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Asymmetric synthesis of pre-protected α,α-disubstituted amino acids from *tert*-butanesulfinyl ketimines

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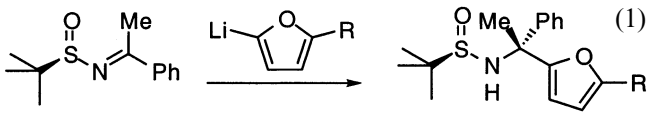
Abstract—A method for the asymmetric synthesis of pre-protected α,α-disubstituted amino acids is described. 5-Methylfuryllithium is added into sulfinyl ketimines **1** in the presence of $AlMe_3$ to afford the sulfinamides **2** in 75–97% yields and with diastereoselectivities ranging from 75:25 to 99:1. Subsequent oxidation with $RuCl_3/NaIO_4$ affords *tert*-butanesulfonyl (Bus)-protected α,α-disubstituted amino acids **3** in 62–69% yields. Bus-protected amino acids readily undergo amide bond formation, after which the Bus group can be removed with $TfOH/CH_2Cl_2$ to afford the free amine.

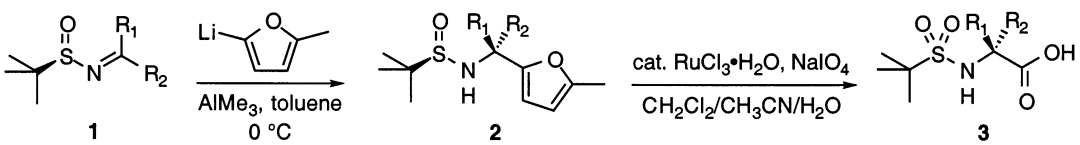
α,α-Disubstituted amino acids have displayed powerful effects on the conformation and the biological activity of molecules in which they are incorporated.[1] As a result, α,α-disubstituted amino acids have served as key components in numerous bioactive peptides, potential therapeutic agents, and natural products.[2] The most widely used methods for the asymmetric synthesis of α,α-disubstituted amino acids rely on diastereoselective enolate alkylation.[2] However, this approach prohibits the general use of poor S_N2 substrates, such as aryl halides or sterically demanding alkylating agents. Moreover, harsh conditions are often necessary to liberate the free acid from the alkylation product.

An alternative disconnection is the 1,2-addition of oxidizable carbanions to ketimines.[3] We have recently reported the one-step preparation of sulfinyl ketimines **1** in high yields by condensation of enantiomerically pure *tert*-butanesulfinamide with ketones.[4] Additions of organolithiums to **1** proceed cleanly and with high diastereoselectivities.[5] Herein, we report the application of this methodology to the asymmetric synthesis of pre-protected α,α-disubstituted amino acids. Specifically, the high-yielding and diastereoselective 1,2-addition of 5-methylfuryllithium to **1** followed by oxidation with $RuCl_3$(cat.)/$NaIO_4$ affords *tert*-butanesulfonyl (Bus)-protected amino acids **3** in two steps from sulfinyl ketimine **1** (Scheme 1).[6]

We began by evaluating the 1,2-addition of oxidizable nucleophiles to sulfinyl ketimine **1a** (Eq. (1)). Ketimine **1a** was added to furyllithium and 5-methylfuryllithium under the optimal conditions we have previously reported, namely, with toluene as solvent and with 1 equiv. of $AlMe_3$ at −78°C.[5] Unfortunately, due to the poor solubility of the furyllithium derivatives in toluene, poor conversions (≤30%) were observed even when the reaction mixtures were allowed to warm to room temperature prior to quenching. By performing the reactions at 0°C a good yield (80%) and excellent diastereoselectivity (99:1 dr) was observed for the addition of 5-methylfuryllithium and a moderate yield (55%) and comparable diastereoselectivity was observed for the addition of furyllithium.



1a **2** R = Me, 80%; R = H, 55% (1)



1 **2** **3**

Scheme 1.

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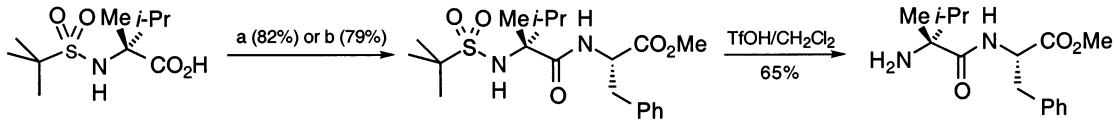
Table 1. 1,2-Addition of 2-methylfuryllithium to sulfinyl ketimines **1** (Scheme 1)

Ketimine	R^1	R^2	**2**, Yield (%)	**2**, dr	**3**, Yield (%)
1a	Me	Ph	80	99:1[c]	62[a]
1b	Bu	Ph	87	97:3[d]	67[b]
1c	Me	*i*-Pr	97	94:6[d]	63[a]
1d	Bu	*i*-Pr	91	80:20[e]	69[b]
1e	Me	*i*-Bu	75	75:25[e]	69[b]

[a] Absolute configuration determined by chemical correlation.[8]
[b] Absolute configuration tentatively assigned on the basis of consistent diastereofacial selectivity observed for **1a**, **1c** and previously reported 1,2-addition reactions to sulfinyl ketimines.[5]
[c] Diastereoselection determined by chiral HPLC analysis of the acetamide formed after sulfinyl cleavage.
[d] Diastereoselection determined by chiral HPLC analysis of the benzamide formed after sulfinyl cleavage.
[e] Diastereoselection determined by ^{1}H NMR.



Scheme 2. (a) HATU, Et_3N, DMF, then HCl·Phe-OMe; (b) i. $SOCl_2$, CH_2Cl_2, cat. DMF. ii. HCl·Phe-OMe, Na_2CO_3/$NaHCO_3$, CH_2Cl_2/H_2O.

The generality of the 1,2-addition of 5-methylfuran to *tert*-butanesulfinyl ketimines was then investigated (Table 1).[7] Good to high yields were obtained for both dialkyl and aryl alkyl sulfinyl ketimines. The diastereoselection was highly dependent on the imine substitution. Thus, the diastereoselection was very high for imines with highly differentiated substituents (**1a**–**1c**), but dropped significantly when the substituents were of similar steric size (**1d**–**1e**).

Oxidation of sulfinamide **2a** with $RuCl_3{\cdot}H_2O$ (1 mol%) and $NaIO_4$ (15 equiv.) in 1:1:1.5 CH_2Cl_2/MeCN/H_2O[6] went to completion in 2 h to afford the Bus-protected amino acid **3a** in 62% yield after acid/base extraction (Scheme 1, Table 1). When sulfinamide **2c** was oxidized under the same conditions, a 4:1 mixture of Bus-protected amino acid **3c** and the corresponding ketoacid was isolated after acid/based extraction. It was found that ketoacid formation could be partially suppressed (<10%) by oxidation with minimal acetonitrile (1:0.04:0.7 CH_2Cl_2/MeCN/H_2O), though the reaction was slower under these conditions (18 h). Acid/base extraction followed by recrystallization afforded analytically pure **3c** in 63% yield.[9,10] Employing these modified conditions, Bus-protected amino acids **3b**, **3d** and **3e** were all obtained in good yields (Table 1). To demonstrate that no racemization occurs during the oxidation and Bus-protecting group removal steps, **3b** was converted to the (+)- and (−)-MTPA amides of α-butyl phenylglycine methyl ester by treatment with diazomethane, Bus deprotection with TfOH/CH_2Cl_2,[6] and derivatization with (+)- or (−)-MTPACl, respectively. From starting carbinamine **2b** (97:3 dr), the MTPA amides were obtained in 97:3 dr as determined by HPLC analysis establishing that no degradation of stereochemical purity occurs during this synthesis sequence.

The utility of Bus-protected α,α-disubstituted amino acids as reagents for peptide synthesis was investigated by coupling amino acid **3c** with L-phenylalanine methyl ester (Scheme 2). Two coupling conditions were evaluated.[11] **3c** was activated in situ with HATU (1.3 equiv.) and Et_3N in DMF and coupled with 2 equiv. of HCl·Phe-OMe to deliver dipeptide **4** in 82% yield. Alternatively, **3c** could be converted to the acid chloride and then coupled with HCl·Phe-OMe in H_2O/Na_2CO_3-$NaHCO_3$/CH_2Cl_2[12] to deliver **4** in 79% yield. Significantly, despite the extremely hindered nature of the reactants, only 1.1 equiv. of the hydrochloride salt of phenylalanine methyl ester was required to achieve a high yield in this reaction. Subsequent cleavage of the Bus group from dipeptide **4** using TfOH/CH_2Cl_2[6] afforded the free amine **5** in 65% yield.[13]

In conclusion, we have demonstrated the utility of *tert*-butanesulfinyl ketimines **1** for the asymmetric synthesis of pre-protected α,α-disubstituted amino acids in two steps. Carboxylic acid equivalent 5-methylfuryllithium can be added into both aryl alkyl and dialkyl ketimines in high yield and in moderate to high diastereoselectivities. The resulting sulfinamides are oxidized with $RuCl_3$(cat.)/$NaIO_4$ to afford Bus-protected α,α-disubstituted amino acids in 62–69% yields. Bus-protected α,α-disubstituted amino acids can be activated either as the acid chloride or with HATU to provide excellent coupling partners for amide bond formation, and should be versatile intermediates for the synthesis of hindered peptides and drugs.

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References

1. (a) Balaram, P. *Curr. Opin. Struct. Biol.* **1992**, *2*, 845–851; (b) Veber, D. F.; Freidinger, R. M. *Trends Neurosci.* **1985**, *8*, 392–396.
2. For reviews on α,α-disubstituted amino acid syntheses, see: (a) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599. (b) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989.
3. Previously, the 1,2-addition of oxidizable carbanions to aldimines has been applied to the synthesis of α-monosubstituted amino acids: Alvaro, G.; Martelli, G.; Savoia, D.; Zoffoli, A. *Synthesis* **1998**, 1773–1777.
4. Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278–1284.
5. Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268–269.
6. Bus group: (a) Sun, P.; Weinreb, S. M. *J. Org. Chem.* **1997**, *62*, 8604–8608. (b) Gontcharov, A. V.; Liu, H.; Sharpless, K. B. *Org. Lett.* **1999**, *1*, 783–786.
7. General procedure for 5-methylfuryllithium additions to sulfinyl ketimines: (a) 5-methylfuryllithium was prepared by addition of 2.5 M *n*-BuLi in hexanes (5 equiv.) to a 5 M solution of 2-methylfuran (6 equiv.) in Et_2O at −10°C. The resulting solution was allowed to warm to room temperature and stirred overnight. (b) To a 1 M solution of sulfinyl ketimine (1 equiv.) in toluene at 0°C was slowly added a 1 M solution of $AlMe_3$ in toluene (1.1 equiv.). The resulting solution was stirred for 5 min before it was added over the course of 30 min to a 0°C solution of 5-methylfuryllithium diluted to 0.5 M with toluene. Stirring was continued at 0°C for 3–4 h before the mixture was allowed to warm slowly to room temperature. Saturated aq. Na_2SO_4 was added dropwise until gas was no longer evolved upon addition, and solid $MgSO_4$ was added. The slurry was stirred for 5 min before it was filtered through a Celite pad and the filter cake was rinsed with EtOAc. Chromatography of the residue left after concentration of the filtrate afforded sulfinamides **2a**–**e**. Product characterization for sulfinamide (*R*)-**2c**: IR: 1064, 1363, 1387, 1455 cm^{-1}. ^1H NMR (400 MHz) δ 0.76 (d, $J=6.8$, 3H), 0.93 (d, $J=6.9$, 3H), 1.17 (s, 9H), 1.43 (s, 3H), 2.19–2.25 (m, 4H), 3.37 (s, 1H), 5.83–5.84 (m, 1H), 6.11 (d, $J=3.0$, 1H). ^{13}C NMR (101 MHz) δ 13.57, 16.79, 17.58, 19.12, 22.54, 36.81, 55.72, 59.81, 105.72, 107.28, 151.03, 156.30. Anal. calcd for $C_{14}H_{25}NO_2S$: C, 61.95; H, 9.28; N, 5.16. Found: C, 61.85; H, 9.27; N, 5.15.
8. Compound **2a** was converted to the methyl ester of α-methyl-D-phenylglycine hydrochloride, and **2c** was converted to the methyl ester of α-methyl valine (see Ref. 10).
9. Alternatively, the ketoacid could be scavenged from the product by overnight treatment of the crude material with 1 equiv. of polystyrene-*p*-toluenesulfonyl hydrazide resin in dichloroethane at 40°C.
10. General procedure: $RuCl_3 \cdot H_2O$ (1 mol%) was added to a mixture of $NaIO_4$ (15 equiv.) in CH_2Cl_2/MeCN/H_2O (1.0:0.04:0.7), and the mixture was stirred for 1 h. A solution of **2** in CH_2Cl_2 was added rapidly to the mixture via cannula. The final concentration of **2** was 0.03 M. Upon completion, as determined by TLC, the mixture was acidified to pH 1 with 1N $NaHSO_4$. The mixture was filtered through a plug of Celite and the organic layer was separated and washed once with brine followed by extraction with 5% K_2CO_3 (3×). The aqueous layer was acidified to pH 1 with solid $NaHSO_4$ and then extracted with EtOAc (3×). The combined organic portions were dried (Na_2SO_4) and concentrated. For amino acid **3c**, acid/base extraction was followed by recrystallization from toluene. Product characterization for amino acid (*R*)-**3c**: IR: 1125, 1305, 1710, 1730, 2979, 3261 cm^{-1}. ^1H NMR (400 MHz) δ 0.99 (d, $J=6.8$, 3H), 1.02 (d, $J=6.9$, 3H), 1.42 (s, 9H), 1.56 (s, 3H), 2.11 (m, 1H), 4.47 (s, 1H), 10.28 (br s, 1H). ^{13}C NMR (101 MHz) δ 16.98, 17.08, 17.33, 24.35, 36.96, 60.15, 65.88, 179.39. Anal. calcd for $C_{10}H_{21}NO_4S$: C, 47.79; H, 8.42; N, 5.57. Found: C, 47.71; H, 8.30; N, 5.59. The product was determined to have the (*R*) configuration upon straightforward conversion to α-methyl-D-valine methyl ester. $[\alpha]_D^{23}$ −13.0 (*c* 6.1, $CHCl_3$). Lit. for α-methyl-L-valine methyl ester: $[\alpha]_D^{23}$ +13.5 (*c* 2.4, $CHCl_3$). Tabcheh, M.; El Achqar, A.; Pappalardo, L.; Roumestant, M.-L.; Viallefont, P. *Tetrahedron* **1991**, *47*, 4611–4618.
11. General procedure for coupling of **3c** with Phe-OMe:
    Method A: HATU (1.3 equiv.) was added to a 0.4 M solution of amino acid **3c** (1 equiv.) and Et_3N (4 equiv.) in DMF. After stirring for 1 h, HCl·Phe-OMe (2 equiv.) was added. Upon completion, as determined by TLC, the mixture was diluted with 3:1 hexanes/CH_2Cl_2 and washed with 1N $NaHSO_4$ (3×). The organic layer was washed with 0.1 M K_2CO_3 (3×), dried (Na_2SO_4), and concentrated. Chromatography with 85:15 hexanes/EtOAc afforded dipeptide **4**.
    Method B: This procedure is a modification of the reaction conditions reported by Vedejs (Ref. 12). (a) To a 0.2 M solution of amino acid **3c** (1 equiv.) and $SOCl_2$ (3 equiv.) in CH_2Cl_2 was added a catalytic amount of DMF. After stirring for 2 h, the solution was concentrated, dissolved in dry toluene, and concentrated again to yield the acid chloride, which was used without further purification. (b) To a stirred solution of HCl·Phe-OMe, $NaHCO_3$ (3.2 equiv.), and Na_2CO_3 (2 equiv.) in 1:1 CH_2Cl_2:H_2O (0.1 M) at 0°C was added a 0.1 M solution of the acid chloride in dry CH_2Cl_2. After stirring for 1 h, the reaction mixture was diluted with hexanes (3:1 hexanes/CH_2Cl_2 final ratio). The aqueous layer was washed with 3:1 hexanes/CH_2Cl_2 (3×). The combined organic layers were washed once with 0.5% HCl and then brine. Chromatography with 85:15 hexanes/EtOAc afforded dipeptide **4** in 79% yield.
12. *N*-sulfonyl-protected amino acid chlorides are markedly more stable than *N*-carbamate-protected amino acids, which decompose readily to the considerably less reactive oxazolinones. For the synthesis and application of *N*-sulfonyl amino acid chlorides, see: Vedejs, E.; Lin, S.; Klapars, A.; Wang, J. *J. Am. Chem. Soc.* **1996**, *118*, 9796–9797.

13. Deprotection of dipeptide **4** [this procedure is a modification of the conditions developed by Weinreb (Ref. 6a)]: To a solution of **4** in anisole (20 equiv.) was added a 0.4 N solution of TfOH in CH_2Cl_2 (6 equiv.). After stirring for 24 h, the mixture was washed with saturated $NaHCO_3$ (3×). After drying (Na_2SO_4) and concentration, chromatography (hexanes/EtOAc) afforded amine **5**.