Concise Asymmetric Synthesis of α-Amino Acid Derivatives from *N*-Sulfinylimino Esters

Franklin A. Davis* and William McCoull

*Department of Chemistry, Temple University,
Philadelphia, Pennsylvania 19122*

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Glyoxylate imines provide access to nonproteinogenic α-amino acid derivatives through ene reactions,[1] cycloaddition reactions,[2,3] radical addition,[4] or nucleophilic addition.[5–8] However, a major drawback with glyoxylate imines is the absence of regioselectivity. Only allylating reagents have been found synthetically useful for such transformations.[5i,6,7] We have shown that the *N*-sulfinyl group in sulfinimines is an excellent imine auxiliary that activates the C=N bond for nucleophilic addition, exerts a powerful stereodirecting effect, and is easily deprotected in the product.[9–11]

In this communication we describe our initial results in the use of chiral *N*-sulfinyl auxiliaries for the activation of glyoxylate sulfinimines toward regioselective attack by organometallic reagents.[9,12] Sulfinimines **2a/b**, solid and oil, respectively, were prepared by 4 Å MS mediated condensation[13] of (*S*)-(+)-*p*-toluenesulfinamide[13] (**1a**) or (*R*)-(+)-*tert*-butanesulfinamide[14] (**1b**) with ethyl glyoxylate (Scheme 1). Initial studies with (*S*)-**2a** found that BnMgCl added regio-

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Scheme 1

selectively at the imino carbon to give (*S*S,2*R*)-**3** and (*S*S,2*S*)-**4** in 56% combined yield (82:18 diastereomer ratio). These diastereomers were not separable by chromatography, and using other solvents (toluene, THF, Et₂O) failed to give improved yields or diastereoselectivity. Oligomerization was identified as the major competing reaction pathway.[15] Precomplexation of (*S*)-**2a** with BF₃·OEt₂ (2 equiv) significantly reduced this oligomerization, but at the expense of yield (31%), diastereoselectivity (63:37), and activation of addition to sulfur to produce *p*-toluene benzyl sulfoxide[16] (*p*-tolyl-SOBn) in 36% yield. The more sterically demanding *tert*-butanesulfinyl auxiliary was envisaged to reduce the likelihood of reaction at sulfur.

Initial results (Table 1, entries 1 and 2) for the reaction of BnMgCl (typically 0.25 mmol) with (*R*)-(−)-**2b** indicated some improvement in the crude diastereoselectivity. The diastereomers were separable by chromatography, but the major diastereomer was isolated in poor yield (24%). Surprisingly, oligomerization did still occur, and significant amounts of *tert*-butane benzyl sulfoxide (*t*-BuSOBn)[17] were isolated corresponding to reaction at sulfur despite being adjacent to the bulky *tert*-butyl group. Lewis acids were precomplexed with sulfinimine (*R*)-**2b** in an effort to increase the desired reaction at the imine group. Ellman has used trimethylaluminum to increase the reaction yield of organolithiums with *N*-*tert*-butanesulfinyl ketimines,[18] but in our glyoxylate sulfinimine case, yields were not improved and oligomerization and *t*-BuSOBn formation were not suppressed greatly although the diastereoselectivity was enhanced (Table 1, entries 3 and 4). It was found that BF₃·OEt₂ (1 equiv) improved the desired reaction yield and diastereoselectivity (92:8). Use of a second equivalent of BF₃·OEt₂ further improved diastereoselectivity (94:6), and (*R*S,2*R*)-(−)-**5** was isolated in 70% yield. Oligomerization and *t*-BuSOBn formation were virtually eliminated. In addition, 2 equiv of BnMgCl were also found necessary for optimal yield and diastereoselectivity (Table 1, entries 5–7). Other Lewis acids (ZnCl₂, SnCl₄) gave inferior results, and BnZnCl gave no desired product (Table 1, entries 8–10).

Application of our optimized conditions to other Grignard reagents gave good diastereoselectivity and isolated yields (Scheme 2, Table 2). Sulfinimine (*R*)-**2b** was precomplexed with 2 equiv BF₃·OEt₂ in CH₂Cl₂ at −78 °C for 5 min and

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Table 1. Addition of Benzyl Organometallic Reagents to Glyoxylate Sulfinimine (*R*)-2b

entry	lewis acid (min)[a]	time (min)	reagent	$(R_S,2R)$−**5**,[b] %	$(R_S,2R)$−**5**/$(R_S,2S)$−**6**[c]	*t*-BuSOBn, %
1	none	20	1 equiv of BnMgCl	24	90:10	23
2	none	10	2 equiv of BnMgCl	28	89:11	10
3	1.1 equiv of AlMe₃ (5)	40	2 equiv of BnMgCl	23	93:7	12
4	2.1 equiv of AlMe₃ (10)	20	2 equiv of BnMgCl	28	93:7	8
5	1 equiv of BF₃·OEt₂ (5)	20	2 equiv of BnMgCl	50	92:8	3
6	2 equiv of BF₃·OEt₂ (5)	10	2 equiv of BnMgCl	70	94:6	trace
7	2 equiv of BF₃·OEt₂ (10)	40	1.2 equiv of BnMgCl	48	92:8	8
8	2 equiv of ZnCl₂ (10)	40	2 equiv of BnMgCl	30	77:23	20
9	2.1 equiv of SnCl₄ (10)	210	2.1 equiv of BnMgCl	17	*e*	*e*
10	none	210	2 equiv of BnZnCl[d]	none	*e*	28

[a] Glyoxylate sulfinimine was precomplexed with Lewis acid at −78 °C for time indicated in parentheses. [b] Isolated yield after chromatography. [c] Measured by 500 MHz ¹H NMR of crude reaction mixture. [d] Prepared in situ from BnMgCl and ZnCl₂ at −78 °C. [e] Not determined.

Scheme 2
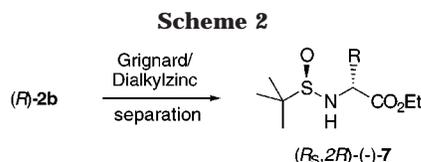
Table 2. Preparation of α-amino Acid Derivatives $(R_S,2R)$-(−)-7 Using Grignard/Dialkylzinc Reagents

R	method[a]	$(R_S,2R)$−**7**	crude dr
Bn	A	70%	94:6
Ph	A	70%	84:16
Et	A	27%[b]	>99:1
Et	B	88%[c]	>99:1
Me	A	59%	83:17
Me	B	43%[d]	92:8

[a] Method A: precomplexation with 2 equiv BF₃·OEt₂ (5 min, −78 °C) and then RMgX (10−20 min, −78 °C). Method B: 2−3 equiv R₂Zn, −78 °C. [b] 16% *t*-BuSONHCH₂CO₂Et also isolated. [c] 25 min at −78 °C. [d] 3 h at −78 °C.

the Grignard reagent added in one portion at this temperature. The reaction was generally complete within 20 min and quenched using NH₄Cl (satd aq) allowing, after aqueous workup, chromatographic separation of diastereomers. Most notable is the isolation of $(R_S,2R)$-(−)-**7** (R = Me) in 59% yield since MeMgBr has been reported to give desulfinylation in the presence of *p*-toluenesulfinimine.[19] Ethylmagnesium bromide gave only one detectable diastereomer by ¹H NMR (500 MHz) analysis, but reduction of the imine bond lowered the yield. Use of Et₂Zn circumvented this problem, affording 88% yield of $(R_S,2R)$-(−)-**7** (R = Et) as a single diastereomer even in the absence of Lewis acid activation. The less reactive Me₂Zn gave increased diastereoselectivity over the

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(21) The X-ray structure of *N*-benzylidene-*p*-toluenesulfinamide indicates that it adopts a syn-periplanar arrangement of the C−N−S−O unit. Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy. G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Thimma Reddy, R.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 2555−2563. However, we cannot rule out the possibility of a chelated intermediate containing a *Z*-imino bond as a result of *E* to *Z* isomerization during the BF₃·OEt₂ precomplexation.

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(25) Selected properties: (*S*)-(+)-**2a**: mp 37 °C, [α]²⁰_D +307 (*c* 0.945, CHCl₃); (*R*)-(−)-**2b**: oil, [α]²⁰_D −313 (*c* 1.01, CHCl₃); $(R_S,2R)$-(−)-**5**: oil, [α]²⁰_D −60.9 (*c* 1.06, CHCl₃); $(R_S,2R)$-(−)-**7** (R = Ph): oil, [α]²⁰_D −183 (*c* 0.59, CHCl₃); $(R_S,2S)$-(+)-**7** (R = Ph): oil, [α]²⁰_D +55 (*c* 0.55, CHCl₃); $(R_S,2R)$-(−)-**7** (R = Et): oil, [α]²⁰_D −100 (*c* 1.23, CHCl₃); $(R_S,2R)$-(−)-**7** (R = Me): oil, [α]²⁰_D −98.2 (*c* 0.815, CHCl₃).

Figure 1.

Grignard reagent, but the reaction was slow (3 h) and the yield was 43%.

Removal of the *N-tert*-butanesulfinyl group was readily accomplished using methanolic HCl[18] to give the known α-amino esters (R = Bn, 74%; R = Ph, 88%) and allowed assignment of the absolute stereochemistry.[20] As anticipated no epimerization occurred during the cleavage procedure as evidenced by preparation of Mosher amide derivatives (R = Me, Ph, Bn).

A rationale for the observed stereoselectivity is that (*R*)-**2b** adopts the conformation shown in Figure 1a[21] where the sulfinyl oxygen coordinates to BF₃ and sterically shields the *Si* face of the imine to give the Cram product. A second equivalent of BF₃ may act to further activate the imine bond. Indeed a similar Lewis activation has been proposed in the sulfinimine-mediated asymmetric Strecker synthesis.[22] This open transition state model is similar to that proposed by Yamamoto[6b,23] and contrasts with the analogous sulfinimine case where the opposite induction can be explained by a chelated transition state as shown in Figure 1b.[18,22,24] This difference is obviously due to the presence of the ester functionality, and we speculate that chelation of the incoming organometallic reagent by the ester carbonyl disrupts and prevents the chelated transition state forming.

In summary, *N*-sulfinylimino esters **2** represent a new chiral glycine cation equivalent for the asymmetric synthesis of α-amino acids. Problems of regiochemistry that plague nucleophilic additions to most glyoxylate imines are avoided because the *N*-sulfinyl group selectively activates the C=N bond for addition as well as being an effective stereodirecting group.

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

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