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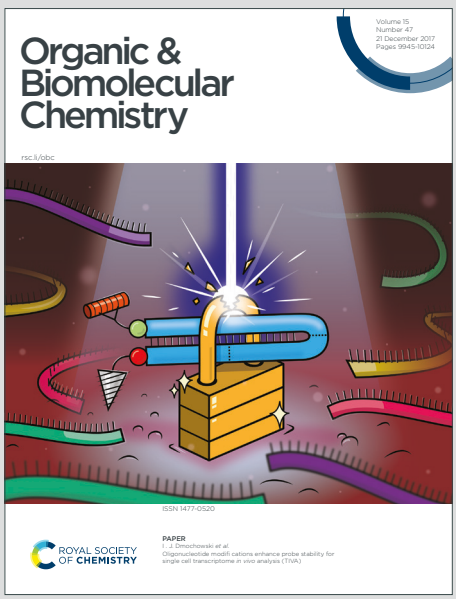

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Iridium-Catalyzed Diastereoselective Amination of Alcohols with Chiral *tert*-Butanesulfinamide by the Use of Borrowing Hydrogen Methodology

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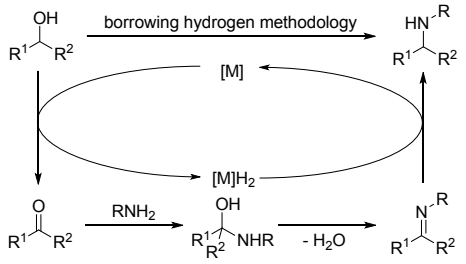
An iridium-catalyzed diastereoselective amination of alcohols with chiral *tert*-butanesulfinamide was developed under basic condition, affording the optically active secondary sulfinamides in high yields and diastereoselectivities. The removal of sulfinyl group from sulfonamides allowed a facile access to a wide range of α-chiral primary amines. This synthetic strategy was further applied in the synthesis of the marketed pharmaceuticals (*S*)-Rivastigmine and NPS *R*-568.

The direct amination of alcohols by using borrowing hydrogen methodology is a highly atom economical and environmentally benign protocol for the synthesis of amines.[1,2] This redox-neutral process generally begins with transition-metal-catalyzed dehydrogenative oxidation of alcohol to give an electrophilic carbonyl compound, which is further attacked by an amine nucleophile and then dehydrated to form imine intermediate. The hydrogen "*borrowed*" by the transition-metal catalyst finally returns, reducing imine intermediate to afford the amine product.[3,4] The overall conversion avoids using any stoichiometric reagents (oxidants, reductant, or base) and usually generates water as the sole by-product (Scheme 1). When we prepared this manuscript, Xiao and coworkers reported a NaOH-catalyzed process to realize the diastereoselective N-Alkylation of sulfinamides with racemic alcohols.[4g]



Scheme 1. Direct amination of alcohols by using borrowing hydrogen methodology

Although enantiopure amines are of great importance in pharmaceutical and biological chemistry,[5] only a few examples of asymmetric version of borrowing hydrogen methodology were developed to synthesize chiral amines.[6] In 2014, Zhao group reported the first example of enantioselective amination of alcohols catalyzed by an iridium complex and a chiral Brønsted acid cooperatively.[7] Similar cooperative catalytic systems were then applied to not only the dynamic kinetic resolution of β-branched racemic alcohols to form chiral amines in high enantioselectivities and diastereoselectivities,[8a] but also the enantioselective synthesis of 2-substituted 1,2,3,4-tetrahydroquinolines from amino alcohols.[8b]

The hydrogenation or transfer hydrogenation of chiral *N*-*tert*-butanesulfinyl imines catalyzed by various transition-metal complexes has been long recognized as a versatile synthetic approach to access the *tert*-butanesulfinyl-protected amines,[9,10] and the removal of sulfinyl group under acidic condition effectively leads to the formation of α-chiral primary amines.[11] Most recently, Guan, Dong and co-workers reported a Ru-catalyzed diastereoselective amination of racemic alcohols using chiral *tert*-butanesulfinamide as the equivalent of amine nucleophiles, providing a highly efficient way to synthesizeα-chiral amines.[12] However, a number of challenges still remain in this reaction. For instance, the reported ruthenium(II) PNP-type pincer catalyst is hardly able to convert the sterically hindered substrates to the desired products. To overcome the substrate limitations and improve the reaction selectivity, we herein report an iridium-catalyzed diastereoselective amination of alcohols with chiral *tert*-butanesulfinamide.[13]

Our studies were initiated with the optimization of reaction conditions for racemic 1-phenylethanol **1a** and (R)-*tert*-butanesulfinamide **2** under Ir(III) catalysis (Table1). No desired product was detected when $[Cp^*IrCl_2]_2$ was used even if KOH was added to promote the dehydrogenation of alcohol **1a** (entries 1 and 2). On the basis of literature reports, iridacyclic complexes **4** and **5** were chosen as catalysts since they have proven highly efficient in transfer hydrogenation of ketones,[14,15] racemization of chiral

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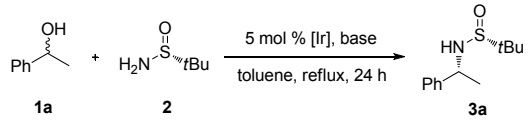
alcohols, and the synthesis of chiral 1,2,3,4-tetrahydroquinoline from amino alcohols.[8] Unfortunately, no reaction occurred in the absence

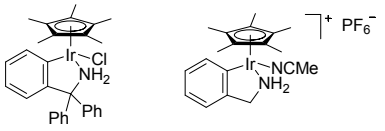
Table1.Optimization of the reaction conditions[a]



1a 2 3a

Entry	[Ir]	Base	Yield[b]	dr[c]
1	$[Cp^*IrCl_2]_2$	-	NR	-
2	$[Cp^*IrCl_2]_2$	KOH (20mol %)	NR	-
3	**4**	-	NR	-
4	**5**	-	NR	-
5	**4**	KOH (20mol %)	98%	>19:1
6	**5**	KOH (20mol %)	< 5%	-
7	**4**	NaOH (20mol %)	95%	>19:1
8	**4**	Cs_2CO_3(20mol %)	95%	>19:1
9	**4**	KO^{t}Bu (20mol %)	90%	>19:1
10	**4**	K_2CO_3 (20mol %)	29%	>19:1
11	**4**	EtONa (20mol %)	13%	>19:1

[a]Reaction condition: **1a** (0.6 mmol), **2** (0.5 mmol), [Ir] (5 mol %), in a toluene (1.5 mL) at 111°C under N_2 for 24 h. [b]Yield was determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard. [c]The dr value was determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

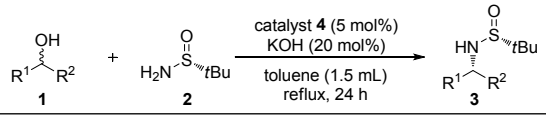


4 5

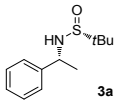
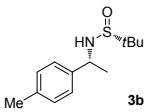
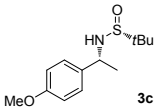
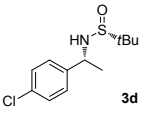
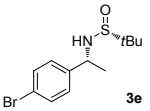
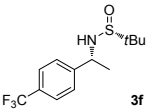
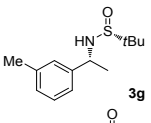
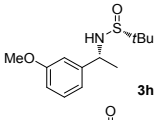
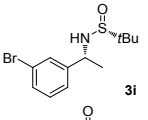
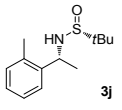
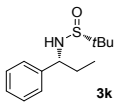
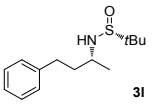
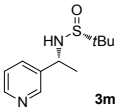
of base (entries 3 and 4). To our delight, desired product **3a** was obtained in 98% yield and > 19:1 dr in the presence of 20 mol % of KOH when neutral iridacyclic complex **4** was employed as a catalyst (entry 5).However, switching to cationic iridacyclic complex **5** led to much lower yield. Further optimization revealed that KOH was our best choice among different bases (entries 7-11).

With the optimal reaction conditions in hand, we next examined the scope and generality of this transformation. The electronic effect of the substrates was investigated by using a series of 1-phenylethanol derivatives. The substrates bearing electron-donating groups, such as Me or OMe, at *para*-or *meta*-position of phenyl ring could afford the desired products (**3b-3c** and **3g-3h**) in 72~94% yields with excellent diastereoselectivities (>19:1 dr). The electron-deficient substrates were also well-tolerated, yielding the corresponding products(**3d-3f** and **3i**) in 70%~83% yields, however, the diastereoselectivities were slightly decreased to 17:1. Compared with the reported ruthenium(II) PNP-type pincer catalyst,[12]iridacyclic complex **4** exhibits a relatively higher catalytic reactivity for the sterically hindered substrates. For example,**1j**, having methyl group at the *ortho*-position of phenyl ring, could be successfully converted to **3j** in 50% yield with high dr (>19:1 dr). Notably, this catalytic system could also be applied to the ethyl-substituted substrates, affording **3k** without significant decrease in yields or diastereoselectivities. However, in case of alkyl-alkyl-substituted alcohol **1l**, the diastereoselectivity of desired product **3l** dropped dramatically to 4:1 because of the small size difference of

Table 2. The scope of alcohols used in amination of alcohol



1 2 3

Entry	Alcohol	Product	Yield[b]	dr[c] (RR:RS)
1	**1a**	 **3a**	80%	>19:1
2	**1b**	 **3b**	75%	>19:1
3	**1c**	 **3c**	82%	>19:1
4	**1d**	 **3d**	71%	17:1
5	**1e**	 **3e**	83%	17:1
6	**1f**	 **3f**	70%	17:1
7	**1g**	 **3g**	72%	>19:1
8	**1h**	 **3h**	94%	>19:1
9	**1i**	 **3i**	72%	17:1
10	**1j**	 **3j**	50%	>19:1
11	**1k**	 **3k**	75%	>19:1
12	**1l**	 **3l**	70%	4:1
13	**1m**	 **3m**	84%	17:1

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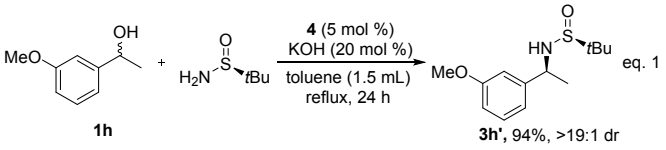
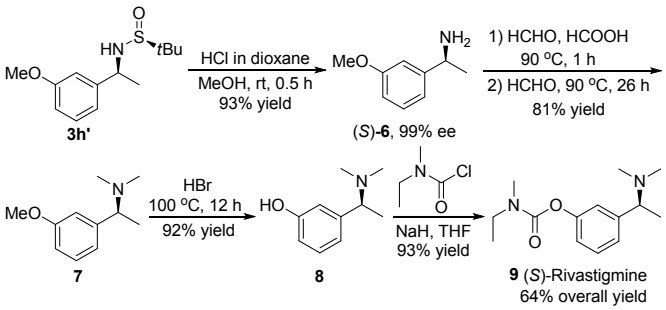
[a]Reaction condition: **1a** (0.6 mmol), **2** (0.5 mmol), **4** (5 mol %), in toluene (1.5 mL) at 111°C under N_2 for 24 h. [b]Isolate yield. [c]The dr value was determined by ^{1}H NMR analysis.

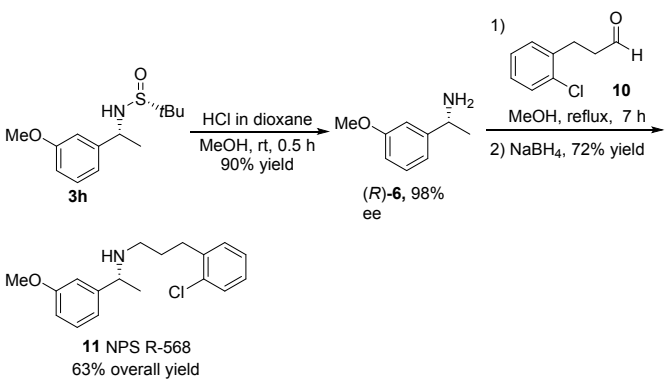
β-substituents. In order to expand the substrate scope, we have also explored racemic alcohols containing heteroatoms, resulting in chiral pyridine derivatives (**3m**) in 84% yield with high diastereoselectivity (17:1 dr). Additionally, when the same set of reaction conditions used in Table 2 is applied to **1h** and (S)-*tert*-butanesulfinamide, **3h'** could be obtained in good yield and excellent diastereoselectivity (eq. 1).



To further highlight the application of iridium-based catalytic system, it was utilized in the synthesis of (S)-Rivastigmine,[16] an acetylcholinesterase inhibitor which is generally used to treat the dementia caused by Alzheimer's or Parkinson's disease. The removal of sulfinyl group in **3h'** under acidic condition was carried out to form the α-chiral amine (*S*)-**6** in 93% yield and 99%ee. Subsequently, *N*, *N*-dimethylation of (*S*)-**6** with access amount of formic acid and formaldehyde yielded **7**, which was then converted to **8** in 92% yield by removing *O*-methyl group in the presence of aqueous HBr. Finally, the carbamoylation of **8** with commercially available *N*-ethyl-*N*-methylcarbamoylchloride afforded (*S*)-Rivastigmine (> 99% ee) in 64% overall yield after recrystallization (Scheme 2). Similarly, the synthesis of NPS R-568,[17] which is a type II calcimimetic compound of pharmaceutical importance, could be realized in 63% overall yield and 99% ee (Scheme 3) by removing sulfinyl group in **3h**, followed by reductive amination with **10**.



Scheme 2. Synthesis of (*S*)-Rivastigmine from 3h'



Scheme 3. Synthesis of NPS *R*-568 from 3h

Conclusions

In conclusion, we developed a novel Ir-based catalytic system for the diastereoselective amination of alcohols with chiral *tert*-butanesulfinamide. A wide range of optically active secondary sulfinamides were obtained from racemic alcohols in good to high yields with excellent diastereoselectivities. This catalytic system enabled us to accomplish the synthesis of marketed pharmaceuticals (S)-Rivastigmine and NPS *R*-568.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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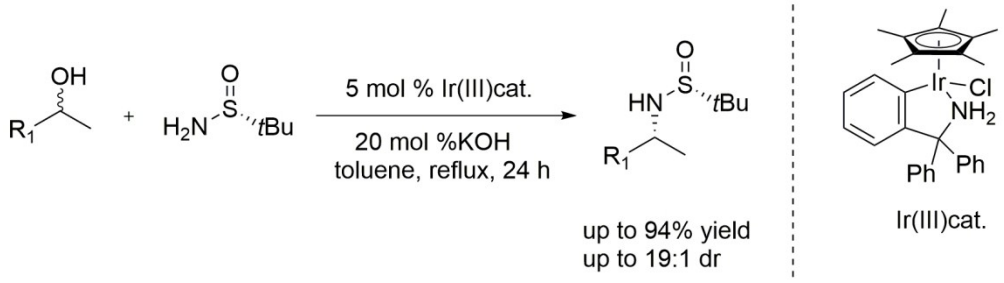

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