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无金属条件下叔丁基亚磺酰胺衍生物在 B_2pin_2/D_2O 体系中的氘代还原

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摘要 利用廉价易得的氘代试剂 D_2O 作为氘源，在无金属条件下实现了叔丁基亚磺酰胺类衍生物与 B_2pin_2(联硼酸频那醇酯)的氘代还原反应. 通过对碱、溶剂、B_2pin_2 的用量等进行筛选，在较优的反应条件下以中等到较好的收率得到了一系列相应的氘代二级胺. 该方法反应条件温和，操作简单，放大到克级规模也不影响反应收率. 通过脱除 *N*-叔丁基亚磺酰基，能以较高的收率得到环戊烷-1-*d*-1-胺.

关键词 氘代还原; 叔丁基亚磺酰胺类衍生物; 联硼酸频那醇酯; 氘代二级胺

Transition Metal-Free Deuteride Reduction of *N-tert*-Butanesulfinyl Ketimines Derivatives via B_2pin_2/D_2O System

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Abstract A transition metal-free deuteride reduction protocol of *N-tert*-butanesulfinyl ketimines with B_2pin_2 has been developed. After screening of reaction parameters, such as base, solvent, and the amount of B_2pin_2, a series of deuterated secondary amines were obtained in reasonable yields with excellent deuterium purity by using D_2O as the deuterium source. Mild reaction conditions, operational simplicity, and easily scaled up to gram scale are the considerable advantages of this methodology. After deprotection of *tert*-butanesulfinyl, cyclopentan-1-*d*-amine is obtained in high yield.

Keywords deuteride reduction; *N-tert*-butanesulfinyl ketimines; bis(pinacolate)diboron; deuterated secondary amines

1 Introduction

The introduction of one or a few deuterium atoms to an organic compound can normally maintain its bioactivity and selectivity because shape and size of electron clouds of deuterium atom are basically the same as hydrogen.[1] Meanwhile, the C—D bond vibrates at a frequency different from the normal C—H bond, which can affect the absorption, distribution, or metabolism of some drugs.[2] In recent years, deuterated drugs have emerged as novel drugs that display better stability or bioavailability than their non-deuterated ones (Figure 1).[3] For example, deutetrabenazine, the first deuterated drug approved by the US Food and Drug Administration (FDA), has longer half-life, less frequent dosing and lower side effect than trabenazine in treatment of chorea in Huntington's disease.[3a] Donafenib tosylate, which is an antitumor agent, shows a more significant effect of inhibiting tumor growth than sorafenib.[3b] The deuterated enzalutamide (known as HC-11119) exhibits stronger antitumor potency due to the higher drug exposure level.[3c] Introduction of deuterium atom into the molecule of telaprevir which is known as an inhibitor of the hepatitis C virus improved its bioavailability.[3d] Moreover, deuterated molecules are also exploited for studies on reaction mechanisms,[4] used as deuterated NMR solvents[5] or employed as internal standards for mass spectrometric analysis.[6]

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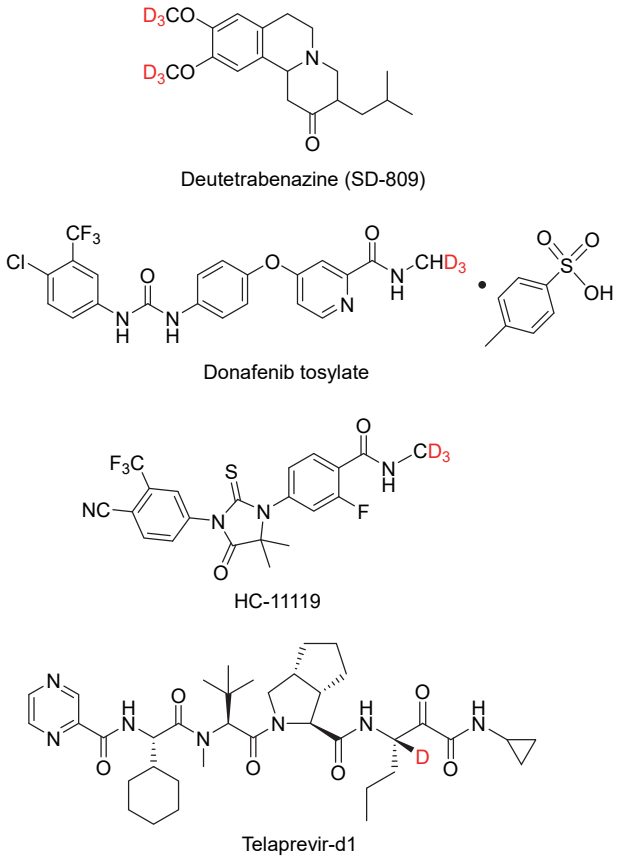
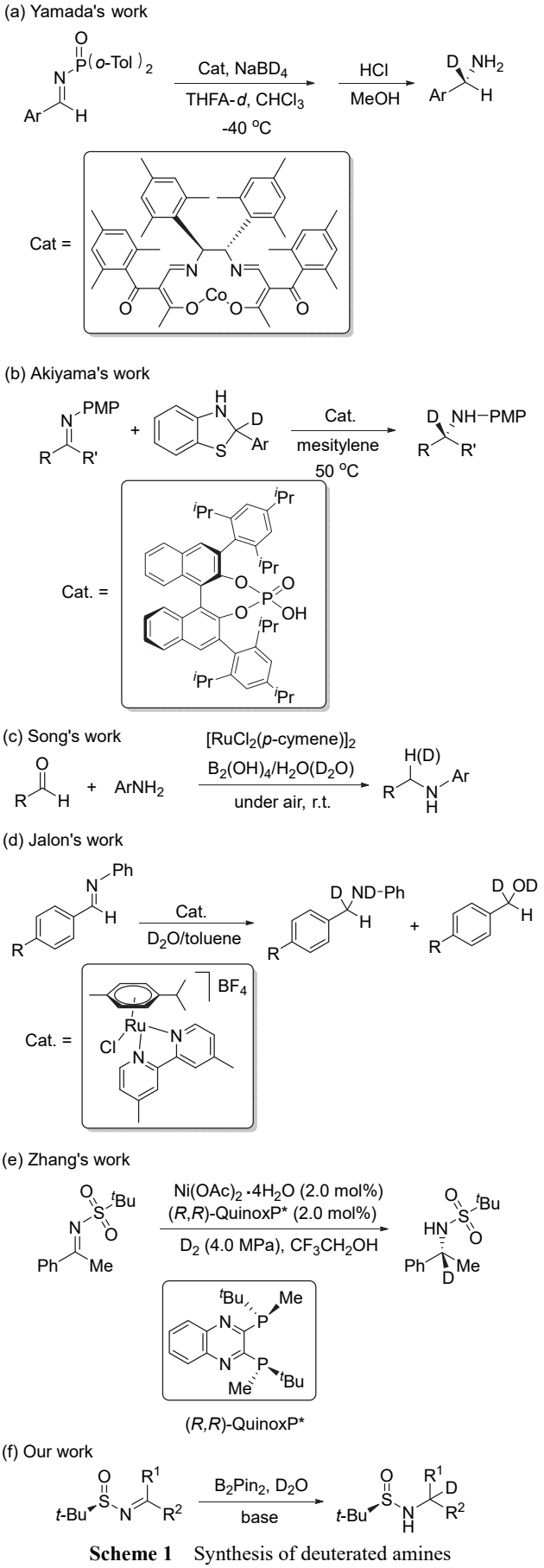


Figure 1 Structures of deuterated pharmaceuticals

Deuterated amines are key intermediates for the preparation of many biologically active compounds, so the synthesis of deuterated amines attracts increasing interest of chemists.[7] The deuteride reduction of imines is one of the common and effective approaches for the synthesis of deuterated amines. In 2003, Yamada and co-workers[8] reported the Co-catalyzed reduction of aldimines employing $NaBD_4$ as reductant (Scheme 1a). In 2012, Akiyama and co-workers[9] found that chiral phosphoric acid could catalyze the reduction of ketimines using deuterated benzothlazoline as a deuterium donor (Scheme 1b). In 2017, Song and co-workers[10] investigated Ru-catalyzed reductive amination in $B_2(OH)_4/D_2O$ system employing D_2O as both deuterium source and solvent (Scheme 1c). In 2018, Jalón's group[11] developed Ru catalyzed deuteration of imines in a biphasic medium (D_2O/toluene) (Scheme 1d). In 2019, Zhang's group[12] reported the nickel-catalyzed asymmetric hydrogenation or deuteration of *N*-sulfonyl imines using H_2 or D_2 (Scheme 1e). Although significant achievements have been made, the above examples have suffered from utilizing complex catalysts or expensive deuterium reagents. Therefore, it is desirable to develop an alternative economical and efficient method for the deuteride reduction of ketimines under mild conditions.

Bis(pinacolate)diboron (B_2Pin_2) is a reagent which is usually used in borylation reactions.[13] The transfer hydrogenation employing H_2O as hydrogen source and B_2Pin_2 as activator has been studied.[14] The reduction re-



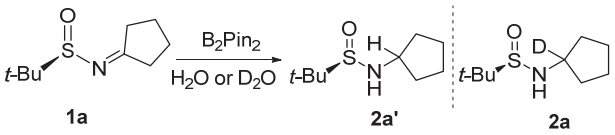
Scheme 1 Synthesis of deuterated amines

action using B_2Pin_2 as reductant has been explored.[15] Recently, D_2O has also been used as efficient deuterium donor for the synthesis of deuterated compounds.[16] In continuation of our research interest in deuteration reaction[17] and the synthesis of various valuable compounds by using organoborane as reagents,[18] herein we aim to find a more convenient and efficient protocol to obtain the deuterated amines starting from ketimines in B_2Pin_2/D_2O system.

2 Results and discussion

The chiral imine **1a** derived from (*R*)-*tert*-butanesulfinamide and cyclopentanone was used as substrate for the optimization of the reaction conditions in deuteride reduction with B_2pin_2 in the presence of D_2O. Considering the economy of D_2O, H_2O was used in the reaction condition screening stage and the results were summarized in Table 1. The reaction gave the desired product **2a'** in 33% yield within 3 h by using B_2pin_2 (1.2 equiv.) as reductant, K_3PO_4 (1.0 equiv.) as base, and H_2O (2 mL) as solvent (Table 1, Entry 1). Several bases such as KOH, NaOAc, K_2CO_3, Cs_2CO_3, CsF, CsOAc, Na_2CO_3 were examined in the reaction, while the moderate yield was obtained when Cs_2CO_3 was used as base (Table 1, Entries 2～8). Then the amount of base was screened and the best result was obtained when 1.2 equiv of Cs_2CO_3 was used (Table 1, Entries 5 vs 9～10). Decreasing the amount of B_2pin_2 to 1.0 equiv. or increasing the amount of B_2pin_2 to 1.5 equiv. afforded the desired **2a'** in a declined yield (Table 1, Entries 9 vs 11～12). Other mixed solvents were found to be less effective for this reduction reaction (Table 1, Entries 13～15). When D_2O was used instead of H_2O, the corresponding deuterated product was received in a good yield with 91 atom% D (Table 1, Entry 16). In order to explore the competitiveness of H and D, a control experiment using a mixture of H_2O and D_2O ($n(D_2O)$∶$n(H_2O)$=1∶1) as solvent was conducted, and the result showed that deuterium/hydrogen ratio is nearly 1∶1 (Table 1, Entry 17). In consequence, it was speculated that the low deuterated purity of the product was due to the presence of H_2O in Cs_2CO_3 and the starting materials. To improve the deuterated purity of the desired product, a higher purity of Cs_2CO_3 (from 98% to 99.9%) was used. The result indicated that the yield and deuterated purity of **2a** reached a good value (93%, 95% D) (Table 1, Entry 18). Increasing the volume of D_2O led to an improvement in the deuterated purity of **2a** (Table 1, Entries 19～20). Employment of 2 mL of D_2O afforded a good deuterated purity. When the volume of D_2O was increased to 3.0 mL, the deuterated purity did not increase further. Under the same conditions, when anhydrous B_2pin_2 was used, the deuterated purity of **2a** reached to 98% (Table 1, Entry 21). Finally, the optimized reduction reaction conditions were determined as **1a** (1.0 equiv., 0.5 mmol), B_2pin_2 (1.2 equiv.) in the presence of Cs_2CO_3 (1.2 equiv.) in D_2O (2.0 mL) at room temperature under Ar for 3 h.

Table 1 Optimization of reaction conditions[a]



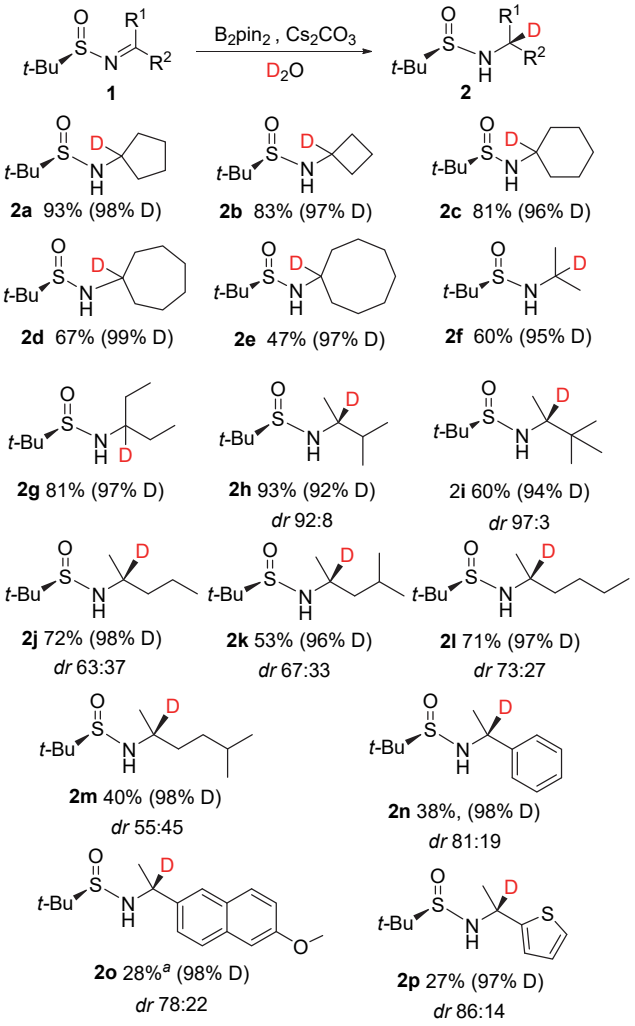
1a 2a' 2a

Entry	B_2pin_2 (equiv.)	Base (equiv.)	Solvent	Yield[b]/%
1	B_2pin_2 (1.2)	K_3PO_4 (1.0)	H_2O	33
2	B_2pin_2 (1.2)	KOH (1.0)	H_2O	Trace[c]
3	B_2pin_2 (1.2)	NaOAc (1.0)	H_2O	ND[d]
4	B_2pin_2 (1.2)	K_2CO_3 (1.0)	H_2O	64
5	B_2pin_2 (1.2)	Cs_2CO_3 (1.0)	H_2O	69
6	B_2pin_2 (1.2)	CsF (1.0)	H_2O	10
7	B_2pin_2 (1.2)	CsOAc (1.0)	H_2O	ND[d]
8	B_2pin_2 (1.2)	Na_2CO_3 (1.0)	H_2O	62
9	B_2pin_2 (1.2)	Cs_2CO_3 (1.2)	H_2O	85
10	B_2pin_2 (1.2)	Cs_2CO_3 (1.5)	H_2O	78
11	B_2pin_2 (1.0)	Cs_2CO_3 (1.2)	H_2O	65
12	B_2pin_2 (1.5)	Cs_2CO_3 (1.2)	H_2O	69
13	B_2pin_2 (1.2)	Cs_2CO_3 (1.2)	DMF/H_2O (V∶V=1∶1)	56
14	B_2pin_2 (1.2)	Cs_2CO_3 (1.2)	Dioxane/H_2O (V∶V=1∶1)	33
15	B_2pin_2 (1.2)	Cs_2CO_3 (1.2)	MeOH/H_2O (V∶V=1∶1)	68
16	B_2pin_2 (1.2)	Cs_2CO_3 (1.2)	D_2O	83 (91)
17[e]	B_2pin_2 (1.2)	Cs_2CO_3 (1.2)	D_2O/H_2O (n∶n=1∶1)	88 (54)
18[f]	B_2pin_2 (1.2)	Cs_2CO_3 (1.2)	D_2O	93 (95)
19[f,g]	B_2pin_2 (1.2)	Cs_2CO_3 (1.2)	D_2O	93 (93)
20[f,h]	B_2pin_2 (1.2)	Cs_2CO_3 (1.2)	D_2O	93 (96)
21[f,i,j]	B_2pin_2 (1.2)	Cs_2CO_3 (1.2)	D_2O	93 (98)

[a] Reaction conditions: **1a** (0.5 mmol), B_2pin_2, base, solvent (2.0 mL), 3 h, Ar. [b] GC-MS yield with biphenyl as internal standard; deuterated purity determined by ^1H NMR is shown in parentheses. [c] Yield＜5%. [d] Not detected. [e] D_2O (50 mmol), H_2O (50 mmol). [f] Purity of Cs_2CO_3 is 99.9%. [g] D_2O (1.0 mL). [h] D_2O (3 mL). [i] Using anhydrous B_2pin_2. [j] Isolated yield.

With the optimized reaction conditions in hand, the ketimines **1a**～**1p** derived from (*R*)-*tert*-butanesulfinamide and various ketones were investigated (Scheme 2). The substrates derived from cyclic ketones gave the desired *N*-*tert*-butanesulfinyl amines **2a**～**2e** in moderate to good yields. Increasing the carbon number in cyclic ketones, the yield gradually decreased, except for **2a**. The *N*-*tert*-butanesulfinyl imines from aliphatic ketones (**2f**～**2m**) proceeded smoothly under the optimized reaction condition to afford the desired product in moderate to good yields. In the case of *tert*-butanesulfinyl imines derived from symmetrical acetone or pentan-3-one (**1f**～**1g**), the corresponding target products could be obtained in 60% and 81% yield, respectively. The hindered ketones seemed to give higher diastereosective ratio, whereas, unhindered ketones gave the desired products in lower diastereosective ratio (**2h**～**2m**). For example, the target product (**2i**) derived from 3,3-dimethylbutan-2-one could be obtained in

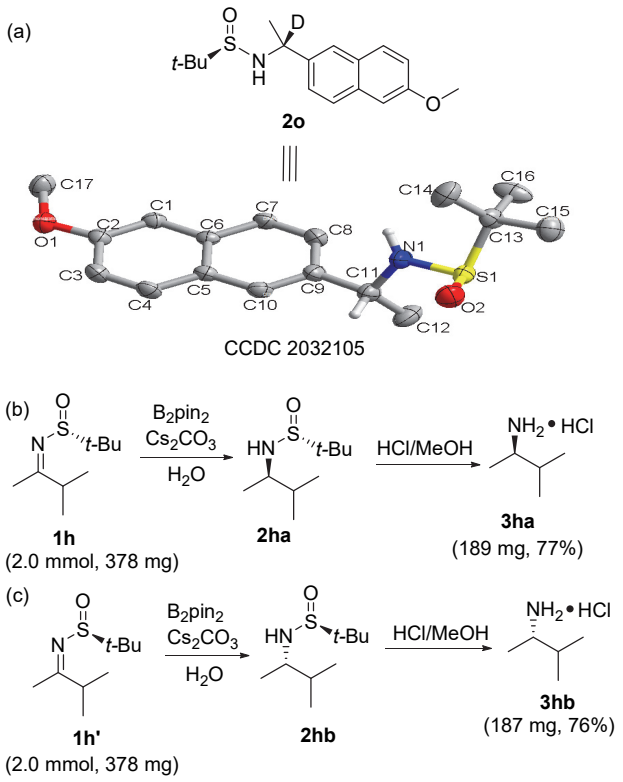
medium yield with high diastereosective ratio (97∶3). The imines **1j**～**1m** gave the target products in medium yields (40%～72%) with lower diastereosective ratio. The substrates derived from aromatic methyl ketones (**2n**～**2p**) gave the desired amines in lower yields.



Reaction conditions: **1** (0.5 mmol, 1.0 equiv.), B_2pin_2 (0.6 mmol, 1.2 equiv.), Cs_2CO_3 (0.6 mmol, 1.2 equiv.), D_2O (2.0 mL), Ar, r.t. Isolated yields. Deuterated purity determined by ^1H NMR is shown in parentheses. [a] 60 ℃ D_2O (2.0 mL), THF (0.4 mL).

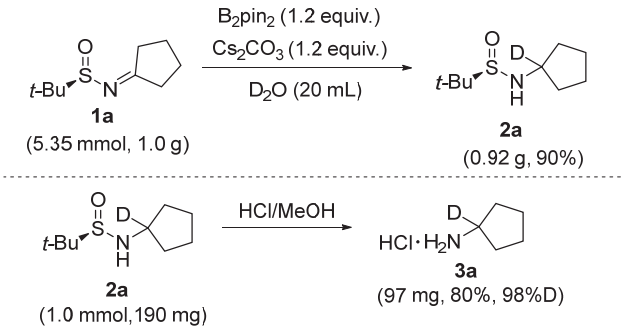
Scheme 2 Substrate scope

In order to determine the configuration of the main product, the single crystal of dominant product of **2o** was prepared. The X-ray diffraction analysis indicated that the deuteride reduction formed the product **2o** in *R*-configuration. To further confirm the absolute configuration of the products, the reduction amination reaction of **1h** and **1h'** in H_2O was conducted. The obtained *tert*-butanesulfinyl amines **2ha** and **2hb** could be easily hydrolyzed to give the chiral 3-methylbutan-2-amine hydrochlorides **3ha** and **3hb**, as shown in Scheme 3. The *R* configuration of **3ha** was confirmed by comparison of the optical rotations with that reported in the literature[19] {$[\alpha]_D^{30}$ +1.96 (*c* 0.46, MeOH)}. Whereas, **3hb** was confirmed to possess *S* configuration in accordance with the literature report[19] {$[\alpha]_D^{28}$ −1.50 (*c* 0.6, MeOH)}.



Scheme 3 Determination of configuration

To show the synthetic utility of the protocol, a gram scale synthesis was performed to give the product **2a** in 90% yield (Scheme 4). The transformation is scalable and practical since a gram scale reaction was equally efficient. Then the deprotection of **2a** was conducted to afford the product **3a** in 80% yield. It is a good choice for the synthesis of cyclopentan-1-*d*-amine **3a**, which is an important intermediate of deuterated palbociclib.[20]



Scheme 4 Gram-scale reaction and deprotection of **2a**

3 Conclusions

In conclusion, we have developed a transition metal-free deuterated reduction protocol of *N*-*tert*-butanesulfinyl ketimines with B_2pin_2. A series of deuterated secondary amines were obtained in reasonable yields with excellent deuterium purity by using D_2O as the deuterium source. Mild reaction conditions, operational simplicity, and easily

scaled up to gram scale are the considerable advantages of this methodology. Owing to the facile strategy and the use of D_2O as the deuterium source at room temperature, this method is a better alternative for the synthesis of deuterated secondary amines.

4 Experimental section

4.1 General information

All manipulations were performed in dried glass reaction tube equipped with a magnetic stir bar under argon atmosphere. Cesium carbonate was dried in muffle furnace at 300 ℃ for 3 h. B_2pin_2 was dried with phosphorus pentoxide in a vacuum at 50 ℃ for 12 h. Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. Flash column chromatography was performed using silica gel (60-Å pore size, 32～63 μm, standard grade). Thin-layer chromatography was performed using silica gel 60 GF254 plates. The transformation progress and mass spectra were indicated by GC-MS (Thermo Fisher Scientific ISQ). NMR spectra were obtained on Bruker AVANCE III systems using $CDCl_3$ or DMSO-d_6 as solvent, TMS as internal standard substance, at 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR, 128 MHz for ^{11}B NMR. The high resolution mass spectra were received via an Agilent Technologies 6540 UHD Accurate-mass Q-Tof LC/MS with ESI as ion source. Melting points were recorded by an XT4A microscopic apparatus. Optical rotations were measured with a WZZ-3A Automatic Polarimeter in MeOH.

4.2 General procedure for the reaction

4.2.1 Preparation of products

A dried glass reaction tube equipped with a magnetic stir bar was charged with B_2pin_2 (0.6 mmol, 1.2 equiv.) and Cs_2CO_3 (0.6 mmol, 1.2 equiv.). The vial vessel was evacuated and backfilled with argon three times. *N*-*tert*-Butanesulfinyl ketimines (0.5 mmol, 1.0 equiv.), D_2O (2 mL) were added through a needle. The reaction mixture was then stirred at room temperature and reaction progress was monitored by thin-layer chromatography (TLC). After the reaction was complete, the mixture was diluted with H_2O (100 mL) and ethyl acetate (100 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified via flash column chromatograph on silica gel to give the pure products.

(*R*)-*N*-(Cyclopentyl-1-d)-2-methylpropane-2-sulfinamide (**2a**): 88.3 mg, 93% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.73～3.67 (m, 0.02H), 3.02 (s, 1H), 1.97～1.77 (m, 2H), 1.66～1.39 (m, 6H), 1.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 56.1 (t, $J_{C\text{-}D}$=21.4 Hz), 55.1, 34.6, 33.2, 23.4, 23.2, 22.5; HRMS (ESI) calcd for $C_9H_{19}DNOS$ $[M+H]^+$: 191.1323, found 191.1321.

(*R*)-*N*-(Cyclobutyl-1-d)-2-methylpropane-2-sulfinamide (**2b**): 73.3 mg, 83% yield. White solid, mp: 60～62 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.90～3.74 (m, 0.03H), 3.34 (s, 1H), 2.33～2.23 (m, 2H), 1.99～1.86 (m, 2H), 1.75～1.57 (m, 2H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.2, 50.8 (t, $J_{C\text{-}D}$=21.9 Hz), 32.5, 31.6, 22.5, 15.0; HRMS (ESI) calcd for $C_8H_{17}DNOS$ $[M+H]^+$: 177.1166, found 177.1163.

(*R*)-*N*-(Cyclohexyl-1-d)-2-methylpropane-2-sulfinamide (**2c**): 83.0 mg, 81% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.16～3.09 (m, 0.04H), 2.97 (s, 1H), 1.91～1.88 (like d, 2H), 1.69～1.63 (m, 2H), 1.55～1.51 (m, 1H), 1.31～1.16 (m, 5H), 1.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.1, 53.7 (t, $J_{C\text{-}D}$=20.7 Hz), 35.1, 33.9, 25.5, 24.7, 24.5, 22.5; HRMS (ESI) calcd for $C_{10}H_{21}DNOS$ $[M+H]^+$: 205.1479, found 205.1481.

(*R*)-*N*-(cycloheptyl-1-d)-2-methylpropane-2-sulfinamide (**2d**): 72.5 mg, 67% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.44～3.36 (m, 0.01H), 2.96 (s, 1H), 2.03～1.91 (m, 2H), 1.67～1.38 (m, 10H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.9 (t, $J_{C\text{-}D}$=20.8 Hz), 55.2, 37.2, 35.6, 28.0, 27.9, 23.8, 23.5, 22.6; HRMS (ESI) calcd for $C_{11}H_{23}DNOS$ $[M+H]^+$: 219.1636, found 219.1634.

(*R*)-*N*-(Cyclooctyl-1-d)-2-methylpropane-2-sulfinamide (**2e**): 54.0 mg, 47% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.48～3.40 (m, 0.03H), 2.92 (s, 1H), 1.91～1.83 (m, 2H), 1.68～1.44 (m, 12H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.2, 54.9 (t, $J_{C\text{-}D}$=20.9 Hz), 34.1, 32.2, 27.4, 27.3, 25.2, 23.3, 23.1, 22.6; HRMS (ESI) calcd for $C_{12}H_{25}DNOS$ $[M+H]^+$: 233.1792, found 233.1791.

(*R*)-2-Methyl-*N*-(propan-2-yl-2-d)propane-2-sulfinamide (**2f**): 49.1 mg, 60% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.57～3.49 (m, 0.05H), 2.95 (s, 1H), 1.22 (s, 3H), 1.18 (s, 9H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.2, 46.8 (t, $J_{C\text{-}D}$=21.1 Hz), 24.7, 23.5, 22.5; HRMS (ESI) calcd for $C_7H_{17}DNOS$ $[M+H]^+$: 165.1166, found 165.1165.

(*R*)-2-Methyl-*N*-(pentan-3-yl-3-d)propane-2-sulfinamide (**2g**): 77.8 mg, 81% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.12～3.05 (m, 0.03H), 2.93 (s, 1H), 1.61～1.40 (m, 4H), 1.20 (s, 9H), 0.95～0.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 58.7 (t, $J_{C\text{-}D}$=20.9 Hz), 55.7, 28.4, 27.4, 22.7, 9.9, 9.7; HRMS (ESI) calcd for $C_9H_{21}DNOS$ $[M+H]^+$: 193.1479, found 193.1478.

(*R*)-2-Methyl-*N*-((R)-3-methylbutan-2-yl-2-d)propane-2-sulfinamide (**2h**): 89.5 mg, 93% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.30～3.23 (m, 0.08H), 3.10 (s, 1H), 1.82～1.71 (m, 1H), 1.20 (s, 9H), 1.09 (s, 3H), 0.97 (dd, J=5.8, 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.3, 55.2 (t, $J_{C\text{-}D}$=21.1 Hz), 33.9, 22.6, 18.7, 17.1, 16.7; HRMS (ESI) calcd for $C_9H_{21}DNOS$ $[M+H]^+$: 193.1479, found 193.1478.

(*R*)-*N*-((*R*)-3,3-Dimethylbutan-2-yl-2-d)-2-methylpropane-2-sulfinamide (**2i**): 61.8 mg, 60% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.23 (s, 1H), 3.13～3.10 (m, 0.06H), 1.21 (s, 9H), 1.13 (s, 3H), 0.92 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 58.5 (t, $J_{C\text{-}D}$=21.0 Hz), 55.4, 34.3, 26.1, 22.6, 15.8; HRMS (ESI) calcd for $C_{10}H_{23}DNOS$ $[M+H]^+$: 207.1636, found 207.1634.

(*R*)-2-Methyl-*N*-((*R*)-pentan-2-yl-2-d)propane-2-sulfinamide (**2j**): 68.8 mg, 72% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.38～3.32 (m, 0.02H), 2.85 (s, 1H), 1.52～1.30 (m, 4H), 1.26 (s, 3H), 1.20 (s, 9H), 0.91 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.6, 51.9 (t, $J_{C\text{-}D}$=20.9 Hz), 40.2, 23.1, 22.6, 19.0, 13.9; HRMS (ESI) calcd for $C_9H_{21}DNOS$ $[M+H]^+$: 193.1479, found 193.1478.

(*R*)-2-Methyl-*N*-((*R*)-4-methylpentan-2-yl-2-d)propane-2-sulfinamide (**2k**): 54.5 mg, 53% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.47～3.41 (m, 0.04H), 2.99 (s, 1H), 1.71～1.64 (m, 1H), 1.46～1.41 (m, 1H), 1.33～1.25 (m, 1H), 1.19 (s, 9H), 1.14 (s, 3H), 0.91 (dd, J=6.6, 8.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.2, 48.9 (t, $J_{C\text{-}D}$=20.9 Hz), 47.6, 24.8, 22.7, 22.5, 22.4, 21.8; HRMS (ESI) calcd for $C_{10}H_{23}DNOS$ $[M+H]^+$: 207.1636, found 207.1637.

(*R*)-*N*-((*R*)-Hexan-2-yl-2-d)-2-methylpropane-2-sulfinamide (**2l**): 73.1 mg, 71% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.36～3.28 (m, 0.03H), 2.84 (s, 1H), 1.50～1.27 (m, 6H), 1.24 (s, 3H), 1.19 (s, 9H), 0.88 (like t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.6, 52.1 (t, $J_{C\text{-}D}$=20.8 Hz), 37.7, 27.9, 23.1, 22.6, 22.5, 14.0; HRMS (ESI) calcd for $C_{10}H_{23}DNOS$ $[M+H]^+$: 207.1636, found 207.1635

(*R*)-2-Methyl-*N*-((R)-5-methylhexan-2-yl-2-d)propane-2-sulfinamide (**2m**): 43.4 mg, 40% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.35～3.29 (m, 0.02H), 2.86 (s, 1H), 1.55～1.37 (m, 3H), 1.25～1.23 (m, 5H), 1.21 (s, 9H), 0.88 (d, J=6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.6, 52.3 (t, $J_{C\text{-}D}$=21.0 Hz), 35.8, 34.8, 29.7, 27.9, 23.1, 22.6, 22.5; HRMS (ESI) calcd for $C_{11}H_{25}DNOS$ $[M+H]^+$: 221.1792, found 221.1793.

(*R*)-2-Methyl-*N*-((*R*)-1-phenylethyl-1-d)propane-2-sulfinamide (**2n**): 42.9 mg, 38% yield. Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.35～7.29 (m, 4H), 7.24～7.20 (m, 1H), 5.32 (s, 1H), 4.40～4.37 (m, 0.02H), 1.44 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 144.7, 128.1, 126.8, 126.6, 54.9, 54.4 (t, $J_{C\text{-}D}$=21.1 Hz), 24.8, 22.6; HRMS (ESI) calcd for $C_{17}H_{21}DNOS$ $[M+H]^+$: 227.1323, found 227.1321

(*R*)-*N*-((*R*)-1-(6-Methoxynaphthalen-2-yl)ethyl-1-d)-2-methylpropane-2-sulfinamide (**2o**): 42.8 mg, 28% yield. White solid, m.p. 52～54 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74～7.71 (m, 3H), 7.44 (dd, J=1.8, 8.5 Hz, 1H), 7.15 (dd, J=2.6, 8.9 Hz, 1H), 7.12 (d, J=2.4 Hz, 1H), 4.72～4.67 (m, 0.02H), 3.91 (s, 3H), 3.47 (s, 1H), 1.58 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.9, 139.0, 134.2, 129.4, 128.8, 127.5, 125.3, 125.2, 119.1, 105.7, 55.5, 55.3, 53.5 (t, $J_{C\text{-}D}$=22.1 Hz), 22.7, 22.5; HRMS (ESI) calcd for $C_{17}H_{23}DNO_2S$ $[M+H]^+$: 307.1585, found 307.1589.

(*R*)-2-Methyl-*N*-((*R*)-1-(thiophen-2-yl)ethyl-1-d)propane-2-sulfinamide (**2p**): 31.3 mg, 27% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22 (dd, J=1.2, 5.1 Hz, 1H), 7.03 (dd, J=1.2, 3.5 Hz, 1H), 6.95 (dd, J=3.5, 5.1 Hz, 1H), 4.87～4.81 (m, 0.03H), 3.50 (s, 1H), 1.59 (s, 3H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.9, 126.8, 124.7, 124.5, 55.7, 49.8 (t, $J_{C\text{-}D}$=21.2 Hz), 23.7, 22.6; HRMS (ESI) calcd for $C_{10}H_{17}DNOS_2$ $[M+H]^+$: 233.0887, found 233.0888.

4.2.2 Deprotection process

The sulfinyl protected deuteride secondary amines (**2a**, **2ha**, **2hb**) were hydrolyzed to give the target products according to reported procedure.[21] It is noticed that **2ha** and **2hb** were got by crude separation on silica gel.

(*R*)-3-Methylbutan-2-amine hydrochloride (**3ha**)[18]: 189 mg, 77% yield. White solid, m.p. 205～207 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.08 (s, 3H), 2.96～2.90 (m, 1H), 1.85～1.77 (m, 1H), 1.08 (d, J=6.7 Hz, 3H), 0.85 (dd, J=6.9, 10.3 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 51.6, 30.7, 18.8, 16.9, 14.5; $[\alpha]_D^{30}$ = +1.96 (*c* 0.46, MeOH); GC-MS (EI, *m*/*z*): $[M]^+$ 87.1.

(*S*)-3-Methylbutan-2-amine hydrochloride (**3hb**)[18]: 187 mg, 76% yield. White solid, mp: 206～208 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.09 (s, 3H), 2.86～2.85 (m, 1H), 1.81～1.73 (m, 1H), 1.01 (d, J=6.7 Hz, 3H), 0.79 (dd, J=6.9, 10.0 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 51.7, 30.7, 18.9, 16.9, 14.5; $[\alpha]_D^{28}$ = −1.50 (*c* 0.6, MeOH); GC-MS (EI, *m*/*z*): $[M]^+$ 87.1

Cyclopentan-*1*-*d*-amine hydrochloride (**3a**)[19]: 97 mg, 80% yield. White solid, m.p. 203～205 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.36 (s, 3H), 3.67～3.64 (m, 0.02H), 2.13～2.07 (m, 2H), 1.98～1.90 (m, 2H), 1.86～1.72 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 50.8 (t, $J_{C\text{-}D}$=22.3 Hz), 30.5, 23.4; GC-MS (EI, *m*/*z*): $[M]^+$ 86.1.

Supporting Information Optimization of the reaction conditions, proposed mechanism, X-ray crystallographic data of **2o**, copies of ^{1}H NMR, ^{13}C NMR of the products. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

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