **4**. After screening a variety of bases,[24] it was found that lithium hydroxide[25] gave

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(25) Anhydrous LiOH and the monohydrate proved equally effective. This base has been used previously in the Wadsworth−Emmons reaction of ester-stabilized phosphonate carbanions.[33] Magnesium hydroxide proved to be an equally effective base, but only when used in the presence of water (e.g., 5% water in THF). Under the same conditions (5% water in THF), LiOH was much less effective.

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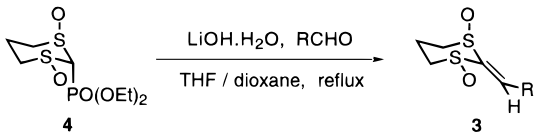
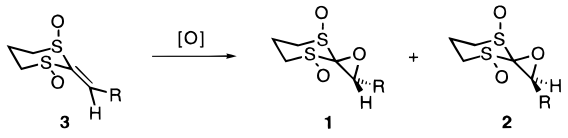
Table 1. Olefination of 2-Phosphoryl-1,3-dithiane 1,3-Dioxide



R in RCHO	solvent	reflux time (h)	product	yield (%)
Ph	1,4-dioxane	3	**3a**	70
p-$O_2NC_6H_4$	THF	2	**3b**	87
p-$MeOC_6H_4$	1,4-dioxane	4	**3c**	62
p-ClC_6H_4	1,4-dioxane	4	**3d**	84
cyclo-C_6H_{11}	1,4-dioxane	4	**3e**	71

Table 2. Nucleophilic Epoxidation of Ketene Dithioacetals



Method A; (i) H_2O_2(aq) (3eq.), NaOH (0.5eq.), 30% CH_2Cl_2 / MeOH. -10°C.
Method B; *t*-BuOOH (1.5eq.), *n*-BuLi (1.1eq.), THF, -78°C-room temperature

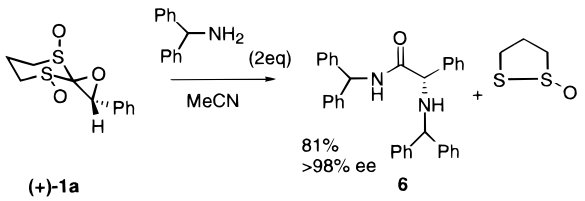
entry	R	method	*T* (°C), reaction time	yield (%)	ratio **1**:**2**
1	Ph	A	−10, 20 min	81	>96:4[a]
2	*p*-$O_2NC_6H_4$	A	−20, 10 min	81	73:27
3	*p*-$O_2NC_6H_4$	B	−78 to rt, 18 h	70	>96:4[a]
4	*p*-$MeOC_6H_4$	A	rt, 72 h	0[b]	
5	*p*-$MeOC_6H_4$	B	−78 to rt, 24 h	0[c]	
6	*p*-ClC_6H_4	A	−10, 10 min	96	>96:4
7	*cyclo*-C_6H_{11}	A	−10, 10 min	98	67:33
8	*cyclo*-C_6H_{11}	B	−78 to rt, 18 h	83	80:20

[a] Only one diastereoisomer was detected in the crude ^1H NMR spectrum. [b] The starting material did not react. [c] Decomposition occurred under the reaction conditions.

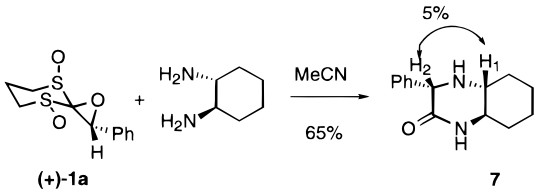
the best results in terms of rate and yield. These conditions were applied to a range of aldehydes, and good yields of the ketene thioacetals were obtained (Table 1).

Epoxidation of the bis-sulfoxides **3** was attempted using the nucleophilic oxidizing agents sodium hydroperoxide and lithium *tert*-butyl peroxide, following procedures developed for the epoxidation of electron deficient alkenes.[26] These conditions have been found to afford high diastereoselectivities in the epoxidation of vinyl sulfoximines.[27] High diastereoselectivity has also been achieved in the epoxidation of a limited range of vinyl sulfoxides,[28] although in several cases concomitant oxidation of the sulfoxide was observed.[29] The results of oxidation of the bis-sulfoxides **3** are shown in Table 2. Substrate **3a** (R = Ph) reacted cleanly and rapidly with sodium hydroperoxide (method A), epoxide **1a** being isolated as a single diastereoisomer (entry 1) simply by addition of water and extraction using dichloromethane. No oxidation at sulfur was observed. Electron-deficient aromatic groups (entry 2) lowered the diastereofacial selectivity, as did aliphatic ones (entries 7 and 8), but high selectivity could be restored in these cases by using lithium *tert*-butyl peroxide as the oxidizing agent (method B). The electron-donating *p*-methoxyphenyl substituent stabilizes substrate **3c** through extended conjugation and would be expected to destabilize the target epoxides **1** and **2**. No reaction occurred with sodium hydroperoxide, and prolonged exposure to lithium *tert*-butyl peroxide resulted only in decomposition.

Scheme 3



Scheme 4



Ring opening of the epoxide **1a** with benzhydrylamine[30,31] using acetonitrile as solvent yielded the protected amino amide **6** in excellent yield (81%) and enantiomeric excess (>98%) (Scheme 3), along with the expected byproduct, 1,2-dithiolane 1-oxide.[14]

The absolute stereochemistry of the newly generated stereocenter was confirmed by reaction of (+)-**1a** with the bidentate nucleophile (1*R*,2*R*)-1,2-diaminocyclohexane, which furnished **7** in good yield (65%) and as a single diastereoisomer. The relative stereochemistry of the product was determined by NOE studies (Scheme 4), which, by inference, proved the stereochemistry of the epoxide **1a**.[31]

In conclusion, we have shown that enantiomerically and diastereomerically pure spirocyclic bis-sulfinyl oxiranes can be prepared in four steps. These novel structures represent potentially versatile chiral substrates for the preparation of a variety of α-heterosubstituted carbonyl compounds. Their synthetic utility has been demonstrated by the synthesis of two amino amides with complete control over the newly generated stereocenter.

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Supporting Information Available: Experimental procedures and spectral data for all compounds (10 pages).

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