Unnatural Chiral *N*-*tert*-Butanesulfinyl α-Amino Acid Synthesis; A General Synthetic Strategy to *N*-Boc-Phenylalanine Analogue Alternatives

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Abstract: This work provides a general approach to unnatural chiral *N*-*tert*-butanesulfinyl α-amino acid synthesis with high yields and excellent diastereoselectivities (dr up to 98:2). The asymmetric addition of organometallic reagents to *N*-*tert*-butylsulfinyl imino acetate proceeded with excellent diastereo- and regioselectivities even on a 10 mmol scale. The sterically constrained 2′,6′-dimethyltyrosine (Dmt) derivative was also readily prepared from commercially available and inexpensive starting materials through simple steps.

Key words: unnatural α-amino acids, peptides, regioselectivity, asymmetric synthesis, chiral auxiliaries

Peptides, due to their high specificity and low toxicity, have attracted growing attention for pharmaceutical applications. The incorporation of unnatural amino acids can play a very important role in enhancing the resistance of peptides to enzymatic degradation and increasing peptide structural diversity as well as bioactivity.[1] To obtain diverse unnatural amino acids, a variety of methodologies have been developed[2] such as asymmetric Strecker reaction,[3] direct functionalization of glycinate,[4] chiral template directed alkylation of glycinate,[5] and asymmetric addition to glyoxylate imine.[6] Among these protocols, direct asymmetric addition of Grignard reagents to glyoxylate imines,[7] which can afford protected chiral amino acids, was undoubtedly one of the most practical and convenient approaches. However, generally, significant background reactions always occur, which leads to poor stereoselectivity caused by the bidentate chelation effect of the glyoxylate imine. The use of chiral sulfinyl as a chiral auxiliary is a promising solution. Although sulfinyl imines have been widely exploited in various synthetic approaches,[8] few reports have been disclosed on the asymmetric synthesis of chiral α-amino acids via the nucleophilic addition to *N*-sulfinyl imino acetates.[9] As an electrophilic reagent, *N*-sulfinyl imino acetate (Figure 1) shows complex reactivity, which always limited the nucleophile scope. In fact, nucleophilic additions of Grignard-type reagents can occur at both the ester group and the imino group of **1**. Davis and co-workers obtained poor yields and regioselectivities by using either BnMgCl or BnZnCl, or BnMgCl combined with $ZnCl_2$ as the nucleophile.[9a] Reports also indicated that either the *N*-sulfinyl group[9a] or the *tert*-butyl group of sulfinyl[9e] can be readily substituted by the corresponding nucleophile. Rhodium(I)[10a] and palladium(II)[10b,10c] catalyzed additions of arylboronic acids to chiral *N*-*tert*-butanesulfinyl imino esters have been reported. However, these studies were limited to the synthesis of arylglycine derivatives.[10] Thus, it is highly desirable to find a general and practical nucleophilic reagent for direct asymmetric addition to *N*-sulfinyl imino acetate **1** for chiral α-amino acid synthesis.

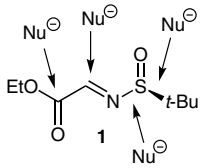

Figure 1 *N*-*tert*-Butanesulfinyl imino acetate **1** as a complex electrophile

Recently, Knochel and co-workers reported several protocols for the preparation and application of a series of multi-metallic organometallic reagents (Figure 2).[11] An impressive lithium chloride effect that could be used to finely tune the nucleophilicity and alkaline properties of these organozinc halides or organomagnesium halides was disclosed. Unlike the usual Grignard reagent, these Knochel reagents are ester-tolerant, highly nucleophilic, and weakly alkaline.[12] Type **I**/**II** Knochel reagents,[13] which possess the unique properties mentioned above, are the most easily accessible and the most widely functional group compatible. There is no need to preactivate magnesium or zinc. Although Ellman's group reported the addition of Knochel reagents to sulfinyl imine, application of the reagent to amino acid synthesis was not disclosed. Herein, we report the highly diastereoselective addition of Type **I** Knochel reagents to *N*-*tert*-butylsulfinyl imino acetate **1** for the asymmetric synthesis of chiral α-amino acids.[14]

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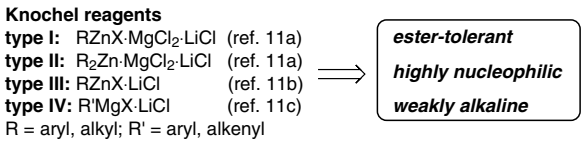
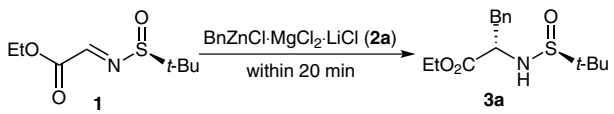


Figure 2 Typical multi-metallic organometallic reagents

In our preliminary studies, solvent and temperature effects were studied in detail to improve the yield and stereoselectivity of the model reaction; the results are summarized in Table 1. All the reactions were accomplished favorably at –78 °C within 20 min. When the reaction was carried out in hexane, poor yield (40%) and diastereoselectivity (74:26 dr) were observed (entry 1). When using CH_2Cl_2 and toluene as solvents, **3a** was afforded with similarly moderate yields (58 and 51%) and high dr values (93:7 and 92:8) (entries 2 and 3), respectively. Higher yield (76%) of **3a** was afforded when the reaction was conducted in isopropyl ether but with a lower dr value (89:11) (entry 4). The use of methyl *tert*-butyl ether (MTBE) failed to improve the result (entry 5). Tetrahydrofuran (THF) proved to be the optimal solvent, giving **3a** with excellent diastereoselectivity (97:3) and moderate yield (60%) (entry 6). Either the yield or the diastereoselectivity of the model addition decreased sharply at higher reaction temperature (entries 7–9). It was found that the optical rotation of ethyl phenylalaninate hydrochloride derived from **3a** was consistent with ethyl L-phenylalaninate hydrochloride. Thus, the absolute configuration of **3a** was (S_s,*S*).

Table 1 Solvent and Temperature Screening[a,b]



Entry	Solvent	Temp. (°C)	Yield (%)[c]	dr[d]
1	hexane	–78	40	74:26
2	CH_2Cl_2	–78	58	93:7
3	toluene	–78	51	92:8
4	*i*-Pr_2O	–78	76	89:11
5	MTBE	–78	52	88:12
6	THF	–78	60	97:3
7	THF	–40	58	87:13
8	THF	–20	56	82:18
9	THF	0	44	78:22

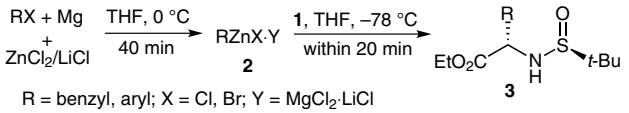
[a] Reaction conditions (unless otherwise noted): **1** (0.2 mmol), **2a** (0.3 mmol, 0.45 M in THF), solvent (1 mL), 20 min.
[b] The absolute configuration of **3a** was confirmed to be (S_s,*S*) (see the Supporting Information).
[c] Isolated yield of the major diastereomer.
[d] Determined by ^{1}H NMR analysis of the crude product.

The applicability of this approach was examined under the optimal conditions and the results are combined in Table 2. A series of phenylalanine analogue derivatives was successfully afforded. All the additions of benzyl zinc **2** to **1** were rapidly accomplished within 20 minutes. In addition, the stereoselectivity and the yield were not significantly affected by the concentration of reagent **2**. High yield of **3a** could also be obtained starting from benzyl bromide with excellent diastereoselectivity (95:5) (entry 1). Similar results were observed in the addition of multi-metallic benzyl zinc with either electron-withdrawing (**2d**) or electron-donating (**2b** and **2c**) substitutes and afforded **3b**–**d** with high yields and excellent dr values (entry 2–4). Mono-/multi-halide substituted benzyl zinc was also tolerated in this approach. The diastereoselectivities as well as yields were not obviously affected by the substitution sites. Excellent dr values of **3e**–**i** with moderate to high yields were obtained (entries 5–10). 1-Naphthylalanine derivative **3j** was also obtained with high yield (94%) and diastereoselectivity (90:10) (entry 11). The addition of **2j** to **1** proceeded smoothly to give the 4-vinyl phenylalanine derivative with an excellent dr value (97:3) and good yield (69%, entry 12), which can potentially be applied as a chiral ligand as well as in peptide immobilization. It was pleasing to find that arylglycine **3l** could also be highly diastereoselectively synthesized through the present protocol with a dr of 92:8 and a yield of 60% (entry 13).

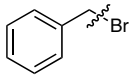
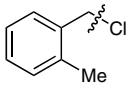
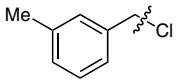
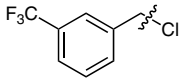
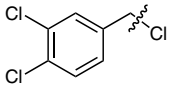
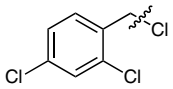
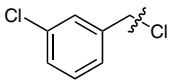
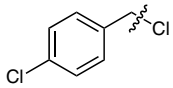
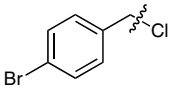
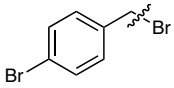
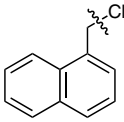
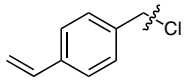
Extensive studies clearly indicated the introduction of 2′,6′-dimethyltyrosine (Dmt) to peptides, especially opioid peptide synthesis, was vital for improving the peptide structure–activity relationship.[15,16] However, commercial Dmt is very expensive. The asymmetric synthesis of Dmt was rather limited due to the steric hindrance of the chiral carbon center.[17] One approach involved Rh-catalyzed asymmetric hydrogenation under harsh conditions,[17b–e] and a relatively expensive chiral catalyst was used. An alternative approach involved a Ni-template strategy,[17c] which suffered low diastereoselectivity, long linear steps, and troublesome purification procedures. Chiral (*S*)-phenylethylamine-induced asymmetric synthesis of Dmt was reported recently, but the use of corrosive HI was critical to release the unprotected Dmt.[17d] Therefore, the present protocol was applied in the asymmetric synthesis of selectively protected Dmt.

The synthesis of 2′,6′-dimethyltyrosine (Dmt) is outlined in Scheme 1. Benzyl halides **5a** and **5b** were readily prepared from inexpensive and commercially available 4-hydroxy benzaldehyde (**4**) with excellent isolated yield. Knochel reagent **2m** (0.45 M) and **2n** (0.22 M) were afforded under the typical procedure (see the Supporting Information). The distinctly different concentrations might be due to the fact that (a) benzyl zinc bromide **2n** has a higher reactivity and nucleophilicity than benzyl zinc chloride **2m**, and cross-coupling of **2n** with benzyl bromide might occur, and (b) the large electron-donating effect of the two sterically hindered methyl groups associating with the benzyloxy group might cause the benzyl zinc bromide **2n** to be more unstable. This is con-

Table 2 Application Scope in Chiral Amino Acid Derivative Synthesis[a]

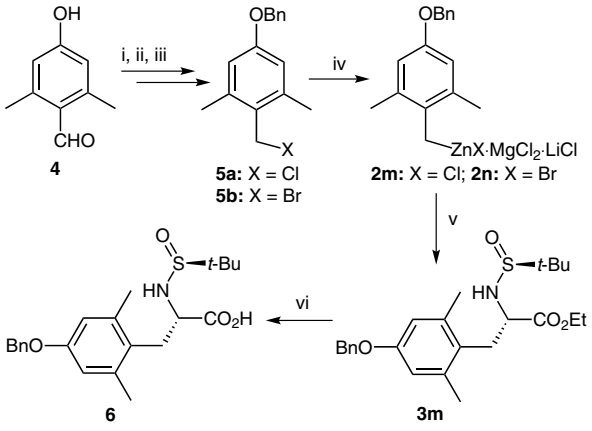


R = benzyl, aryl; X = Cl, Br; Y = $MgCl_2$·LiCl

Entry	RX	**2** (mmol/mL)[b]	Product	Yield (%)[c]	dr[d]	Optical rotation
1		**2a′** (0.51)	**3a**	90	95:5	+
2		**2b** (0.50)	**3b**	73	96:4	+
3		**2c** (0.48)	**3c**	77	94:6	+
4		**2d** (0.42)	**3d**	64	94:6	+
5		**2e** (0.50)	**3e**	66	94:6	+
6		**2f** (0.48)	**3f**	74	95:5	+
7		**2g** (0.51)	**3g**	77	96:4	+
8		**2h** (0.46)	**3h**	82	95:5	+
9		**2i** (0.68)	**3i**	73	92:8	+
10		**2i′** (0.52)	**3i**	60	93:7	+
11		**2j** (0.52)	**3j**	94	90:10	–
12		**2k** (0.46)	**3k**	69	97:3	+

[a] Reaction conditions: (*S*)-**1** (0.2 mmol), **2** (0.3 mmol in THF), 20 min.
[b] Separated by filtration and titrated according to the literature method (see the Supporting Information).
[c] Isolated yield of the major diastereomer.
[d] Determined by ^{1}H NMR analysis of the crude product.

sistent with the finding that complex products were observed in the addition of benzyl zinc bromide **2n** to sulfinyl imino acetate (*S*)-**1**. When 1.2 equiv of **2m** was used instead, selectively protected (*S*)-Dmt **3m** was favorably afforded with an excellent dr of 98:2 and 70% yield on a 10 mmol scale. The *N*-*tert*-butylsulfinyl group, which is an equivalent alternative of N-Boc, can be removed under acidic conditions, while retaining the ester and not affecting the chiral center.[18] The carboxyl group was readily released upon treatment with LiOH[19] to give *N*-*tert*-butyl sulfinyl acid **6** with 90% yield. The phenolic hydroxyl group of **6** can also be readily released by catalytic hydrogenation.



Scheme 1 2′,6′-Dimethyl tyrosine synthesis. *Reagents and conditions*: (i) BnBr, K_2CO_3, acetone, reflux, 3 h; (ii) $NaBH_4$, MeOH, 0 °C, 92% yield from phenol aldehyde **4**; (iii) **5a**: $SOCl_2$, 1 h in CH_2Cl_2, 98%; **5b**: CBr_4, Ph_3P, 1 h in THF, 90%; (iv) Mg, $ZnCl_2$/LiCl (1.1 M/1.5 M in THF), 3 h, 0.45 M for **2m**, 0.22 M for **2n**; (v) **2n** (1.2 equiv), (*S*)-**1** (10 mmol), –78 °C, 30 min, dr 98:2, 70%; (vi) LiOH (1 M, THF–H_2O), overnight at r.t., 90%.

In conclusion, we have developed a facile, convenient, reliable, and inexpensive synthesis of chiral α-amino acids using *N*-*tert*-butanesulfinyl as the chiral auxiliary. The addition of various multi-metallic benzyl zinc halides to *N*-*tert*-butanesulfinyl imino ester gave *N*-*tert*-butanesulfinyl amino esters with high yields and excellent diastereoselectivities. The amino or carboxyl group of the addition product can be selectively deprotected under very mild conditions. Because *N*-*tert*-butanesulfinyl amino acids can be considered as *N*-Boc-α-amino acids alternatives, the present approach is potentially very important in peptide synthesis. The protected sterically constrained (*S*)-Dmt derivative was also readily prepared from inexpensive and commercially available starting material through simple steps with a high overall yield on a multigram scale. Applying the unnatural chiral α-amino acids to related peptide SAR improvement is under investigation.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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