EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201801123

Link to VoR: http://dx.doi.org/10.1002/ejoc.201801123

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10.1002/ejoc.201801123

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Pd/Zn(OTf)$_2$ Co-catalyzed Asymmetric Hydrogenation of Imines under Normal Pressure of Hydrogen

Yang Gao,[a] Fan Yang,[a] Dongdong Pu,[a] Ronibala Devi Laishram,*[a] Ruifeng Fan,[b] Guoli Shen,[a] Xuexin Zhang,[a] Jingchao Chen,[a] and Baomin Fan*[a,b]

Abstract: Efficient method for the asymmetric hydrogenation of cyclic and acyclic *N*-sulfonylimines co-catalyzed by Pd/Zn(OTf)$_2$ using hydrogen gas under ambient pressure is developed. The methodology offers an easy access to generate chiral sulfonylamines in good yields and excellent enantioselectivities.

Introduction

Chiral amines are valuable and prevalent substructures with important biological, agrochemical and pharmacological properties.[1] Thus, the development of expeditious methodologies for the preparation of chiral amines in high enantiopurity is of great significance and highly desirable. Amination of alcohols by the hydrogen auto transfer method has long been recognized as a highly economical and greener method.[2] Since then much progress has been made in the last two decades in search for the development of efficient methodology. Among the most explored methods,[3-5] asymmetric hydrogenation (AH) of imines using hydrogen is the most efficient and elegant method. However, the AH of imines still remains a major challenge due to the poor reactivity of imines towards hydrogenation and also difficulties in obtaining excellent results as the *E* and *Z* isomers of acyclic imines gave different enantioselectivity. In spite of these problems, much progress has been made in asymmetric hydrogenation of imines leading to the discovery of various catalytic systems.[6-11] To the best of our knowledge, the asymmetric hydrogenation of linear *N*-tosylimines has rarely been explored despite continuing progress. Until Zhang et al. reported, the asymmetric hydrogenation of linear *N*-tosylimines was not satisfactory.[12] Then in 2007, Zhou et al. documented Pd/bisphosphines complexes catalyzed highly effective asymmetric hydrogenation under 600 psi of H_2.[13] Very recently Zhou et al. also reported the Pd-catalyzed highly enantioselective hydrogenation of a series of linear and cyclic *N*-tosylimines with the phosphonates group in good to excellent enantioselectivities.[14] Most of these methodologies used high pressure to activate the reaction. However, in our methodology, we used Pd/Zn co-catalytic system under ambient pressure of H_2 to activate the reaction.

Our group has successfully employed the co-catalytic system of Pd/Zn in asymmetric transfer hydrogenation (ATH) of heterobicyclic alkenes using primary and secondary alcohol as hydrogen source[15] and very recently this same catalytic system was successfully utilized in the ATH of *N*-sulfonylimines with alcohol as the hydrogen source.[16] In both the reactions, we hypothesized the generation of hydride intermediate from alcohol by the Pd catalyst for hydrogenation. Therefore, we anticipated this catalytic system also could lead to being an effective catalytic system for AH of *N*-sulfonylimines. Herein, we describe our attempt towards a different approach involving the combination of Lewis acid with Pd(OAc)$_2$/ (*R*)-MeO-BIPHEP complex for the AH of various *N*-sulfonylimines with molecular hydrogen under 1 bar to form the corresponding amines with high reactivity and enantiopurity.

Results and Discussion

We initiated our investigations of AH using *N*-sulfonylimine (**1a**) as the model substrate under 1 bar H_2 in DCE employing Pd(OAc)$_2$, Zn(OTf)$_2$ and protonic acid CF_3SO_2H as a catalytic system (Table **1**). First, we studied the reaction of **1a** using chiral diphosphine ligand (*R*)-SEGPHOS which has found to be a good ligand giving high yield, 90% and *ee*, 95%. To enhance the reactivity we were also tested other chiral diphosphorus ligands like (*R*)-Cl-MeO-BIPHEP, (*R*)-DTB-MeO-BIPHEP, (*R*)-BINAP, (*R*)-BDPP, (*R*)-P-PHOS, (*R*)-SYNPHOS but no appreciable improvement was observed. Notably, (*R*)-MeO-BIPHEP gave the best result with the highest yield 94% and excellent *ee* 97%. While (*R*)-DIOP gave out of the racemic product in poor yield, and monophosporus ligand like (*R*)-MONOPHOS gave no product even after 48 h. We then turned our attention to examine the effect of Lewis acids, additives, solvent, and reaction temperature on reactivity and enantioselectivity (Table **2**). Used of the additive has no influence on the reactivity and enantioselectivity of the reaction since without the use of it also gave the products as high as 90% yield and *ee* 99% (Table **2**, entry **5**). We then studied the influence of Lewis acids on enantioselectivities and reactivities of the reaction. However, Lewis acids like $ZnCl_2$, Fe(OTf)$_3$, CuOTf, Cu(OTf)$_2$, AgOTf, proceeded with the low conversion of the product albeit *ee* of the reaction were relatively high (Table **2**, entries **6**,**11**-**14**) and the result were not impressive for Zn(OAc)$_2$, Yb(OTf)$_3$, Sc(OTf)$_3$, $FeBr_2$ (Table **2**, entries **7**-**9, 15**). But, Fe(OTf)$_2$ gave a trace amount even after the 48 h.

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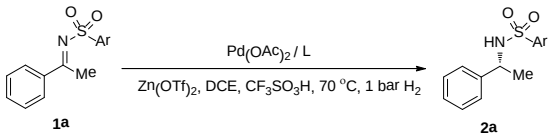
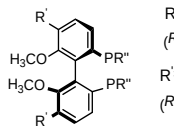
Table 1. Screening of ligands for AH reaction of **1a**

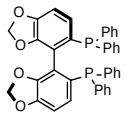




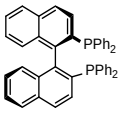
R'=Cl, R''=phenyl
(*R*)-Cl-MeO-BIPHEP,**12 h, 79% yield, 97% *ee***

R'=H, R''=biphenyl
(*R*)-MeO-BIPHEP, **15 h, 94% yield, 97% *ee***

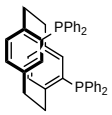
R'=H, R''=1,3-di-*tert*-butyl-2-methoxyphenyl
(*R*)-DTBM-MeO-BIPHEP,**13 h, 85% yield, 90% *ee***



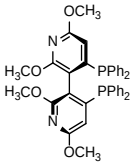
(*R*)-SEGPHOS
12 h, 90% yield, 95% *ee*



(*R*)-BINAP
17 h, 79% yield, 94% *ee*

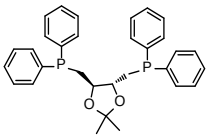


(*R*)-PHANEPHOS
21 h, 15% yield, 45% *ee*

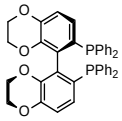


(*R*)-P-Phos
12 h, 88% yield, 94% *ee*

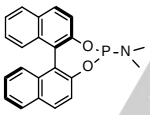
(*R*)-BDPP
21 h, 82% yield, 65% *ee*



(*R*)-DIOP
21 h, 21% yield, 0% *ee*



(*R*)-SYNPHOS
11 h, 77% yield, 97% *ee*



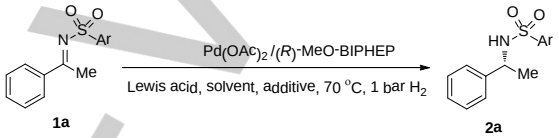
(*R*)-Monophos
48 h, trace

Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (5.0 mol%), L (6.0 mmol%), $Zn(OTf)_2$ (10.0 mmol%), CF_3SO_2H (5.0 mmol%) in DCE (2.0 ml) at 70 °C, H_2 1 bar

Interestingly, $Zn(OTf)_2$ was found to be the most favorable activator with respect to enantioselectivity and turnover (Table **2**, entry **5**). We also examined in absence of Lewis acid, but it does not give product even after 48 h (Table **2**, entry **16**). It implied that Lewis acid played a crucial role in activating the reaction. Next, the solvents effects were extensively studied and found that it also played an important role in promoting the hydrogenation. Other than DCE, solvents like THF, toluene, and 1,4-dioxane were also tested but failed to promote the conversion of the products. Gratifyingly, DCE was proved to be the best solvent with excellent *ee* and good yield at 70 ºC (Table **2**, entry **5**). To further improved the reaction efficiency we studied the effect of reaction temperature, instead of increasing the reactivity of the reaction it leads to the lower conversion of products when the temperature was either increased to 80 ºC or decreased to 60 ºC.

Under optimized conditions, a variety of substituted *N*-sulfonylimines were subjected to investigate the AH and summarized in Table **3**. It was found that the reaction has a wide range of functional group tolerance giving excellent enantioselectivities regardless of the substituents being electron-donating or electron-withdrawing but the position of the substituent has effects on the reactivities. Electron-donating or electron-withdrawing substituents like methyl, methoxy, fluoro, chloro, bromo in *para*-position of aryl imine gave comparatively excellent enantioselectivities (**2b**-**2h**) but the yield was highest when the methyl substituent was in *para*-position 91% (**2b**). Interestingly, unsubstituted aryl imine gave the highest yield 90% and *ee* 99% (**2a**), while naphthyl substituted aryl imine gave the same *ee* with reduced yield (**2i**).

Table 2: Evaluation of reaction conditions[a]



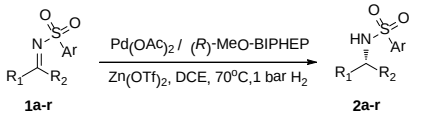
Entry	Lewis Acid	Additive	Solvent	Time (h)	Yield (%)[b]	*ee* (%)[c]
1	$Zn(OTf)_2$	CF_3SO_2H	DCE	15	94	97
2	$Zn(OTf)_2$	CF_3COOH	DCE	11	88	97
3	$Zn(OTf)_2$	Benzoic acid	DCE	11	93	97
4	$Zn(OTf)_2$	L-CSA	DCE	11	77	98
5	$Zn(OTf)_2$	/	DCE	11	90	99
6	$ZnCl_2$	/	DCE	33	47	95
7	$Zn(OAc)_2$	/	DCE	48	trace	/
8	$Yb(OTf)_2$	/	DCE	48	trace	/
9	$Sc(OTf)_3$	/	DCE	12	23	3
10	$Fe(OTf)_2$	/	DCE	48	trace	/
11	$Fe(OTf)_3$	/	DCE	20	57	97
12	CuOTf	/	DCE	20	80	98
13	$Cu(OTf)_2$	/	DCE	12	67	96
14	AgOTf	/	DCE	12	60	85
15	$FeBr_2$	/	DCE	48	trace	/
16	/	/	DCE	48	NR	/
17	$Zn(OTf)_2$	/	THF	48	23	95
18	$Zn(OTf)_2$	/	Toluene	48	38	93
19	$Zn(OTf)_2$	/	1,4-Dioxane	48	17	91
20	$Zn(OTf)_2$	/	CH_3OH	12	25	95
22[d]	$Zn(OTf)_2$	/	DCE	36	85	97
23[e]	$Zn(OTf)_2$	/	DCE	26	77	95

Reaction conditions[a]: **1a** (0.2 mmol), $Pd(OAc)_2$ (5.0 mmol%), (*R*)-MeO-BIPHEP (6.0 mmol%), Lewis acid (10.0 mmol%), additive (5 mmol%) in solvent (2 mL) at 70 ºC, H_2 1 bar. [b]Isolated yield of the products. [c]Determined by HPLC with a Chiralcel OD-H column. [d]Reaction carried out at 60 ºC. [e]Reaction carried out at 80 ºC. NR-no reaction.

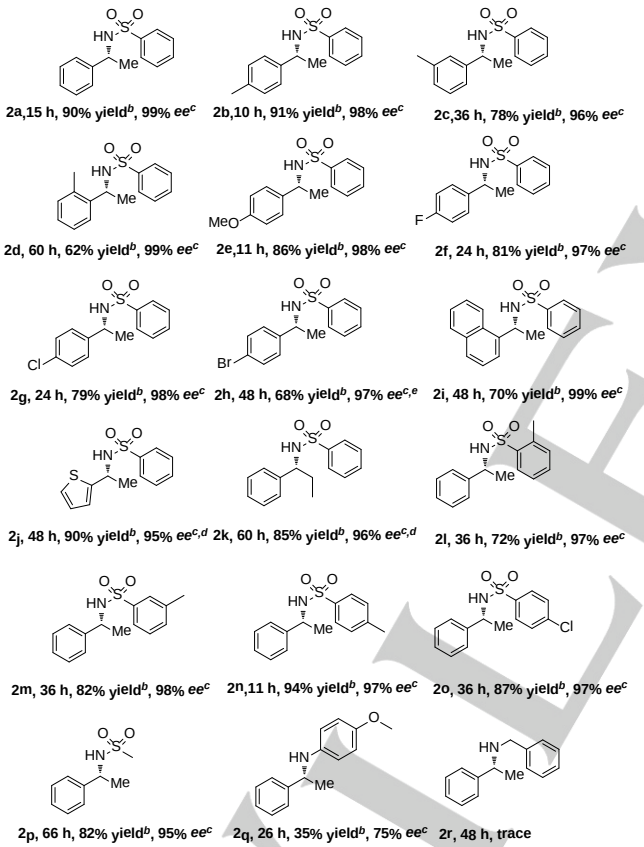
Nevertheless, imine bearing a thiophenyl group gave moderate yield 90% with good *ee* 95% (**2j**). The

enantioselectivity was lowest when the methyl group was replaced by ethyl group (**2k**). In addition, imines with substitution in the sulfonyl group were also subjected to AH, fortunately; it gave good yields and enantioselectivities (**2l**-**2p**). Electronic effects of the substituents on the aryl of the sulfonyl group have no significant effect on the yields and *ee*s of the reactions. Encouraged with the generality of these results we tried with other non-activated imines but the results were not appreciable (**2q, 2r**). The absolute configurations of **2a**-**2p** were established as ''*R*'' by comparing the HPLC spectra with that reported in the literature.[16]

Table 3: Asymmetric hydrogenation of acyclic *N*-sulfonylimines[a]



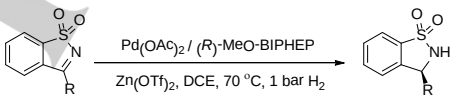
1a-r **2a-r**



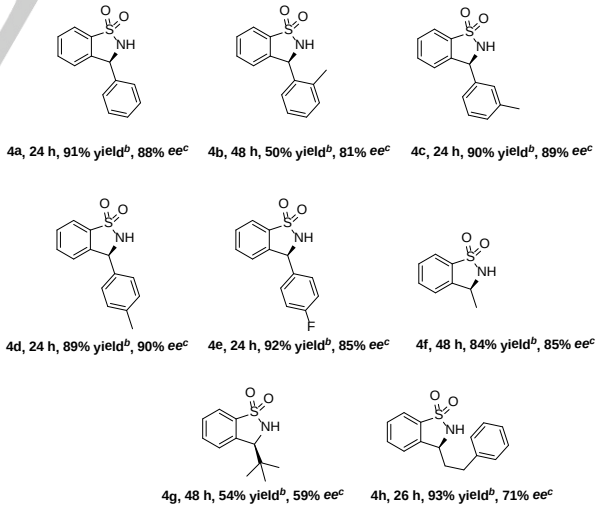
Reaction conditions[a]: **1a-r** (0.2 mmol), $Pd(OAc)_2$ (5.0 mmol%), (*R*)-MeO-BIPHEP (6.0 mmol%), $Zn(OTf)_2$ (10.0 mmol%), in DCE (2 mL) at 70 ºC, H_2 1 bar. [b]Isolated yield of the products. [c]Determined by HPLC. [d]Used protonic acid, CF_3SO_2H (5.0 mmol%). [e]Used 4Å MS (50.0 mg).

Furthermore, in order to demonstrate the versatility of our methodology, a series of cyclic imines were subjected to AH to offered sulfonamides. The cyclic sulfonamides, sultams are important organic synthetic intermediates and privileged substructural units of biological and pharmaceutical products.[17] Pleasingly, our methodology fits well for those cyclic sulfonylimines **3**, and they were successfully converted to the corresponding cyclic sulfonamides, sultams **4** with good to excellent yield and *ee* (Table **4**). It is noteworthy that the electronic effects of the substituents on the aromatic ring have little influence on the *ee*s and the yields of the reaction. With, the fluro substituent on the phenyl ring gave the highest yield 92% with comparable *ee* 85% (**4e**). However, the positions of the substituents have great influenced on the *ee*s and yields of the reaction. Among the *ortho*-, *meta*-, and the *para*-substituent substrates, the *ortho*-methyl substituent on the phenyl ring gave the lowest *ee* and yield (**4b**) while the *para*-methyl substituent gave the highest *ee* 90% with 89 % yield (**4d**). Ethyl phenyl substituted imine also gave good yield 93% and moderate *ee* 71% (**4h**). Simple alkyl substituted imine gave moderate yield and *ee* (**4f**). But, *ee* and yield of the neo butyl substituent was not appreciable. The absolute configurations of **4a**-**4h** were established as ''*S*'' by comparing the HPLC spectra with that reported in the literature.[18] The plausible mechanism of the catalytic cycle of the AH is shown in Scheme 1.

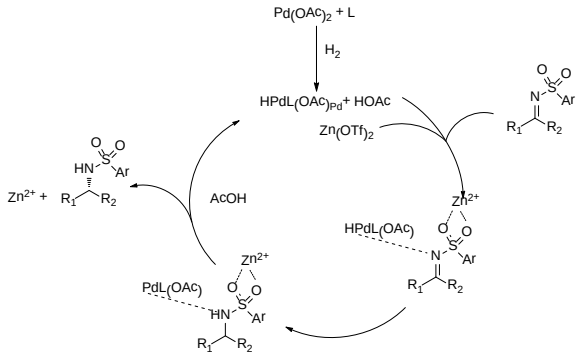
Table 4: Asymmetric hydrogenation of cyclic *N*-sulfonylimines[a]



3a-h **4a-h**



Reaction conditions[a]: **3a-h** (0.2 mmol), (*R*)-MeO-BIPHEP (6.0 mmol%), $Pd(OAc)_2$ (5.0 mmol%), $Zn(OTf)_2$ (10.0 mmol %), in DCE (2 mL) at 70 ºC, H_2 1 bar. [b]Isolated yield of the products. [c]Determined by HPLC.



Scheme 1. Proposed mechanism for Pd(II)/Zn-catalyzed asymmetric hydrogenation.

Conclusions

In summary, we have developed an efficient method for the synthesis of chiral amine and chiral sultams employing $Pd/Zn(OTf)_2$ co-catalytic system *via* the asymmetric hydrogenation of a wide range of acyclic and cyclic *N*-sulfonylimines under ambient pressure of hydrogen. The methodology offered good to excellent yields and enantioselectivities.

Experimental Section

General information:

The reactions and manipulations were performed under an atmosphere of argon by using standard Schlenk techniques and Dry box (Mikrouna, Supper 1220/750). Anhydrous toluene was distilled from sodium benzophenone ketyl prior to use. Anhydrous DCE was distilled from calcium hydride and stored under argon. ^{1}H NMR spectra were recorded on Bruker-Avance 400 MHz spectrometer. $CDCl_3$ was used as solvent. Chemical shifts (δ) were reported in ppm with tetramethylsilane as internal standard, and *J* values were given in Hz. The enantioselective excesses were determined by Agilent 1260 Series HPLC using Daicel AD-H、AS-H、OJ-H and OD-H chiral columns eluted with a mixture of isopropyl alcohol and hexane. Column chromatography was performed with silica gel (200-300 mesh) with petroleum ether and ethyl acetate as eluents.

Typical procedure for the asymmetric hydrogenation reaction of *N*-tosylimine:

$Pd(OAc)_2$ (2.3 mg, 0.01 mmol), (*R*)-MeO-BIPHEP (6.9 mg, 0.012 mmol) and 1.0 mL DCE were added to a Schlenk tube under argon atmosphere. The resulting solution was stirred at room temperature for 30 min, then $Zn(OTf)_2$ (7.3 mg, 0.02 mmol) was added and stirred for additional 10 min, then DCE (1.0 mL) was added followed by the addition of *N*-tosylimine **1a** (51.8 mg, 0.2 mmol). The whole mixture was stirred at 70 °C under H_2 (1 bar) atmosphere with TLC monitoring until the complete consumption of **1a**. The residue was purified by chromatography on a silica gel column to afford the desired product **2a** (47 mg, 90% yield).

(*R*)-*N*-(1-phenylethyl)benzenesulfonamide (2a)

White solid, 90% yield, 99% *ee*. Mp 92-95 °C. $[\alpha]_D^{20}$ = +84 (c = 0.3, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.69 (m, 2H), 7.50–7.43 (m, 1H), 7.36 (dd, *J* = 10.9, 4.5 Hz, 2H), 7.20–7.12 (m, 3H), 7.10–7.05 (m, 2H), 5.42 (d, *J* = 7.2 Hz, 1H), 4.53–4.44 (m, 1H), 1.42 (d, *J* = 6.9 Hz, 3H). The *ee* of **2a** was determined by HPLC analysisusing Daicel Chiralcel OJ-H columns (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH = 70/30, 1.0 mL/min, 240 nm; t_{minor} = 13.3 min, t_{major} = 20.8 min.

(*R*)-*N*-(1-(*p*-tolyl)ethyl)benzenesulfonamide (2b)

White solid, 91% yield, 98% ee. Mp 133-135 °C. $[\alpha]_D^{20}$ = +113.1 (c = 0.54, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.62 (m, 2H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 2H), 6.90 (s, 4H), 5.03 (s, 1H), 4.37 (t, *J* = 6.9 Hz, 1H), 2.19 (s, 3H), 1.34 (d, *J* = 6.9 Hz, 3H). The *ee* of **2b** was determined by HPLC analysis using Daicel Chiralcel OD-H column (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH = 85/15, 0.5 mL/min, 240 nm; t_{major} = 16.7 min, t_{minor} = 19.9 min.

(*R*)-*N*-(1-(*m*-tolyl)ethyl)benzenesulfonamide (2c)

Colorless oil, 78% yield, 96% ee. $[\alpha]_D^{20}$ = +4.1 (c = 0.16, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.61 (m, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.27 (t, *J* = 7.7 Hz, 2H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.84 (dd, *J* = 19.6, 7.6 Hz, 2H), 6.75 (s, 1H), 5.37 (d, *J* = 7.2 Hz, 1H), 4.42–4.31 (m, 1H), 2.10 (s, 3H), 1.33 (d, *J* = 6.9 Hz, 3H). The ee of **2c** was determined by HPLC analysis using Daicel Chiralcel OD-H column (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH = 80/20, 0.5 mL/min, 240 nm; t_{major} = 12.6 min, t_{minor} = 14.7 min.

(*R*)-*N*-(1-(*o*-tolyl)ethyl)benzenesulfonamide (2d)

White solid, 62% yield, 99% *ee*. Mp 101-104 °C. $[\alpha]_D^{20}$ = +39.3 (c = 0.6, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.66 (m, 2H), 7.44 (d, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.09 (d, *J* = 7.3 Hz, 1H), 7.07–6.96 (m, 3H), 5.29 (d, *J* = 6.8 Hz, 1H), 4.76 (t, *J* = 6.8 Hz, 1H), 2.19 (s, 3H), 1.39 (d, *J* = 6.8 Hz, 3H). The *ee* of **2d** was determined by HPLC analysis using Daicel Chiralcel OJ-H column (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH = 70/30, 1.0 mL/min, 240 nm; t_{minor} = 8.4 min, t_{major} = 13.1 min.

(*R*)-*N*-(1-(4-methoxyphenyl)ethyl)benzenesulfonamide (2e)

White solid, 86% yield, 98% *ee*. Mp 95-97 °C. $[\alpha]_D^{20}$ = +88.7 (c = 0.68, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dt, *J* = 8.6, 1.7 Hz, 2H), 7.48–7.35 (m, 1H), 7.31 (dt, *J* = 7.4, 1.7 Hz, 2H), 7.02–6.82 (m, 2H), 6.75–6.48 (m, 2H), 5.19 (d, *J* = 6.9 Hz, 1H), 4.36 (m, 1H), 3.66 (s, 3H), 1.33 (d, *J* = 6.9 Hz, 4H). The *ee* of **2e** was determined by HPLC analysis using Daicel Chiralcel OD-H column (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH = 90/10, 0.8 mL/min, 240 nm; t_{major} = 21.3 min, t_{minor} = 25.0 min.

(*R*)-*N*-(1-(4-fluorophenyl)ethyl)benzenesulfonamide (2f)

White solid, 81% yield, 97% *ee*. Mp 136-138 °C. $[\alpha]_D^{20}$ = +62.3 (c = 0.52, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dt, *J* = 8.6, 1.7 Hz, 2H), 7.52–7.45 (m, 1H), 7.38 (dt, *J* = 7.4, 1.7 Hz, 2H), 7.09–7.01 (m, 2H), 6.86–6.79 (m, 2H), 5.46 (d, *J* = 7.1 Hz, 1H), 4.48 (t, *J* = 7.0 Hz, 1H), 1.39 (d, *J* = 6.9 Hz, 3H). The *ee* of **2f** was determined by HPLC analysis using Daicel Chiralcel OD-H column (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH = 80/20, 0.5 mL/min, 240 nm; t_{major} = 14.5 min, t_{minor} = 17.3 min.

(*R*)-*N*-(1-(4-chlorophenyl)ethyl)benzenesulfonamide (2g)

White solid, 79% yield, 98% *ee*. Mp 147-150 °C. $[\alpha]_D^{20}$ = +79.8 (c = 0.94, CH_2Cl_2).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.5 Hz, 2H), 7.53 (s, 1H), 7.41 (d, *J* = 7.8 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 5.30 (s, 1H), 4.49 (s, 1H), 1.41 (d, *J* = 6.9 Hz, 3H). The *ee* of **2g** was

determined by HPLC analysis using Daicel Chiralcel OJ-H column (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH = 80/20, 0.5 mL/min, 240 nm; t_{major} = 14.9 min, t_{minor} = 17.5 min.

(*R*)-*N*-(1-(4-bromophenyl)ethyl)benzenesulfonamide (2h)

White solid, 68% yield, 97% *ee*. Mp 151-154 °C. $[\alpha]_D^{20}$ = +43.5 (c = 0.2, CH_2Cl_2).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.58 (m, 2H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.31 (s, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.22 (d, *J* = 7.0 Hz, 1H), 4.43–4.33 (m, 1H), 1.31 (d, *J* = 6.9 Hz, 3H). The *ee* of **2h** was determined by HPLC analysis using Daicel Chiralcel AS-H column (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH = 70/30, 1.0 mL/min, 240 nm; t_{major} = 13.8 min, t_{minor} = 20.1 min.

(*R*)-*N*-(1-(naphthalen-1-yl)ethyl)benzenesulfonamide (2i)

White solid, 70% yield, 99% *ee*. Mp 161-163 °C. $[\alpha]_D^{20}$ = -2.5 (c = 0.58, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 5.4, 4.3 Hz, 1H), 7.78 (dd, *J* = 6.8, 2.7 Hz, 1H), 7.71–7.60 (m, 3H), 7.49–7.40 (m, 2H), 7.36 (dd, *J* = 14.9, 7.4 Hz, 2H), 7.24 (dt, *J* = 12.9, 6.5 Hz, 3H), 5.56 (d, *J* = 6.9 Hz, 1H), 5.38–5.27 (m, 1H), 1.57 (d, *J* = 6.8 Hz, 3H). The *ee* of **2i** was determined by HPLC analysis using Daicel Chiralcel OD-H column (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH = 80/20, 0.5 mL/min, 240 nm; t_{major} = 17.7 min, t_{minor} = 23.8 min.

(*R*)-*N*-(1-(thiophen-2-yl)ethyl)benzenesulfonamide (2j)

White solid, 90% yield, 95% *ee*. Mp 92-95 °C. $[\alpha]_D^{20}$ = +49.0 (c = 0.2, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.4 Hz, 2H), 7.55 (s, 1H), 7.47 (d, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 5.1 Hz, 1H), 6.88–6.72 (m, 2H), 5.35 (d, *J* = 7.1 Hz, 1H), 4.79 (s, 1H), 1.55 (d, *J* = 6.8 Hz, 3H). The *ee* of **2j** was determined by HPLC analysis using Daicel Chiralcel OD-H column (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH = 90/10, 1.0 mL/min, 240 nm; t_{major} = 12.7 min, t_{minor} = 14.6 min.

(*R*)-*N*-(1-phenylpropyl)benzenesulfonamide (2k)

White solid, 85% yield, 96% *ee*. Mp 117-120 °C. $[\alpha]_D^{20}$ = +62.9 (c = 0.88, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.55 (m, 2H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.21 (dd, *J* = 15.0, 7.5 Hz, 2H), 7.04 (dd, *J* = 4.2, 2.3 Hz, 3H), 6.92 (dd, *J* = 6.6, 2.9 Hz, 2H), 5.32 (d, *J* = 7.6 Hz, 1H), 4.14 (q, *J* = 7.4 Hz, 1H), 1.74 (dd, *J* = 14.1, 7.0 Hz, 1H), 1.68–1.60 (m, 1H), 0.72 (t, *J* = 7.4 Hz, 3H). The *ee* of **2k** was determined by HPLC analysis using Daicel Chiralcel AD-H column (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH 95/5, 0.5 mL/min, 240 nm; t_{minor} = 51.6 min, t_{major} = 54.8 min.

(*R*)-2-methyl-*N*-(1-phenylethyl)benzenesulfonamide (2l)

White solid, 72% yield, 95% *ee*. Mp 87-90 °C. $[\alpha]_D^{20}$ = +61.2 (c = 0.76, CH_2Cl_2.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.8 Hz, 1H), 7.37 (s, 1H), 7.17 (dd, *J* = 14.1, 4.9 Hz, 5H), 7.09–6.99 (m, 2H), 5.13 (s, 1H), 4.43 (s, 1H), 2.52 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H). The *ee* of **2l** was determined by HPLC analysis using Daicel Chiralcel OJ-H column (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH = 80/20, 0.5 mL/min, 240 nm; t_{minor} = 15.2 min, t_{major} = 26.6 min.

(*R*)-3-methyl-*N*-(1-phenylethyl)benzenesulfonamide (2m)

White solid, 82% yield, 98% *ee*. Mp 145-147 °C. $[\alpha]_D^{20}$ = +75.0 (c = 0.58, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.54 (m, 1H), 7.50 (s, 1H), 7.28 (dd, *J* = 3.9, 1.6 Hz, 2H), 7.24–7.15 (m, 3H), 7.14–7.07 (m, 2H), 5.25 (d, *J* = 7.1 Hz, 1H), 4.51 (s, 1H), 2.32 (s, 3H), 1.46 (d, *J* = 6.9 Hz, 3H). The *ee* of **2n** was determined by HPLC analysis using Daicel Chiralcel OD-H column (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH = 90/10, 1.0 mL/min, 240 nm; t_{major} = 10.9 min, t_{minor} = 12.3 min.

(*R*)-4-methyl-*N*-(1-phenylethyl)benzenesulfonamide (2n)

White solid, 94% yield, 97% *ee*. Mp 99-102 °C. $[\alpha]_D^{20}$ = +68.5 (c = 0.26, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.16 (dd, *J* = 4.8, 3.1 Hz, 5H), 7.10 (dt, *J* = 5.1, 3.9 Hz, 2H), 5.23 (d, *J* = 7.1 Hz, 1H), 4.53–4.38 (m, 1H), 2.37 (s, 3H), 1.41 (d, *J* = 6.9 Hz, 3H). The *ee* of **2m** was determined by HPLC analysis using Daicel Chiralcel OJ-H column (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH = 70/30, 1.0 mL/min, 240 nm; t_{minor} = 12.6 min, t_{major} = 18.9 min.

(*R*)-4-chloro-*N*-(1-phenylethyl)benzenesulfonamide (2o)

White solid, 87% yield, 97% *ee*. Mp 104-105 °C. $[\alpha]_D^{20}$ = +57.4 (c = 0.92, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.56 (m, 2H), 7.33–7.26 (m, 2H), 7.21–7.13 (m, 3H), 7.10–7.03 (m, 2H), 5.48 (d, *J* = 7.2 Hz, 1H), 4.58–4.42 (m, 1H), 1.43 (d, *J* = 6.9 Hz, 3H). The *ee* of **2o** was determined by HPLC analysis using Daicel Chiralcel OJ-H column (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH = 70/30, 1.0 mL/min, 240 nm; t_{minor} = 8.8 min, t_{major} = 14.6 min.

(*R*)-*N*-(1-phenylethyl)methanesulfonamide (2p)

Colorless oil, 82% yield, 97% *ee*. $[\alpha]_D^{20}$ = +56.2 (c = 0.24, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.30 (m, 1H), 7.29 (t, *J* = 2.7 Hz, 2H), 7.27–7.18 (m, 2H), 4.97 (d, *J* = 6.4 Hz, 1H), 4.58 (s, 1H), 2.53 (s, 3H), 1.47 (s, 3H).The *ee* of **2p** was determined by HPLC analysis using Daicel Chiralcel AS-H column (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH = 80/20, 1.0 mL/min, 220 nm; t_{major} = 12.7 min, t_{minor} = 18.1 min.

(*S*)-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole-1,1-dioxide (4a)

White solid, 91% yield, 88% *ee*. Mp 128-131 °C. $[\alpha]_D^{20}$ = +85.2 (c = 0.46, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.81 (m, 1H), 7.57 (dd, *J* = 6.4, 2.8 Hz, 2H), 7.40 (d, *J* = 4.2 Hz, 5H), 7.18–7.12 (m, 1H), 5.74 (d, *J* = 4.1 Hz, 1H), 5.14 (d, *J* = 3.2 Hz, 1H). The *ee* of **4a** was determined by HPLC analysis using Daicel Chiralcel OD-H column (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH = 70/30, 0.8 mL/min, 230 nm; t_{major} = 18.5 min, t_{minor} = 21.0 min.

(*S*)-3-(*p*-tolyl)-2,3-dihydrobenzo[*d*]isothiazole-1,1-dioxide (4b)

White solid, 89% yield, 90% ee. Mp 169-171 °C. [α]D^{20} = +66.5 (c = 0.52, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.9, 2.8 Hz, 1H), 7.61–7.51 (m, 2H), 7.30–7.24 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.15 (dd, *J* = 5.4, 2.9 Hz, 1H), 5.70 (d, *J* = 3.9 Hz, 1H), 5.06 (d, *J* = 3.3 Hz, 1H), 2.37 (s, 3H). The ee of **4b** was determined by HPLC analysis using Daicel Chiralcel AS-H column (25 cm × 0.46 cm ID), conditions: n-Heptane/i-PrOH = 70/30, 0.5 mL/min, 230 nm; t_{major} = 17.4 min, t_{minor} = 23.0 min.

(*S*)-3-(4-fluorophenyl)-2,3-dihydrobenzo[*d*]isothiazole-1,1-dioxide (4c)

White solid, 92% yield, 85% *ee*. Mp 163-67 °C. $[\alpha]_D^{20}$ = +66.9 (c = 0.76, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.81 (m, 1H), 7.58 (d, *J* = 2.8 Hz, 2H), 7.37 (dd, *J* = 8.6, 5.2 Hz, 2H), 7.15 (dd, *J* = 7.6, 5.8 Hz, 1H), 7.10 (d, *J* = 8.6 Hz, 2H), 5.75 (d, *J* = 4.1 Hz, 1H), 5.23 (d, *J* = 3.3 Hz, 1H).The *ee* of **4c** was determined by HPLC analysis using Daicel Chiralcel OD-H column (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH = 70/30, 1.0 mL/min, 230 nm; t_{major} = 9.8 min, t_{minor} = 15.6 min.

(*S*)-3-methyl-2,3-dihydrobenzo[*d*]isothiazole-1,1-dioxide (4d)

White solid, 84% yield, 81% *ee*. Mp 92-95 °C. $[\alpha]_D^{20}$ = -20 (c = 0.38, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.4 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 5.12 (d, *J* = 27.5 Hz, 1H), 4.87–4.75 (m, 1H), 1.61 (dd, *J* = 6.6, 2.6 Hz, 3H). The *ee* of **4d** was determined by HPLC analysis using Daicel Chiralcel OD-H column (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH = 80/20, 0.5 mL/min, 230 nm; t_{major} = 23.0 min, t_{minor} = 29.5 min.

(*S*)-3-phenethyl-2,3-dihydrobenzo[*d*]isothiazole-1,1-dioxide (4e)

White solid, 93% yield, 71% *ee*. Mp 111-114 °C. $[\alpha]_D^{20}$ = -32.8 (c = 0.6, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.62 (s, 1H), 7.53 (s, 1H), 7.34 (dd, *J* = 21.6, 7.5 Hz, 3H), 7.24 (dd, *J* = 7.0, 4.8 Hz, 3H), 5.19 (d, *J* = 5.2 Hz, 1H), 4.79–4.64 (m, 1H), 2.84 (t, *J* = 7.7 Hz, 2H), 2.28 (d, *J* = 3.5 Hz, 1H), 2.18–2.05 (m, 1H). The *ee* of **4e** was determined by HPLC analysis using Daicel Chiralcel AS-H column (25 cm × 0.46 cm ID), conditions: *n*-Heptane/*i*-PrOH = 70/30, 0.5 mL/min, 230 nm; t_{major} = 43.0 min, t_{minor} = 52.2 min.

Acknowledgements

We gratefully thank the National Natural Science Foundation of China (21572198), the Applied Basic Research Project of Yunnan Province (2018FB021, 2017FA004) and the Department of Education of Yunnan Province (2017ZDX046) for financial support.

Keywords: Palladium • co-catalyst • asymmetric • hydrogenation • imine

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