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Asymmetric Synthesis of New Chiral β-Amino Acid Derivatives by Mannich-type Reactions of Chiral *N*-Sulfinyl Imidates with *N*-Tosyl Aldimines

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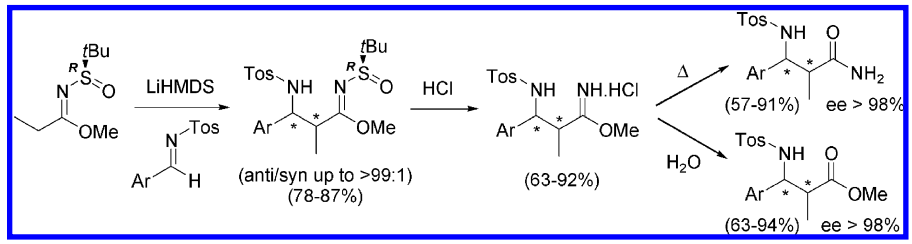
ABSTRACT



New chiral β-(sulfonylamino)sulfinylimidates are synthesized in high overall yield and excellent diastereomeric excess via highly *anti*-selective Mannich-type reactions of chiral *N*-*tert*-butanesulfinyl imidates with *N*-tosyl aldimines. Deprotection of the β-(sulfonylamino)sulfinylimidates gave access to enantiopure imidate hydrochlorides in high yields, as useful intermediates for an easy transformation to new chiral β-sulfonylamino amides upon simple heating in chloroform. Hydrolysis of the imidate hydrochlorides afforded the corresponding chiral β-sulfonylamino esters with >98% ee as new chiral β-amino acid derivatives.

The enantioselective synthesis of β-amino acid derivatives, as biologically active compounds, constituents of biologically active natural products, chiral building blocks and monomers for the preparation of β-peptides,[1] continues to be of significant interest.[2] The asymmetric Mannich-type reaction of enolates with activated imines is one of the most important and versatile methods for the synthesis of optically pure β-amino acid derivatives which is under continuous development.[3] Recently, the Kobayashi group developed a DBU-catalyzed direct Mannich-type addition reaction of α-methyl-substituted sulfonylimidates with activated aldimines leading to racemic β-aryl-α-methyl-substituted β-amino acid derivatives with high *anti*-diastereoselectivity.[4] Subsequently, the same group also developed direct additions of sulfonylimidates to imines with controllable diastereoselectivities catalyzed by alkaline earth metal alkoxides and a preliminary asymmetric addition reaction leading to a β-aryl-α-methyl-substituted β-aminosulfonylimidate in moderate ee.[5] Re-

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cently, our group demonstrated that an efficient and stereoselective α-alkylation of *N*-sulfinyl imidates can be achieved leading to chiral α-substituted *N*-sulfinyl imidates as useful intermediates in the synthesis of enantiopure amides and esters.[6] Therefore, we envisioned that the addition reaction of chiral *N*-*tert*-butanesulfinyl imidates across aromatic *N*-tosyl aldimines could be a valuable alternative approach toward the synthesis of β-aryl-α-methyl-substituted β-amino acid derivatives, and the results are described herein. The interest of this study not only arises from the fact that a new and complementary entry toward chiral β-aryl-α-methyl-substituted β-tosylamino acid derivatives, a synthetically interesting class of compounds,[7] will become accessible, but also previously unreported optically pure β-sulfonylamino imidates, which could serve as valuable chiral building blocks for biologically active compounds,[8] will be synthesized. Whereas enolate additions across sulfinylimines has proven to be a powerful method for the asymmetric synthesis of various β-amino acids,[2d,9] metalloenamines derived from *N*-sulfinyl ketimines have been exploited to a limited extent in Mannich-type additions across imines.[10] Trans-2-aminocyclopentane carboxylic acid has been prepared via an intramolecular self-condensation of the bis-sulfinyl imine derived from hexanedial.[11] Deprotonation of the *N*-sulfinyl ketimine derived from ketones and diastereoselective Mannich-type reaction with *N*-sulfonyl aldimines afforded β-amino imines that were transformed into enantiomeric β-aminoketones and 1,3-diamines.[12] The electron-withdrawing character of the sulfinyl moiety strongly attenuates the nucleophilicity of the metalloenamine, and therefore, the more nucleophilic metalloenamines derived from *N*-*tert*-butanesulfinyl amidines,[13] and *N*-*tert*-butanesulfinyl imidates[6] have been exploited advantageously in α-alkylation reactions and is herein used for asymmetric Mannich-type reactions to β-amino acid derivatives.

The addition reaction of *N*-sulfinyl imidate **1** with *N*-tosyl aldimines **2** was optimized by systematically changing the reaction conditions in the addition reaction of imidate **1** with aldimine **2a** (X = Cl) for the synthesis of β-(sulfonylamino)sulfinylimidates **3a** (Table 1 and Supporting Information Table S1). The synthesis of *N*-sulfinyl imidate **1** was performed by condensation of (R_S)-*tert*-butanesulfinamide and 1,1,1-trimethoxypropane with a catalytic amount of *p*-TsOH without solvent.[6,13] An initial attempt using similar reaction conditions as applied in the synthesis of β-aminosulfonylimidates,[4b] namely reaction of imidate **1** with aldimine **2a** in the presence of a catalytic amount of DBU in DMF, did not result in the formation of addition products, even after prolonged stirring at room temperature (see Supporting Information Table S1). Subsequently the use of LDA to deprotonate imidate **1** gave no reaction with aldimine **2a** at −78 °C, while increasing the temperature to 0 °C for 3 h led to a mixture of unidentified compounds. The use of 2.0 equivalents LiHMDS to deprotonate *N*-sulfinyl imidate **1** at −78 °C resulted, after addition of aldimine **2a** and reaction at −78 °C for 1 h in full conversion to β-(sulfonylamino)sulfinylimidates **3a** with high relative stereocontrol (*anti*/*syn* = 93/7) and moderate absolute stereocontrol in the formation of the *anti*-adducts (see Supporting Information Table S1). By ^{1}H NMR analysis of the crude reaction mixture, only three diastereomers could be detected, namely (R_S,*S*,*R*)-*anti*-**3a**/(R_S,*R*,*S*)-*anti*-**3a**/(R_S,*S*,*S*)-*syn*-**3a** in a 67/26/7 ratio. Better results were obtained when less equivalents of LiHMDS (1.2 equiv) were used leading to complete relative *anti*-diastereoselectivity and acceptable absolute stereocontrol ((R_S,*S*,*R*)-*anti*-**3a**/ (R_S,*R*,*S*)-*anti*-**3a** = 75/25) leading to optically pure β-(sulfonylamino)sulfinylimidates (R_S,*S*,*R*)-*anti*-**3a** and (R_S,*R*,*S*)-*anti*-**3a** in 59% and 21% yield, respectively, after flash chromatography (entry 1). Analogously, several other new chiral imidates **3** were prepared with excellent *anti*-diastereoselectivity (*anti*/*syn* = 93/7 to >99/1) and good yields (84−87%) using the latter optimized reaction conditions (entry 2 and 3). When the addition reaction was performed with aldimine **2b** (X = H) derived from benzaldehyde, β-(sulfonylamino)sulfinylimidate (R_S,*S*,*S*)-*syn*-**3b** could also be isolated by flash chromatography in 5% yield. Noteworthy, the addition reaction of imidate **1** with aldimine **2c** (X = OMe) led to a reversed absolute *anti*-stereocontrol with β-(sulfonylamino)sulfinylimidate (R_S,*R*,*S*)-*anti*-**3c** as major product. The use of KHMDS as a base led to a significant decrease in relative stereocontrol (*anti*/*syn* = 75/25) with an improved absolute stereocontrol of the α-methyl-substituted center (entry 4). The use of NaHMDS led also to a decrease in relative stereocontrol (*anti*/*syn* = 73/27) without an improved absolute stereocontrol (entry 5). The addition of $ZnCl_2$ or HMPA, or the use of toluene instead of THF, did not improve the diastereoselectivity of the reaction (see Supporting Information Table S1). In a last

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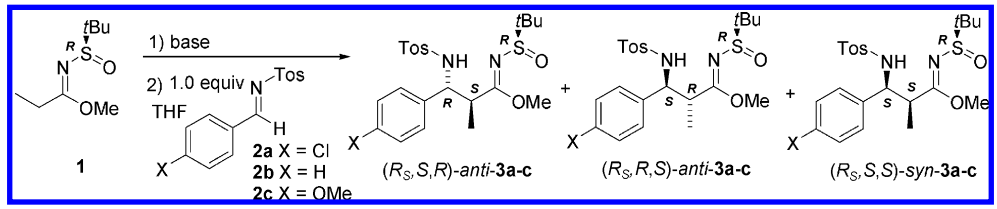
Table 1. Optimization of the Addition Reaction of *N*-Sulfinyl Imidate **1** across Aldimines **2**



entry	X	**1** (equiv)	reaction conditions	(R_S,S,R)-**3**/ (R_S,R,S)-**3**/ (R_S,S,S)-**3**[a]	*anti*/*syn*[a]	yield (%)
1	Cl	1.2	1) 1.2 equiv LiHMDS, THF, −78 °C, 45 min 2) −78 °C, 1 h	75/25/0	>99/1	(R_S,S,R)-**3a** (59), (R_S,R,S)-**3a** (21)
2	H	1.2	1) 1.2 equiv LiHMDS, THF, −78 °C, 45 min 2) −78 °C, 1 h	67/26/7	93/7	(R_S,S,R)-**3b** (58), (R_S,R,S)-**3b** (24), (R_S,S,S)-**3b** (5)
3	OMe	1.2	1) 1.2 equiv LiHMDS, THF, −78 °C, 45 min 2) −78 °C, 1 h	38/60/2	98/2	(R_S,S,R)-**3c** (34), (R_S,R,S)-**3c** (50)
4	Cl	1.2	1) 1.2 equiv KHMDS, THF, −78 °C, 45 min 2) −78 °C, 1 h	63/12/25	75/25	–
5	Cl	1.2	1) 1.2 equiv NaHMDS, THF, −78 °C, 45 min 2) −78 °C, 1 h	51/22/27	73/27	–
6	Cl	1.2	1) 1.2 equiv LiHMDS, THF, −78 °C, 45 min +1.2 equiv $MgBr_2$, 15 min 2) −78 °C, 1 h	87/4/9	91/9	–
7	Cl	1.2	1) 1.2 equiv LiHMDS, THF, −97 °C, 45 min +1.2 equiv $MgBr_2$, 15 min 2) −97 °C, 1 h	91/0/9	91/9	(R_S,S,R)-**3a** (76), (R_S,S,S)-**3a** (6)
8	H	1.2	1) 1.2 equiv LiHMDS, THF, −97 °C, 45 min +1.2 equiv $MgBr_2$, 15 min 2) −97 °C, 1 h	89/6/5	95/5	(R_S,S,R)-**3b** (77), (R_S,R,S)-**3b** (3), (R_S,S,S)-**3b** (4)
9	OMe	1.2	1) 1.2 equiv LiHMDS, THF, −78 °C, 45 min +1.2 equiv $MgBr_2$, 15 min 2) −78 °C, 1 h	93/1/6	94/6	(R_S,S,R)-**3c** (73), (R_S,S,S)-**3c** (5)

[a] Determined via ^{1}H NMR analysis of the crude reaction mixture.

attempt involving addition of $MgBr_2$ as Lewis acid, the relative *anti*-stereoselectivity was maintained. Importantly, the absolute stereocontrol was increased leading to a mixture of diastereomers in a 87/4/9 ratio (entry 6). Even better results were achieved upon performing the reaction at −97 °C leading to high yields of (R_S,S,R)-*anti*-**3a**−**b** (76−77%) after flash chromatography (entry 7−8). Noteworthy, the addition reaction of imidate **1** with aldimine **2c** (X = OMe) at −97 °C led only to a 31% conversion, while performing the reaction at −78 °C led to full conversion and a yield of 73% for (R_S,S,R)-*anti*-**3c** as major product (entry 9).

In a next step, all the chiral β-(sulfonylamino)sulfinylimidates **3** were *N*-deprotected by simple treatment with a saturated solution of anhydrous HCl in dioxane (Scheme 1). Initially, upon treating the chiral β-(sulfonylamino)sulfinylimidates **3** with 20 equivalents HCl in dioxane at room temperature for 1 h, a mixture of imidate hydrochlorides **4** and amides **5** was formed.[6] However full conversion of imidates **3** to imidate hydrochlorides **4** (63−92% yield) was obtained after addition of 2 equivalents HCl (saturated solution of HCl in dioxane) in ethanol at 0 °C for 0.5 h.

Furthermore, these imidate hydrochlorides **4** proved to be excellent intermediates for an easy transformation to new chiral β-sulfonylamino amides **5** upon simple heating at reflux temperature in chloroform for 16 h (Scheme 1). Purification involving recrystallization from diethyl ether afforded the chiral amides **5** in generally high yields (57−91%) and enantiomeric excess (>98% ee). The enantiomeric excess of amides **5** was determined by chiral HPLC (see Supporting Information).

Finally, hydrolysis of the imidate hydrochlorides **4** allowed access to the corresponding new chiral β-sulfonylamino esters **6**. After carefull optimization, it was found that stirring imidate hydrochlorides **4** in water at 55 °C for 7 h afforded the new chiral esters **6** in good to excellent yields (63−94%) and excellent enantiomeric excess (>98% ee) (Scheme 1). The enantiomeric excess of esters **6** was determined by chiral HPLC analysis (see Supporting Information). The synthesis of the racemic mixtures of esters **6a**−**c** was already reported in the literature via a Mannich-type transformation of aldimines with an α,β-unsaturated ester and a hydrosilane catalyzed by a cationic rhodium(I) complex.[14] Comparison of the ^{1}H and ^{13}C NMR spectral data confirmed the assigned

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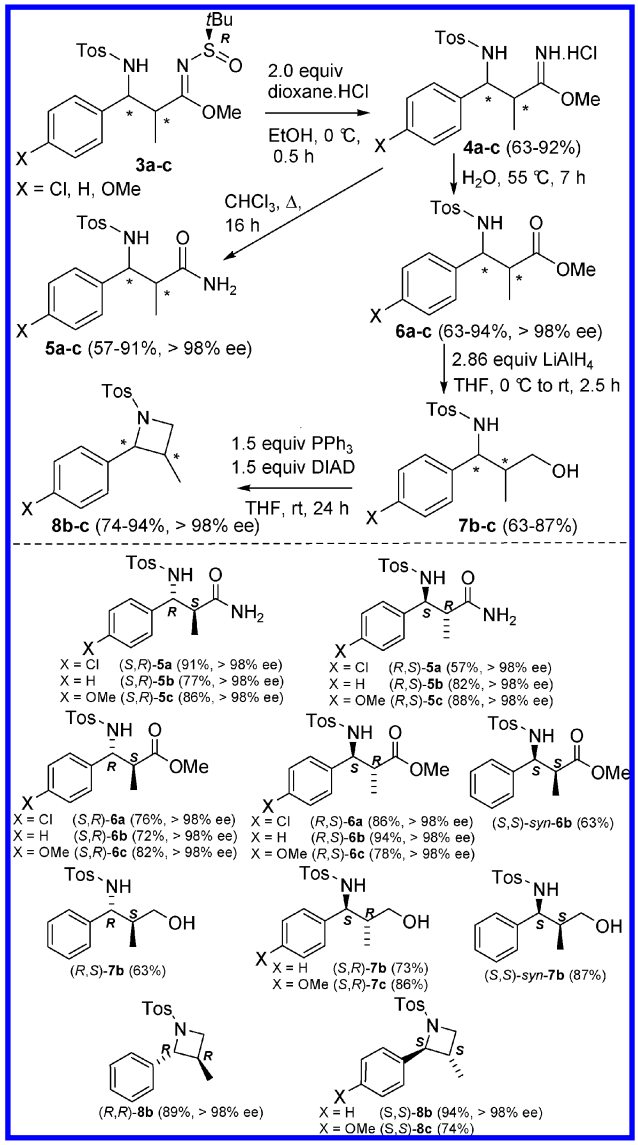
Scheme 1. Synthesis of Chiral β-Sulfonylamino Imidate Hydrochlorides **4**, Amides **5**, Esters **6**, γ-Amino Alcohols **7**, and *N*-Tosylazetidines **8** from β-(Sulfonylamino)sulfinylimidates **3**



relative *anti*-selectivity of the addition reactions of imidate **1** across aldimines **2** for the synthesis of β-(sulfonylamino)-sulfinylimidates **3**.

To determine the absolute stereochemistry of compounds **3**-**6**, γ-sulfonylamino alcohols **7** and *N*-tosylazetidines **8** were synthesized starting from esters **6** according to literature procedures (Scheme 1). Reduction of esters **6** with $LiAlH_4$ in THF for 2.5 h afforded γ-sulfonylamino alcohols **7** in good yields (63−87%).[7c] In a next step these alcohols **7** were cyclized under Mitsunobu conditions to the corresponding *N*-tosylazetidines **8** in high yields (74−94%) with high enantiomeric excess (>98% ee).[15] *N*-Tosylazetidines **8b** are reported compounds in the literature and thus allowed a comparison of the optical rotations ($[\alpha]_D$ (*R*,*R*)-*trans*-**8b** +235.6 (*c* 0.2, $CHCl_3$) vs +238.5 (*c* 1.0, $CHCl_3$, ee >99%) in Lit., $[\alpha]_D$ (*S*,*S*)-*trans*-**8b** −232.9 (*c* 0.3, $CHCl_3$) vs −228.5 (*c* 1.0, $CHCl_3$, ee = 97%) in Lit.)[15] confirming the assigned absolute stereochemistry of the *N*-tosylated 2-arylazetidines **8** and compounds *anti*-**3**-**6**. Also, the (*R*,*R*)-enantiomer of alcohol (*S*,*S*)-*syn*-**7b** is a known compound in the literature, and thus allowed a comparison of the optical rotations ($[\alpha]_D$ (*S*,*S*)-*syn*-**7b** −24.3 (*c* 0.4, MeOH) vs (*R*,*R*)-*syn*-**7b** +25.4 and +26.1 (*c* 1.0, MeOH) in Lit.)[7c,g] confirming the absolute stereochemistry of γ-sulfonylamino alcohol *syn*-**7b** and compounds (R_S,*S*,*S*)-*syn*-**3b**, (*S*,*S*)-*syn*-**4b** and (*S*,*S*)-*syn*-**6b**. The enantiomeric excess of the *N*-tosylated 2-arylazetidines **8** was determined by chiral HPLC analysis (see Supporting Information).

In analogy with a report on the DBU-catalyzed addition reactions of *N*-sulfonyl imidates,[4a] the relative *anti*-diastereoselectivity of the addition reactions of *N*-sulfinyl imidate **1** with *N*-tosyl aldimines **2** can be explained with a model in which the reaction proceeds via transition state **A** instead of **B** (Figure 1). Upon deprotonation of imidate **1**, the

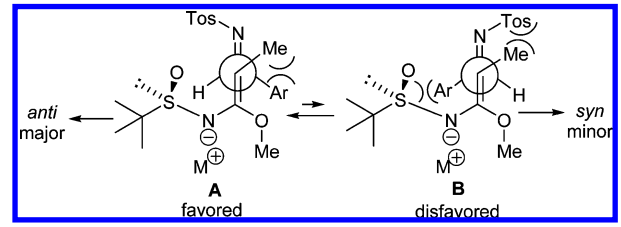


Figure 1. Proposed transition state model.

E-enolate will be preferentially formed with the methyl group and the NSO*t*Bu group at opposite sides of the C−C double bond, while the *N*-tosyl aldimines adopt an *E*-configuration. Considering the steric repulsion between the sulfinyl group of imidate **1** and the aryl group of aldimine **2** and that between the methyl substituent and the tosyl group in transition state **B**, led to the conclusion that transition state **A** may be favored to give the *anti*-diastereomers as major products.

In conclusion, it was demonstrated that new chiral β-(sulfonylamino)sulfinylimidates are formed as new chiral β-amino ester equivalents in high overall yield and excellent diastereomeric excess via high *anti*-selective addition reactions of *N*-sulfinyl imidates across *N*-tosyl aldimines. The β-(sulfonylamino)sulfinylimidates could be deprotected into chiral imidate hydrochlorides in high yields and further transformed into chiral β-sulfonylamino amides and esters by heating in chloroform or hydrolysis, respectively.

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

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