Scalable Synthesis of β-Amino Esters via Reformatsky Reaction with *N-tert*-Butanesulfinyl Imines

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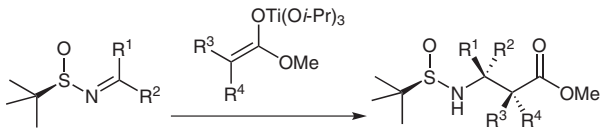
Abstract: The Reformatsky reagents derived from ethyl bromoacetate and *tert*-butyl bromoacetate add cleanly, in high yield, and with good diastereoselectivity to *N-tert*-butanesulfinyl aldimines and ketimines. Importantly, this reaction scales well (>50 mmol), and affords products upwards of 70% yield over three steps, starting from commercially available *N-tert*-butanesulfinamide, aldehydes, and ketones.

Key words: diastereoselectivity, stereoselective synthesis, chiral auxilaries, imines, amino acids

As β-amino acids are important chiral building blocks for total synthesis and medicinal chemistry applications, their asymmetric synthesis remains an active area of research.[1] Many synthetic routes to β-amino acids employ the addition of ester enolate nucleophiles into ketimine or aldimine electrophiles, however, these routes can suffer from modest stereoselectivities or lack substrate generality.[2] In addition, N-substituents necessary for stereoselectivity are often inconvenient to remove.[3] Prompted by Davis' success in the addition of the enolates of acetate esters to a limited set of *N-p*-toluenesulfinyl imines,[4] the methodology was extended to *N-tert*-butanesulfinyl imines.[5]

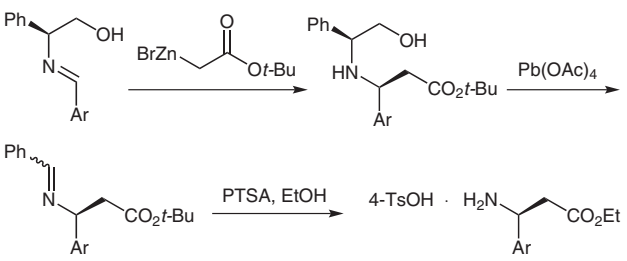
The addition of the titanium enolate of methyl acetate to aryl-, branched alkyl-, and unbranched alkyl-*N-tert*-butanesulfinyl aldimines and ketimines was shown to proceed in high yields and diastereoselectivities with the advantage of facile auxiliary removal. By extension, *N-tert*-butanesulfinyl-protected α,β-disubstituted, α,α,β- and α,β,β-trisubstituted, and α,α,α,β-tetrasubstituted β-amino esters are synthesized in good yields and diastereoselectivities through addition of a variety of ester enolates to *N-tert*-butanesulfinyl aldimines and ketimines (Scheme 1).



Scheme 1 Addition of titanium ester enolates to *N-tert*-butanesulfinyl aldimines and ketimines

While the sulfinamide-based route described above afforded materials in good yields and with excellent diastereoselectivities, the generation of titanium enolates and reagent manipulation at low temperature rendered this method impractical beyond multigram scale. Herein we describe a report on the Reformatsky addition of acetate enolates to *N-tert*-butanesulfinyl aldimines and ketimines that overcome these limitations. The additions proceeded at convenient temperatures, in good yields, and very high diastereoselectivities (94:6 to >99:1) and can be performed on very large scale with no reduction in yield or stereoselectivity.

We required a route that would allow us to access β-amino esters rapidly on large scale (>50 g). Diastereoselective imino-Reformatsky reactions have been used for a process-scale synthesis of a β-amino ester intermediate, however, the use of $Pb(OAc)_4$ for the deprotection of the chiral auxiliary required to impart high levels of diastereoselectivity detracted from this approach (Scheme 2).[6]



Scheme 2 Process-scale diastereoselective imino-Reformatsky reaction

Although the Reformatsky addition of unsubstituted acetate enolates to *N*-sulfinyl imines had not previously been disclosed, Staas had reported the Reformatsky reaction of ethyl bromodifluoroacetate with alkyl- and aryl-substituted *N-tert*-butanesulfinyl imines to afford α,α-difluoro-β-amino acid derivatives with good diastereoselectivity (80:20 to 95:5).[7] We therefore investigated addition of the Reformatsky reagent derived from simple ethyl bromoacetate to *N-tert*-butanesulfinyl benzaldimine (**1**). We were pleased to find that this reaction proceeded cleanly, in high yield, and with excellent diastereoselectivity (>99:1 dr). Removal of the sulfinyl protecting group of **2** was easily effected by reaction with 1.0 M HCl in Et_2O in anhydrous ethanol to afford β-amino ester **3** after basic aqueous workup in good yields (Scheme 3).

The reaction sequence can be increased to 50 mmol scale, without the need for chromatographic purification at any step. The absolute configuration of **3** was determined by

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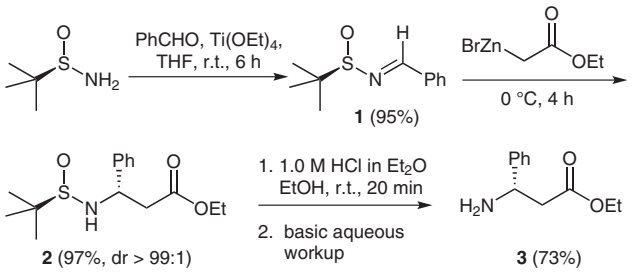


Scheme 3 Scaleable synthesis of (*S*)-3-amino-3-phenylpropionic acid ethyl ester[11–13]

optical rotation which was found to be in good agreement with literature values[8,9] and commercially available material.[10] This result can be rationalized by invoking a closed six-membered transition state arising from the *E*-sulfinyl imine (Figure 1).[7]

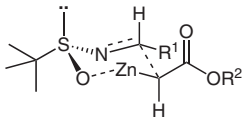
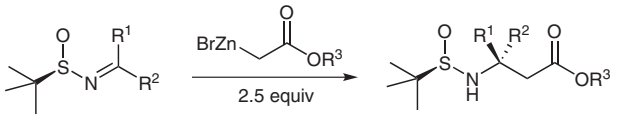


Figure 1 Rationalization of observed diastereoselectivity

The Reformatsky reaction can be applied to ketimines to provide diastereomerically pure or enriched *N*-sulfinyl-protected quaternary substituted β-amino esters (Table 1, entries 4, 5, and 8). When using the Reformatsky reagent derived from ethyl bromoacetate, the reaction was performed at 0 °C to prevent Claisen condensation with the β-amino ester product; this side reaction at room temperature is completely abrogated when *tert*-butyl bromozinc acetate is employed (Table 1, entries 6–8).

Table 1 Reformatsky Reaction with *N-tert*-Butanesulfinylimines



Entry	R^1	R^2	R^3	Temp (°C)	Yield (%)	dr[a]
1	H	Ph	Et	0	97	>99:1
2	H	*i*-Bu	Et	0	82	94:6
3	H	*i*-Pr	Et	0	75	95:5
4	Me	Ph	Et	0	quant.	>99:1
5	Me	*i*-Pr	Et	0	65	96:4
6	H	Ph	*t*-Bu	r.t.	86	>99:1
7	H	*i*-Bu	*t*-Bu	r.t.	88	96:4
8	Me	Ph	*t*-Bu	r.t.	quant.	>99:1

[a] The dr was determined by HPLC analysis of crude β-amino ester products.[14]

In conclusion, the addition of Reformatsky reagents into *N-tert*-butanesulfinyl imines, followed by *N-tert*-butanesulfinamide deprotection, affords highly enantioenriched β-amino esters in good yield and purity. This reaction is general and can afford monosubstituted and disubstituted β-amino acids. Importantly, for the example shown (compound **3**), the stereoselective synthesis of β-amino acids using this methodology can be easily scaled to access large quantities of product in three steps from commercially available starting materials, without the need for chromatographic purification.

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References and Notes

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(10) Acros: (*S*)-3-amino-3-phenylpropionic acid ethyl ester hydrochloride; CAS 167834-24-4.
(11) **Preparation of Zn/Cu**
Large-scale reactions require the preparation of Zn as previously described.[15,16] The zinc was then thoroughly dried in a vacuum oven at 70 °C for at least 24 h. The dried Zn dust and CuCl were then combined in appropriate amounts in a dry mortar, ground to a fine powder, then transferred to the reaction vessel.
(12) **Compound 2**
A three-necked 1 L round-bottom flask, reflux condenser, and addition funnel were oven-dried overnight, assembled with a mechanical stirrer under positive argon pressure and allowed cool to r.t. The flask was charged with Zn dust (31.3 g, 478 mmol, 10 equiv) and CuCl (4.7 g, 47.8 mmol, 1.0 equiv). The two solids were mixed under a slow stream of nitrogen while the flask was dried with a flame. The flask

was allowed to cool to r.t. and dry THF (100 mL) was added to produce a dark slurry. The resulting reaction mixture was heated to reflux temperature and stirred vigorously for 30 min. The heating bath was then removed while maintaining vigorous stirring, and the addition funnel was then charged with ethyl bromoacetate (17.7 mL, 119.5 mmol, 2.5 equiv) and dry THF (44 mL). CAUTION: EXOTHERMIC REACTION. The ethyl bromoacetate solution was slowly and carefully added dropwise until reflux was re-initiated. The addition was continued at a rate that maintained a controllable reflux. Once addition was complete, the reaction mixture was stirred for an additional 30 min at ambient temperature, then at 50 °C for 30 min. The reaction mixture was then cooled to 0 °C, and the addition funnel charged with *N*-*tert*-butanesulfinyl benzaldimine (**1**, prepared as previously described,[17] 10.0 g, 47.8 mmol. 1.0 equiv) and dry THF (50 mL). This solution was then added dropwise to the reaction mixture, which was stirred for an additional 4 h at 0 °C. The reaction mixture was filtered through a pad of Celite, washing the Zn and the filter pad with Et_2O (2 × 100 mL). The filtrate was washed with 0.25 M aq citric acid (200 mL), sat. aq $NaHCO_3$ (2 × 200 mL), sat. aq NaCl (1 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo to afford the *N*-*tert*-butanesulfinyl-protected β-amino ester (13.8 g, 46.5 mmol, 97%) as a clear oil that solidified upon standing. ^{1}H NMR (300 MHz,$CDCl_3$): δ = 7.34–7.26 (m, 5 H), 4.78 (m, 1 H), 4.69 (m, 1 H), 4.09 (q, *J* = 6.9 Hz, 2 H), 2.86 (d, *J* = 6.3 Hz, 2 H), 1.25 (m, 12 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 171.5, 140.9, 128.8, 128.2, 127.5, 61.1, 55.9, 42.5, 22.8, 14.3. ESI-LR: *m/z* calcd for $C_{15}H_{23}NO_3S$ $[M + H]^+$: 298.1; found: 298.0.

(13) **Compound 3**
A 500 mL round-bottom flask was charged with compound **2** (13.0 g, 43 mmol), EtOH (48 mL, 1.1 equiv), and 1 M HCl in Et_2O (87 mL, 87 mmol, 2.0 equiv). The reaction mixture was stirred at r.t. for 30 min. The reaction mixture was concentrated in vacuo, the resultant residue dissolved in 100 mL 0.1 M aq HCl. The solution was washed with Et_2O (100 mL) and hexanes (100 mL), and aqueous layer was basified to pH = 9 by the addition of solid Na_2CO_3. The solution was extracted with EtOAc (2 × 100 mL), washed with brine (1 × 100 mL), the organics dried (Na_2SO_4), and concentrated to afford (*S*)-3-amino-3-phenylpropionic acid ethyl ester (**3**) as a colorless oil (6.05 g, 31.4 mmol, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.23 (m, 5 H), 4.41 (dd, *J* = 7.0 Hz, 6.7, 1 H), 4.15 (q, *J* = 7.0 Hz, 2 H), 2.64 (d, *J* = 6.7 Hz, 2 H), 1.92 (br s, 2 H), 1.23 (3 H, *J* = 7.0 Hz, 3 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 172.2, 144.8, 128.8, 127.6, 126.4, 66.7, 52.8, 44.4, 14.4. $[\alpha]_D^{22}$ –3.8 (*c* 1.0, EtOH); lit. $[\alpha]_D^{22}$ –2.4 (*c* 0.13, EtOH)[8]; $[\alpha]_D^{22}$ –3.6 (c 1.0, EtOH).[9]

(14) **Synthesis of Authentic Diastereomeric Mixtures**
The crude reaction material of *N*-sulfinyl β-amino ester products (5 mg) was dissolved in EtOH (0.5 mL) and 1.0 M HCl in Et_2O (0.5 mL). After stirring at r.t. for 1 h, the reaction was concentrated, the residue dissolved in EtOH (2 mL), and concentrated again. The crude β-amino ester was then dissolved in CH_2Cl_2 (1.0 mL) and DIPEA (0.3 mL), and racemic *tert*-butanesulfinyl chloride (0.15 mL) was added. The reaction was stirred overnight, then concentrated, and filtered through a short SiO_2 column (EtOAc–hexanes, 3:1). The products were resolved by LC-MS and HPLC (20–70% MeCN, 10 min).

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