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Asymmetric Mannich-Type Reactions for the Synthesis of Aspartic Acid Derivatives from Chiral *N-tert*-Butanesulfinylimino Esters

Mikkel F. Jacobsen and Troels Skrydstrup*

Department of Chemistry, University of Aarhus, Langelandsgade 140, 8000 Aarhus C, Denmark

ts@chem.au.dk

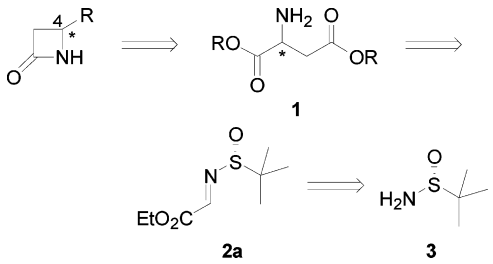
Received April 6, 2003

Abstract: Addition of ketene acetals to sulfinimines derived from homochiral *N-tert*-butanesulfinamide using various Lewis acids furnishes derivatives of aspartic acid in diastereomeric ratios up to 97:3. Following an easy removal of the *N-tert*-butanesulfinyl chiral auxiliary, optical active β-amino esters are obtained.

β-Amino acids have received considerable attention due to the unique properties and the interesting biological activities of β-peptides incorporating such monomers.[1] The β-amino acid, aspartic acid, and derivatives thereof, are useful building blocks for many natural products and pharmaceutical agents.[2] Their synthesis using glyoxylate imines in Mannich-type reactions with ketene acetals seems attractive for its simplicity; however, only a few asymmetric variants of such an approach have been published.[3]

In our previous work on the SmI_2-mediated diastereoselective construction of functionalized proline derivatives from racemic β-lactams precursors, key stereocontrol in the reaction came from the C4-stereocenter of the β-lactam.[4] Motivated by this and the fact that aspartic acid derivatives are excellent precursors of C4-functionalized β-lactams,[5] we speculated whether it would be possible to obtain homochiral aspartic acid derivatives **1** from the reaction between ketene acetals and enantiomerically pure glyoxylate imine **2a** using the *N-tert*-butanesulfinyl auxiliary. If so, easy access to homochiral β-lactams would be at hand (Scheme 1). Following Ellman's development of an efficient catalytic, enantioselective synthesis of homochiral *N-tert*-butanesulfinamide **3**,[6] imines derived from it have attracted much attention in the addition reactions of organometallic reagents (including Grignards, organolithiums, and Reformatsky-type reagents).[7] In many cases, the *N-tert*-butanesulfinyl group has provided enhanced diastereofacial selectivity compared to other *N*-sulfinyl auxiliaries, such as the *p*-tolylsulfinyl group.[8,3d] This auxiliary also serves to activate the C═N bond of the glyoxylate imine **2a** toward nucleophilic attack in a regioselective manner, and it is easily removed under acidic conditions.[8d]

SCHEME 1



Sulfinimine **2a** was prepared by $CuSO_4$-mediated condensation of ethyl glyoxylate and (*R*)-(+)-*tert*-butanesulfinamide.[9] Initial results obtained with racemic **2a** and ketene acetal **4a** indicated that the reaction does require the presence of a Lewis acid (Table 1, entry 1). The best diastereoselectivity was obtained at −78 °C using 2 equiv of $BF_3{\cdot}OEt_2$, though the yield was higher when using TMSOTf (entry 2 and 5). Previously, Davis has demonstrated that $BF_3{\cdot}OEt_2$ gives superior activation of **2a** toward addition of some Grignard reagents both in terms of diastereoselectivity and yield,[8d] while Ellman used $AlMe_3$ to increase the yield in the addition of organolithiums to *N-tert*-butanesulfinyl ketimines.[8e] In our case,

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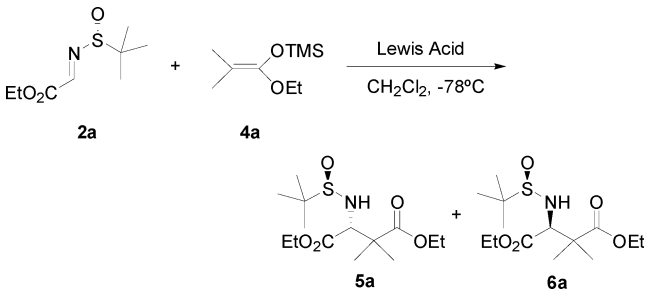
10.1021/jo034436j CCC: $25.00 © 2003 American Chemical Society
Published on Web 08/08/2003

TABLE 1. Effect of Different Lewis Acid on Addition to *N-tert*-Butanesulfinylimino Ester 2a[a]



entry	Lewis acid (equiv)	yield **5** + **6** (%)	dr (**5**/**6**)[b,c]
1	none	~0	
2	BF_3·OEt_2 (2.0)	81	87:13
3	BF_3·OEt_2 (3.0)	81	86:14
4	BF_3·OEt_2 (4.5)	87	83:17
5	TMSOTf (1.4)	95	78:22
6	$AlMe_3$ (2.0)	50	80:20
7[d]	$Yb(OTf)_3$ (0.6)	50	81:19

[a] Racemic **2a** was employed in the reactions. [b] The diastereomeric ratio was determined from analysis of ^{1}H NMR spectra of crude product. [c] Configuration of the major diastereomer was tentatively designated as shown for **5a**; see the text. [d] −78 °C to room temperature.

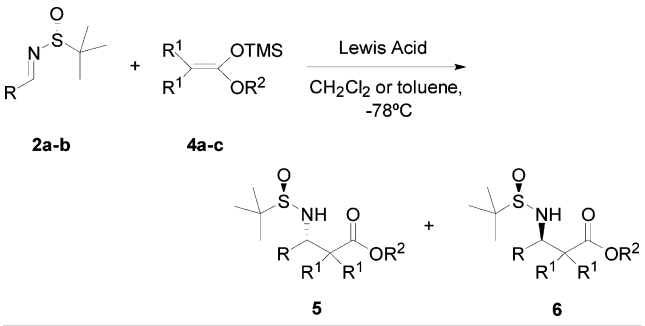
the yield was diminished considerably when using $AlMe_3$ or the milder Lewis acid $Yb(OTf)_3$ (entries 6 and 7),[10] where in the latter case even higher temperatures were required for the reaction to proceed to any extent. On the other hand, the diastereoselectivity in both cases was comparable to that of BF_3·OEt_2. Increasing the amount of Lewis acid seemed to have little effect on both the diastereoselectivity and yield (entries 2−4). In all cases, the imine was precomplexed with the Lewis acid for 20 min prior to addition of the ketene acetal, and the reactions were generally complete within 5−7 h.

Application of our conditions to the reaction of **2a** with other ketene acetals gave good diastereoselectivities and isolated yields (Table 2, entry 1−9) with diastereomeric ratios ranging from 77:23 to 97:3. Surprisingly, there seemed to be some discrepancies in the choice of the most effective Lewis acid for different ketene acetals, e.g., best yield and diastereoselectivity with **4a** and **4b** was obtained using BF_3·OEt_2 and $AlMe_3$, respectively (Tables 1 and 2, entry 3).

The yield was slightly reduced when the solvent was changed to toluene, and in the case of the ketene acetal **4c** the diastereoselectivity was lowered (entries 4 and 9). The conversion to product with **4b** was less clean using BF_3·OEt_2 or TMSOTf as evident from TLC and ^{1}H NMR (400 MHz) spectra of the crude product (entries 1 and 2). As expected, the more sterically demanding *tert*-butyl ketene acetal **4c** boosted the diastereofacial selectivity of the reaction somewhat; however, 8 equiv of the ketene acetal was needed in order to obtain a good yield (entries 6−9).

The result was less fruitful when similar conditions were applied to the reaction of the known imine **2b**[9] with

TABLE 2. Reaction of Various Ketene Acetals with (*R*)-*N-tert*-butanesulfinylimines 2[a]



entry	Lewis acid (equiv)	R	R^1, R^2	products	yield **5** + **6** (%)	dr (**5**/**6**)[b]
1	BF_3·OEt_2 (2.0)	EtO_2C	H, Et (**4b**)	**5b**, **6b**	67	90:10
2	TMSOTf (1.4)	EtO_2C	H, Et (**4b**)	**5b**, **6b**	65	92:8
3	$AlMe_3$ (2.0)	EtO_2C	H, Et (**4b**)	**5b**, **6b**	92	93:7
4	$AlMe_3$ (2.0)	EtO_2C	H, Et (**4b**)	**5b**, **6b**	78	93:7
5[c]	$Yb(OTf)_3$ (0.6)	EtO_2C	H, Et (**4b**)	**5b**, **6b**	62	77:23
6	BF_3·OEt_2 (2.0)	EtO_2C	H, *t*-Bu (**4c**)	**5c**, **6c**	17	96:4
7	$AlMe_3$ (2.0)	EtO_2C	H, *t*-Bu (**4c**)	**5c**, **6c**	28	97:3
8[d]	$AlMe_3$ (2.0)	EtO_2C	H, *t*-Bu (**4c**)	**5c**, **6c**	86	97:3
9[d]	$AlMe_3$ (2.0)	EtO_2C	H, *t*-Bu (**4c**)	**5c**, **6c**	72	90:10
10[e]	TMSOTf (1.4)	Ph	Me, Et (**4a**)	**5d**, **6d**	89	72:28
11[c,e]	BF_3·OEt_2 (3.0)	Ph	Me,Et (**4a**)	**5d**, **6d**	92	50:50
12[e]	BF_3·OEt_2 (3.0)	Ph	Me, Et (**4a**)	**5d**, **6d**	~0	
13[e]	$AlMe_3$ (2.0)	Ph	Me, Et (**4a**)	**5d**, **6d**	~ 0	

[a] The reactions were performed in CH_2Cl_2 except for entries 4 and 9 where toluene was employed. [b] The diastereomeric ratio was determined from analysis of ^{1}H NMR spectra of crude product. [c] Performed at room temperature. [d] 8 equiv of ketene acetal **4c** was employed. [e] Racemic **2b** was employed.

ketene acetal **4a**. In fact, the ratio of diastereomers using TMSOTf was only 78:22 (entry 10). Changing to BF_3·OEt_2 led only to a reaction when performed at room temperature, and no selectivity was observed (entries 11 and 12). Also, $AlMe_3$ failed to activate the imine at −78 °C, and product formation could not be detected by ^{1}H NMR (entry 13). The reduced reactivity of **2b** compared to **2a** was anticipated since it lacks the activation from the neighboring electron-withdrawing carbonyl group.

Structural assignment of the major diastereomers **5b** and **5c** was accomplished through removal of the *N-tert*-sulfinyl auxiliary (**5b** and **5c**) (HCl in MeOH or EtOH) and transesterification (**5c**) ($SOCl_2$, EtOH) to give the known 2-aminosuccinic acid diethyl ester **7**[11] in 78% and 45% (three steps) yield, respectively.[12] The optical rotation of the esters was compared to that of pure (*S*)-(−)-**7** prepared from (*S*)-(+)-aspartic acid. The configuration of the major diastereomers **5a** and **5d** was only tentatively designated as shown in Table 1 in agreement to structural assignments made for **5b** and **5c**.

Figure 1 provides a rationale for the observed sense of diastereoselectivity. The attack by the nucleophile on the *Re* face of the imine bond can be explained by 2-fold coordination of Lewis acid as shown in the open transition-state model **A**, which translates to the Cram product. One equivalent of the Lewis acid coordinates to the sulfinyl oxygen thus sterically shielding the *Si* face of the imine bond, while another supposedly serves to

(10) Substoichiometric amounts of $Yb(OTf)_3$ has been shown to activate imines toward addition of ketene acetals; see: (a) Annunziata, R.; Cinquini, M.; Cozzi, F.; Molteni, V.; Schupp, O. *J. Org. Chem.* **1996**, *61*, 8293. (b) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233. (c) Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773.

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(12) See the Supporting Information.

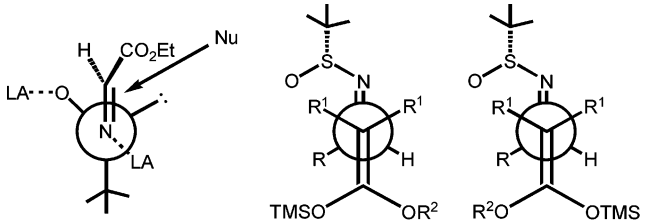
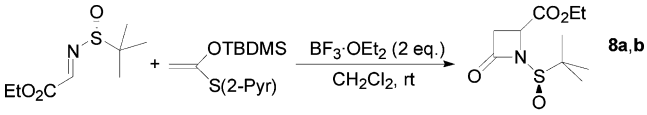


FIGURE 1.

SCHEME 2



coordinate to the imine nitrogen atom thereby activating it toward nucleophilic attack. Similar transition-state models has been proposed in both the asymmetric Strecker synthesis with sulfinimines[13] and the Lewis acid mediated addition of certain Grignard reagents to sulfinimines.[8d,14] Alternative Newman-type representations **B** and **C** are depicted in Figure 1.

In an effort to expand the scope of the reaction further, the reported one-pot approach to β-lactams using Lewis acid promoted condensation of imines and silyl ketene thioacetals (SKTA) was attempted (Scheme 2).[15,10a] Using silyl ketene thioacetal **4d** derived from 2-pyridyl thioacetate and imine **2a**, various conditions were screened. However, the reaction only occurred at room temperature in the presence of 2 equiv of $BF_3{\cdot}OEt_2$. The yield was moderate (40%) and scarce stereoselectivity was observed (63:37 dr).[16]

In conclusion, an efficient asymmetric synthesis of aspartic acid derivatives has been developed using the *N-tert*-butanesulfinyl group as a chiral auxiliary. The auxiliary performs well as a stereodirecting group. The reactions seem highly dependent on the Lewis acid employed both in terms of yield and diastereoselectivity. An attempt to extend the reaction to include a ketene thioacetal for the direct synthesis of β-lactams was met with limited success.

Experimental Section

General Procedure for Preparation of *N-tert*-Butanesulfinyl-*β*-amino Acid Esters. To a stirred solution of **2** (61.6 mg, 0.30 mmol) in CH_2Cl_2 or toluene (2.0 mL) was added dropwise the Lewis acid (0.60 mmol) at the temperature indicated in Table 1 or 2. The solution was stirred for 20 min. A solution of the ketene acetal or silyl enol ether (0.60 mmol) in CH_2Cl_2 or toluene (1.0 mL) was added dropwise, and the reaction mixture was stirred for 5−7 h, the progress of the reaction being monitored by TLC. Saturated aqueous NH_4Cl was added. The aqueous phase was extracted several times with CH_2Cl_2. The combined organics were dried over $MgSO_4$ and evaporated to dryness in vacuo to yield the crude product. Diastereoselectivity was determined by NMR integration of the crude product (Tables 1 and 2). The identity of the minor diastereomer was confirmed by ^{1}H NMR analysis of a chromatographically enriched sample of the minor diastereomer. Flash chromatography (pentanes/CH_2Cl_2, gradient elution) afforded mixtures of diastereoisomers.

2,2-Dimethyl-3-(2-methylpropane-2-sulfinylamino)succinic Acid Diethyl Ester (5a and 6a). Data for the diastereomeric mixture of **5a** and **6a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.16−1.35 (m, 42H), 4.05−4.30 (m, 10H), 4.40 (d, J = 8.8 Hz, 1H, major diastereomer), 4.68 (d, J = 9 Hz, 1H, minor diastereomer); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2 (2C), 21.6 (2C), 21.8 (2C), 22.4, 22.6, 22.8 (6C), 45.2, 46.7, 56.4, 56.8, 61.0, 61.2, 61.5, 62.1, 63.3, 65.4, 170.9, 171.4, 174.9, 175.6; MS (electrospray) m/z 344.2 (M + Na); HRMS m/e calcd for $C_{14}H_{27}NNaSO_5$ (M + Na) 344.1508, found 344.1495.

2-(2-Methylpropane-2-sulfinylamino)succinic Acid Diethyl Ester (5b and 6b). Data for the diastereomeric mixture of **5b** and **6b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 18H), 1.24−1.34 (m, 12H), 2.81 (dd, J = 5.6, 16.4 Hz, 1H, major diastereomer), 2.85 (dd, J = 5.6, 16.4 Hz, 1H, major diastereomer), 2.96 (dd, J = 5.2, 17.2 Hz, 1H, minor diastereomer), 3.01 (dd, J = 5.2, 17.2 Hz, 1H, minor diastereomer), 4.14 (q, J = 7.4 Hz, 2H, major diastereomer), 4.26 (q, J = 7.4 Hz, 2H, major diastereomer), 4.10−4.40 (m, 8H). Major diastereomer: ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 14.3, 22.6, 38.7, 54.1, 56.1, 61.0, 62.3, 169.9, 171.5. MS (electrospray) m/z 316.0 (M + Na); HRMS m/e calcd for $C_{12}H_{23}NNaSO_5$ (M + Na) 316.1195, found 316.1188.

2-(2-Methylpropane-2-sulfinylamino)succinic Acid 4-*tert*-Butyl Ester 1-Ethyl Ester (5c and 6c). Data for the diastereomeric mixture of **5c** and **6c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 9H, major diastereomer), 1.24 (s, 9H, minor diastereomer), 1.27 (t, J = 7.6 Hz, 3H, minor diastereomer), 1.30 (t, J = 7.6 Hz, 3H, major diastereomer), 1.44 (s, 9H, major diastereomer), 1.45 (s, 9H, minor diastereomer), 2.71 (dd, J = 5.2, 16.0 Hz, 1H, major diastereomer), 2.78 (dd, J = 5.6, 16.0 Hz, 1H, major diastereomer), 2.87 (dd, J = 5.2, 16.0 Hz, 1H, minor diastereomer), 2.93 (dd, J = 5.2, 16.0 Hz, 1H, minor diastereomer), 4.16−4.28 (m, 6H), 4.34 (d, J = 5.6 Hz, 1H, major diastereomer), 4.37 (d, J = 8.8 Hz, 1H). Major diastereomer: ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.7, 28.2, 39.7, 54.1, 56.2, 62.2, 81.6, 169.0, 171.8; MS (electrospray) m/z 344.1 (M + Na); HRMS m/e calcd for $C_{14}H_{27}NNaSO_5$ (M + Na) 344.1508, found 344.1509.

2,2-Dimethyl-3-(2-methylpropane-2-sulfinylamino)-3-phenylpropionic Acid Ethyl Ester (5d and 6d). Data for the diastereomeric mixture of **5d** and **6d**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.13 (s, 6H, major diastereomer), 1.15 (s, 6H, minor diastereomer), 1.18 (s, 9H, minor diastereomer), 1.19 (s, 9H, major diastereomer), 1.25 (t, J = 7.4 Hz, major diastereomer), 1.27 (t, J = 7.4 Hz, minor diastereomer), 4.01−4.23 (m, 4H), 4.31 (d, J = 9.4 Hz, major diastereomer), 4.47 (d, J = 9.4 Hz, major diastereomer), 4.47 (d, J = 3.0 Hz, 1H, minor diastereomer), 4.58 (d, J = 3.0 Hz, 1H, minor diastereomer); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2 (2C), 20.7 (2C), 22.6 (2C), 24.3, 24.7, 46.9, 47.8, 55.7, 56.5, 60.9, 61.3, 64.7, 66.7, 127.9 (3C), 128.1, 128.3, 129.2, 138.2, 139.1, 176.2, 176.5; MS (electrospray) m/z 348.2 (M + Na); HRMS m/e calcd for $C_{17}H_{27}NNaSO_3$ (M + Na) 348.1609, found 348.1621.

Acknowledgment. We are indebted to Danish National Science Foundation, the University of Aarhus, the Carlsberg Foundation, the Leo Pharmaceutical Research Foundation, and the Lundbeck Research Foundation for generous financial support.

Supporting Information Available: Determination of configuration for compounds **5b**,**c**, experimental procedures for compounds **8a**,**b**, and copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **5a**−**c**, **6a**−**c**, and **8a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034436J

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(16) The configuration of the major diastereomer was not determined.