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Asymmetric synthesis of δ-amino acid derivatives *via* diastereoselective vinylogous Mannich reactions between *N-tert*-butanesulfinyl imines and dioxinone-derived lithium dienolate†

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A diastereoselective vinylogous Mannich reaction between the *N-tert*-butanesulfinyl imines and dioxinone-derived lithium dienolate was developed. A variety of aldimines, ketimines and isatin-derived ketimines are suitable for this process. On the basis of X-ray crystallography of products, a predictive model for this transformation was provided.

Introduction

Chiral δ-amino acids and their derivatives are commonly found in many bioactive natural alkaloids, drugs, and drug candidates,[1–4] *e.g.* the vasodilator vincamine,[1] the α_2-adrenoceptor antagonist yohimbine,[2] clinically important anticancer drugs vinblastine and vincristine,[3] and the antibiotic cephalosporin C[4] (Fig. 1). In addition, chiral δ-amino acid derivatives **1** are useful building blocks for asymmetric organic synthesis (Scheme 1),[5–8] in particular for the synthesis of chiral δ-amino β-ketoesters **2** which are versatile intermediates for various piperidine and pyrrolidine alkaloids.[5] As a consequence, some effective methods have been developed towards the synthesis of chiral δ-amino acid derivatives **1**.[6–8]

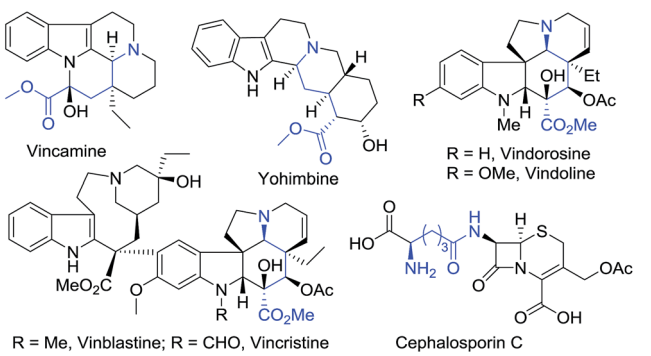
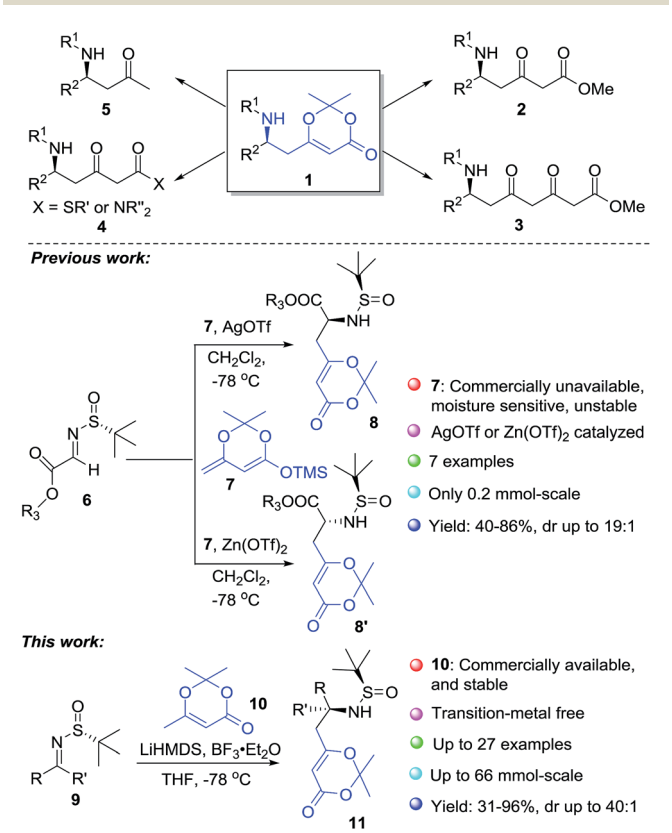


Fig. 1 Selected compounds containing chiral δ-amino acid units.



Scheme 1 Application and synthesis of δ-amino acid derivatives.

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In our recent efforts towards the synthesis of vindoline and vindorosine (Fig. 1),[9] we needed a scalable process (>10 g) for the preparation of chiral δ-amino acid derivatives **11** as starting materials. Because the chiral *tert*-butanesulfinamide has been widely used as a versatile reagent for the asymmetric introduction of amine units,[10,11] we planned to synthesize the chiral δ-amino acid derivatives **1** based on vinylogous Mannich reactions between *N-tert*-butanesulfinyl imines and dioxinone-derived dienolate (Scheme 1). Although an elegant vinylogous Mannich reaction between *N-tert*-butanesulfinyl imines **6** and dioxinone-derived silyl dienolate **7** mediated by Lewis acid has been reported by Chen's group (Scheme 1),[7b] the moisture-sensitive and unstable silyl dienolates[6–8,12,13] were not deemed suitable for large-scale preparation in our laboratory. After a few experiments, we could not get the desired products in large quantities. Therefore, we decided to develop a practical process using dioxinone-derived lithium dienolates directly as nucleophiles.

In this paper, we report full details of the general and practical diastereoselective approach towards the synthesis of δ-amino acid derivatives in gram-scale by vinylogous Mannich reactions between *N-tert*-butanesulfinyl imines and dioxinone-derived lithium dienolate.

Results and discussion

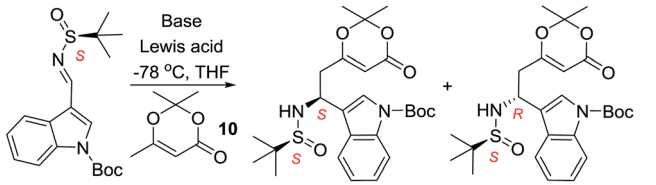
We began our research using indolyl *N-tert*-butanesulfinyl aldimine **9a** and commercially available dioxinone **10** as substrates. A systematic screening of reaction conditions was conducted to optimize the yield and diastereoselectivity of the vinylogous Mannich reaction (Table 1). Initially, the reactions were carried out in the presence of bases without adding any Lewis acid (entry 1 and 2). Treatment of **10** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C followed by sulfinyl aldimine **9a** resulted in a complex mixture, with the desired product being isolated in only 8% yield.

Changing the base to lithium bis(trimethylsilyl)amide improved the yield to 27%, unfortunately, both the yield and stereoselectivity were unacceptable (entry 2). Introductions of transition metal Lewis acids to activate the imines were attempted but failed to provide the desired products. To our delight, the same reaction conducted in the presence of $BF_3\cdot Et_2O$ provided the desired products in 65% yield (entry 7, **11a** + **11a′**). Finally the optimized reaction conditions were found (entries 8). Mannich addition of dioxinone-derived lithium dienolate (2.0 eq.) towards sulfinyl aldimine in the presence of $BF_3\cdot Et_2O$ (1.0 eq.) provided desired product (**11a**) and its diastereomer (**11a′**) in 87% and 2% isolated yields (1 mmol scale) respectively (entry 8). The reactions could be scaled up to 5 mmol, 14.9 mmol and 66.0 mmol without significant loss in yields and diastereoselectivity of the desired products (entries 9–11).

With the optimized reaction conditions in hand, the scope of the diastereoselective vinylogous Mannich reactions between *N-tert*-butanesulfinyl imines **9** and dioxinone-derived lithium dienolate (generated *in situ* from **10**) activated by $BF_3\cdot Et_2O$ was investigated (Table 2). For substrate 6-methoxyindolyl *N-tert*-butanesulfinyl aldimine **9b**, major product **11b** and its diastereomer were obtained in 87% yield and with high d.r. (>40 : 1). For phenyl *N-tert*-butanesulfinyl aldimine **9c**, excellent yield (96%) and diastereoselectivity (>40 : 1 d.r.) were obtained (Table 2, entry 2). Next, the influence of the substitution at the aromatic rings (**9d–9h**) was examined (entries 3–7). All these aldimines afforded good to excellent yields and diastereoselectivity. The electron rich 3,4-dimethoxybenzaldimine **9d** gave the best result, which provided product **11d** in 95% yield and >40 : 1 d.r. (Table 2, entry 3). The substrate **9h** bearing an electron deficient nitro group also afforded the corresponding product (**11h**) in 89% yield and high diastereoselectivity (entry 7, >40 : 1). Benzofuran-derived *N-tert*-butanesulfinyl aldimine **9i** and quinoline-derived *N-tert*-butanesulfinyl aldimine **9j** were also investigated (entries 8 and 9). Benzofuran-derived *N-tert*-butanesulfinyl aldimine **9i** provided the expected product in 80% yield and 10.4 : 1 d.r. (Table 2, entry 8).

It was of interests to note that the quinoline-derived *N-tert*-butanesulfinyl aldimine required two equivalents of $BF_3\cdot Et_2O$ and the corresponding product **11j** could be isolated in 86% yield and >40 : 1 d.r. (Table 2, entry 9). This interesting result indicated that the first equivalent of BF_3 might coordinate to the more basic quinoline nitrogen and the second equivalent of BF_3 activated the sulfinyl aldimine in this vinylogous Mannich reaction. Changing the substrate to aliphatic butanesulfinyl aldimine **9k** resulted in 37% yield and moderate

Table 1 Optimization of the vinylogous Mannich reaction[a]

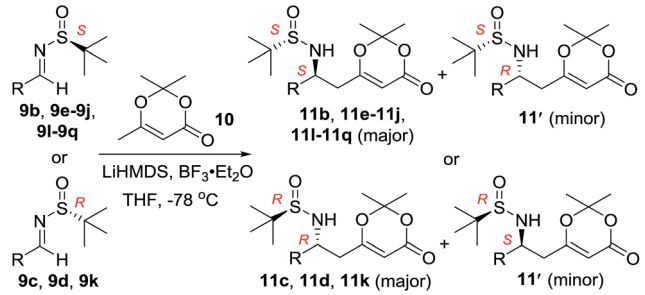


9a **11a** (major) **11a′** (minor)

Entry	Base	Lewis acid	Product (yield%)	d.r.
1[b]	LDA	None	**11a** + **11a′**: 8	3 : 1
2[b]	$LiN(SiMe_3)_2$	None	**11a** + **11a′**: 27	3.5 : 1
3[b]	$LiN(SiMe_3)_2$	$ZnCl_2$	No desired product	—
4[b]	$LiN(SiMe_3)_2$	$Cu(OTf)_2$	Complex mixture	—
5[b]	$LiN(SiMe_3)_2$	$TiCl_4$	Complex mixture	—
6[b]	$LiN(SiMe_3)_2$	AgOTf	Complex mixture	—
7[b]	$LiN(SiMe_3)_2$	$BF_3\cdot Et_2O$	**11a**: 63; **11a′**: 1.5	>40 : 1
8[c]	$LiN(SiMe_3)_2$	$BF_3\cdot Et_2O$	**11a**: 87; **11a′**: 2	>40 : 1
9[d]	$LiN(SiMe_3)_2$	$BF_3\cdot Et_2O$	**11a**: 87; **11a′**: 2	>40 : 1
10[e]	$LiN(SiMe_3)_2$	$BF_3\cdot Et_2O$	**11a**: 86; **11a′**: 2	>40 : 1
11[f]	$LiN(SiMe_3)_2$	$BF_3\cdot Et_2O$	**11a**: 83; **11a′**: 2	>40 : 1

[a] Yields represent isolated yields. Reactions were conducted in THF at −78 °C (acetone-dry ice bath). Entries 1–4, 6 and 10 were reported in our recent work (see ref. 9). [b] Reactions were performed using 1.0 mmol of **9a** (348.0 mg), 1.5 mmol of **10**, 1.6 mmol of $LiN(SiMe_3)_2$ and 1.0 mmol of Lewis acids. [c] The reaction was conducted using 1.0 mmol of **9a**, 2.0 mmol of **10** (2.0 eq.), 2.4 mmol of $LiN(SiMe_3)_2$ (2.4 eq.) and 1.0 mmol of $BF_3\cdot Et_2O$ (1.0 eq.). [d] With 5.0 mmol of **9a** (1.74 g). [e] The reaction was conducted with 14.9 mmol of **9a** (5.20 g). [f] The reaction was performed using 66.0 mmol of **9a** (23.0 g).

Table 2 Aldimines in the vinylogous Mannich reaction[a]



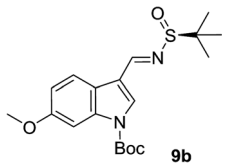
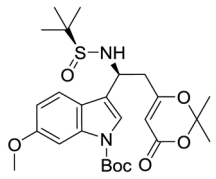
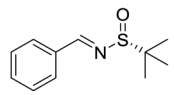
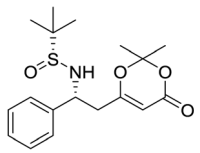
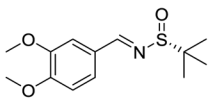
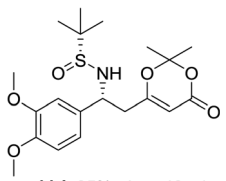
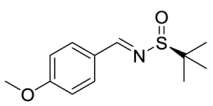
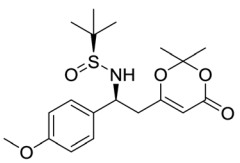
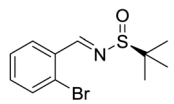
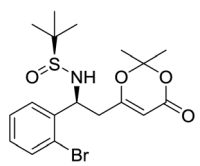
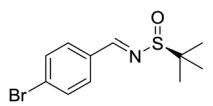
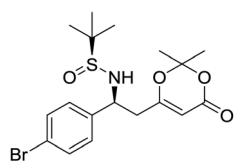
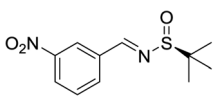
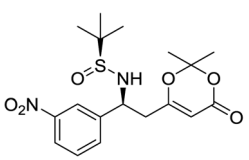
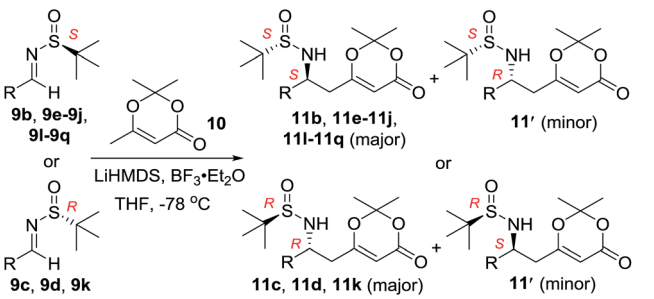
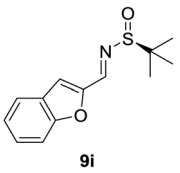
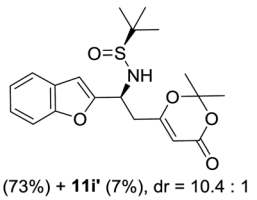
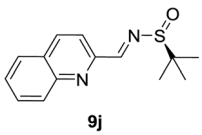
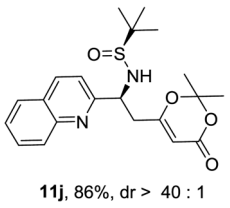
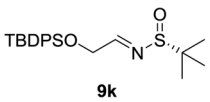
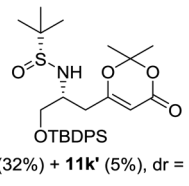
Entry	Substrates	Products, yield and d.r.
1[b]	 9b	 **11b** (85%) + **11b'** (2%), dr > 40 : 1
2[c]	 9c	 **11c**, 96%, dr > 40 : 1
3[c]	 9d	 **11d**, 95%, dr > 40 : 1
4	 9e	 **11e**, 89%, dr > 40 : 1
5[d]	 9f	 **11f** + **11f'**, 90%, dr = 4.9 : 1
6[b]	 9g	 **11g** (77%) + **11g'** (14%), dr = 5.5 : 1
7	 9h	 **11h**, 89%, dr > 40 : 1

Table 2 (*Contd.*)



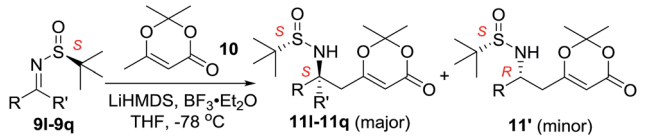
Entry	Substrates	Products, yield and d.r.
8[b]	 9i	 **11i** (73%) + **11i'** (7%), dr = 10.4 : 1
9	 9j	 **11j**, 86%, dr > 40 : 1
10[b,c]	 9k	 **11k** (32%) + **11k'** (5%), dr = 6.4 : 1

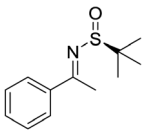
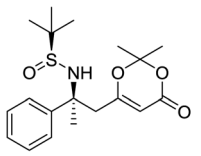
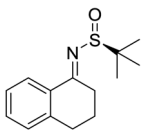
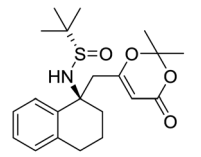
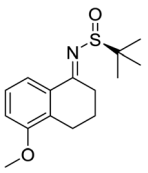
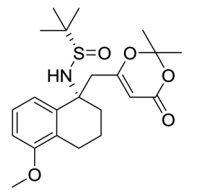
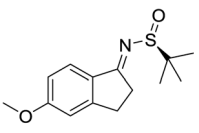
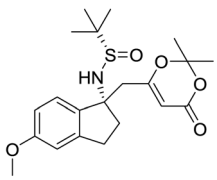
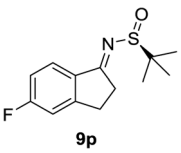
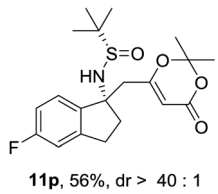
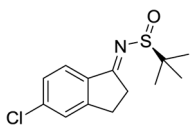
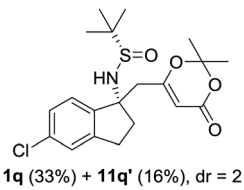
[a] Yields represent isolated yields. Reactions were conducted at 1.0 mmol scale in THF at −78 °C (acetone-dry ice bath). (S_s)-*tert*-Butanesulfinamide was used in all reactions except **9c** (entry 2) **9d** (entry 3), and **9k** (entry 10). [b] Major products and their diastereomers could be isolated by flash column chromatography. [c] (R_s)-*tert*-Butanesulfinamide was used in the reactions. [d] Major product and its diastereomer could not be separated by flash column chromatography. The d.r. value was established by ^{1}H NMR analysis of the mixed products. TBDPS = *t*-butyldiphenylsilyl.

diastereoselectivity (Table 2, entry 10, 6.4 : 1). The low isolated yield was mainly caused by decomposition of aliphatic *N-tert*-butanesulfinyl aldimine in the presence of Lewis acid.

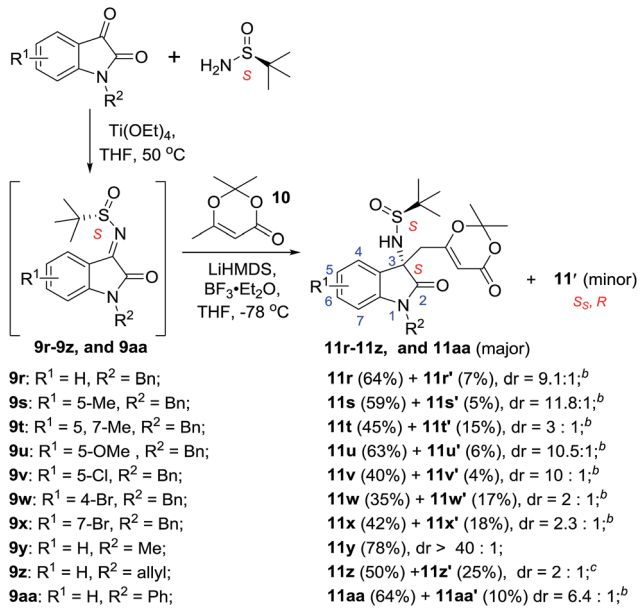
Next, the phenyl *N-tert*-butanesulfinyl ketimines **9l–9q** were examined (Table 3). Due to the thermal sensibility and hydrolytical instability,[11e] substrates **9l–9q** provided the corresponding products **11l–11q** in low yields and with moderate to excellent diastereoselectivities. For the phenylethanimine **9l**, only 1.2 : 1 d.r. was observed (Table 3, entry 1). However, treatment of the phenyl cyclic ketimines **9m–9q** under the same optimized reaction conditions resulted in mild to excellent diastereoselectivities (d.r. 2 : 1 to >40 : 1, entries 2–6). Although

Table 3 Ketimines in the vinylogous Mannich reaction[a]



Entry	Substrates	Products, yield and d.r.
1[b]	 9l	 11l (20%) + 11l' (17%), dr = 1.2 : 1
2[c]	 9m	 11m (24%) + 11m' (7%), dr = 3.4 : 1
3	 9n	 11n, 32%, dr > 40 : 1
4[c]	 9o	 11o (32%)+ 11o' (11%), dr = 2.9 : 1
5	 9p	 11p, 56%, dr > 40 : 1
6[b]	 9q	 11q (33%) + 11q' (16%), dr = 2 : 1

[a] Yields represent isolated yields. Reactions were conducted at 1.0 mmol scale in THF at −78 °C (acetone-dry ice bath). [b] Major products and their diastereomers could be isolated by flash column chromatography. [c] Major products and their diastereomers could be isolated by preparative chromatography.



Scheme 2 Isatin-derived ketimines in the vinylogous Mannich reaction.[a] Yields represent isolated yields for two steps. Reactions were conducted at 1.0 mmol scale in THF at −78 °C (acetone-dry ice bath). (S_s)-*tert*-Butanesulfinamide was served in all reactions.[b] Major products and their diastereomers could be isolated by flash column chromatography.[c] Major products and their diastereomers could be isolated by preparative chromatography. Bn = benzyl, Ph = phenyl.

the yields were moderate, to the best of our knowledge, these were the first reported examples on diastereoselective vinylogous Mannich reaction of *N*-*tert*-butanesulfinyl ketimines.

Isatin, a valuable building block for the synthesis of diverse biologically active compounds, has attracted considerable attention in chemical society.[14] It was our interests to use it as starting material in the diastereoselective vinylogous Mannich reactions. The isatin-derived *N*-*tert*-butanesulfinyl ketimines (**9r–9aa**) were then prepared and reacted with dioxinone-derived lithium dienolate (Scheme 2).

For isatin-derived ketimine **9r**, good yield (71%) and high level of diastereoselectivity (9.1 : 1 d.r.) were observed (Scheme 2). The isatin-derived ketimines (**9s**, **9u** and **9v**) bearing one substituted group (methyl, methoxyl, or chloro) at the 5-position usually gave the products (**11s**, **11u** and **11v**) with better diastereoselectivities. While the isatin-derived ketimines (**9t**, **9w** and **9x**) bearing substituted group at the 4-position or 7-position resulted in moderate isolated yields with lower diastereoselectivities (**11t**, **11w** and **11x**).

Finally, the influence of the substitution at 1-position (*N*-substituent) was investigated. As a result, the methyl-substituted substrate (**9y**) provided the best result in terms of yields and diastereoselectivities (**11y**, 78% yield, >40 : 1 d.r.).

For this $BF_3 \cdot Et_2O$-mediated vinylogous Mannich reaction, we provided a transition state model for predicting the absolute configuration of the products (Fig. 2). The imine was activated by coordination with $BF_3 \cdot Et_2O$ and *Si*-face addition of the dioxinone-derived lithium dienolate leads to the major products with *S*-configuration for the newly formed stereo center. X-ray crystallographic experiments established the absolute configurations of **11c**, **11h** and **11w** (Fig. 3), and the absolute configurations of **11c**, **11h** and **11w** were determined to be (R_s,

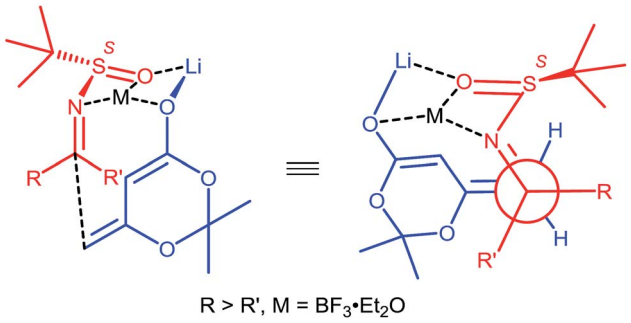


Fig. 2 Proposed transition state model for the vinylogous Mannich reaction between (*S*)–*N*-*tert*-butanesulfinyl imines and dioxinone-derived lithium dienolate.

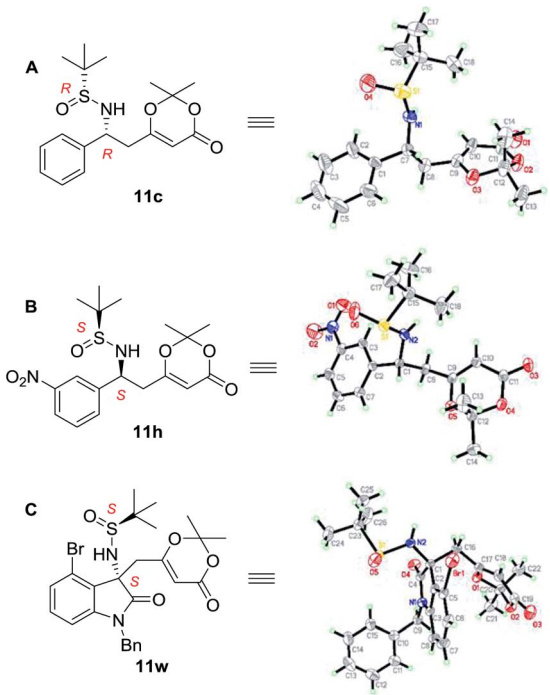


Fig. 3 X-ray crystal structures of compound **11c**, **11h** and **11w**. Thermal ellipsoids are shown at 30% probability.

R), (S_s, *S*) and (S_s, *S*), respectively.[15] The X-ray crystallographic experimental results are in fully accordance with our model prediction.

Conclusions

In conclusion, we have established a general and diastereoselective method for the synthesis of δ-amino acid derivatives. The $BF_3{\cdot}Et_2O$ mediated vinylogous Mannich reactions between *N*-*tert*-butanesulfinyl imines and dioxinone-derived lithium dienolate are practical and could be conducted in gram-scale. To validate our method as a means to access complex natural products, the asymmetric total synthesis of (−)-vindorosine has been accomplished based on this procedure recently.[9] This new approach should find more applications in the synthesis of complex natural products and drug candidates.

Experimental

General

Melting points were obtained on a XT-4 melting-point apparatus and were uncorrected. The infrared (IR) spectra were measured on a Nicolet iS10 FTIR spectrometer with 4 cm^{-1} resolution and 32 scans between wavenumber of 4000 cm^{-1} and 400 cm^{-1}. Samples were prepared as KBr disks with 1 mg of samples in 100 mg of KBr. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained on a Bruker Avance 400 spectrometers at 400 MHz. Carbon-13 nuclear magnetic resonance (^{13}C-NMR) was obtained on Bruker Avance 400 spectrometers at 100 MHz. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS) for all recorded NMR spectra. High Resolution Mass spectra were taken on AB QSTAR Pulsar mass spectrometer or Aglient LC/MSD TOF mass spectrometer. Optical rotations were recorded on a JASCO P-2000 polarimeter. All new compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS. The known compounds were characterized by ^{1}H NMR and ^{13}C NMR. Silica gel (200–300 mesh) for column chromatography and silica GF_{254} for TLC were produced by Merck Chemicals Co. Ltd. (Shanghai). THF used in the reactions were dried by distillation over metallic sodium and benzophenone. Starting materials and reagents used in reactions were obtained commercially from Acros, Aldrich, Adamas-beta®, and were used without purification, unless otherwise indicated. All moisture-sensitive reactions were conducted in dried glassware under a positive pressure of dry nitrogen or argon. Reagents and starting materials were accordingly transferred *via* syringe or cannula. Unless otherwise stated, all other reactions were also performed under a dry nitrogen atmosphere.

General procedure for aldimines and phenyl ketimines (11a–11q)

To a solution of sulfinimines **9** (1.0 mmol) in THF (10 mL) was added $BF_3{\cdot}Et_2O$ (0.13 mL, 1.0 mmol) at −78 °C. In the mean time, to a stirred solution of dioxinone **10** (284 mg, 2.0 mmol) in THF (10 mL) was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 2.4 mL, 2.4 mmol) at −78 °C. The resulting mixtures were stirred at −78 °C for 1 h. Then, the solution of dioxinone-derived lithium dienolate was cannulated to the solution of sulfinimine at −78 °C. Stirring was continued at −78 °C for 3 h. The reaction was then quenched with saturated aq. NH_4Cl (3 mL) at −78 °C. The cooling bath was removed and the mixture was warmed to rt, followed by extraction with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with petroleum ether/EtOAc (5 : 1 to 2 : 1) or purified by preparative chromatography to afford sulfinamides **11** and their diastereomer **11′**. Caution: 2 mmol

$BF_3 \cdot Et_2O$ was added for quinoline-derived *N-tert*-butanesulfinyl aldimine **9j**. See ESI† file for characterization data.

General procedure for isatin-derived ketimines (11r–11aa)

A mixture of isatin-derived substrate (1.0 mmol), (*S*)-*tert*-butanesulfonamine (146 mg, 1.2 mmol) and titanium ethoxide (1.6 mL, 2.5 mmol) in dichloromethane (10 mL) was stirred under reflux for 12 h. The reaction was quenched with water and the resulting suspension was filtered through a short pad of anhydrous sodium sulfate. The solid cake was washed with dichloromethane, and the separated organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was dissolved in THF (10 mL). $BF_3 \cdot Et_2O$ (0.13 mL, 1 mmol) was added at −78 °C. In the mean time, to a stirred solution of dioxinone **10** (284 mg, 2.0 mmol) in THF (10 mL) was added lithium bis(trimethylsilyl) amide (1.0 M in THF, 2.4 mL, 2.4 mmol) at −78 °C. The resulting mixtures were stirred at −78 °C for 1 h. Then, the solution of dioxinone-derived lithium dienolate was cannulated to the solution of sulfinimine at −78 °C. Stirring was continued at −78 °C for 3 h. The reaction was then quenched with saturated aq. NH_4Cl (3 mL) at −78 °C. The cooling bath was removed and the mixture was warmed to rt, followed by extraction with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with petroleum ether/EtOAc (5 : 1 to 2 : 1) or purified by preparative chromatography to afford isatin-derived sulfinamides and their diastereomer. Yields represent isolated yields for two steps. See ESI† file for characterization data.

Conflicts of interest

There are no conflicts of interest to declare.

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