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Enantioselective synthesis of tetrahydroisoquinoline derivatives *via* chiral-at-metal rhodium complex catalyzed [3+2] cycloaddition†

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An asymmetric [3+2] cycloaddition of *C*,*N*-cyclic azomethine imines with α,β-unsaturated 2-acyl imidazoles catalyzed by a chiral-at-metal rhodium complex has been developed. The corresponding C-1-substituted tetrahydroisoquinoline derivatives were obtained in high yields (>90%) with excellent stereoselectivities (up to 99% ee and >20 : 1 dr). The reaction can be conducted on a gram-scale using a low catalyst loading (0.5 mol%) with high yield and selectivity.

Nitrogen-containing heterocycles are an attractive molecular pool for bioactive natural alkaloids as well as significant structural units of pharmaceuticals.[1] As an important branch, chiral multifunctionalized tetrahydroisoquinolines, especially those having a chiral stereocenter at the C1-position, have been identified as pharmacologically important molecules with diverse biological activities[2] (Fig. 1). For example, (*S*)-norcoclaurine has been proven to be an effective β-1 and β-2 adrenergic agonist, which has been used in traditional Chinese medicine as extracts from natural plants.[3] (*S*)-Coclaurine is a nicotinic acetylcholine receptor antagonist, which has been isolated from a variety of plant sources such as *Nelumbo nucifera*.[4] Jamtine, which is isolated from the climbing shrub *Cocculus hirsutus*, is one of the medicinal alkaloids having significant antihyperglycemic activity.[5] Canadine is a protoberberine alkaloid that can act as a calcium channel blocker.[6] Considering such distinct biological and pharmacological properties and potential clinical values of chiral tetrahydroisoquinoline derivatives, the development of effective protocols for the asymmetric synthesis of these valuable molecules and analogues is desirable.

C,*N*-Cyclic azomethine imines were discovered by Tamura[7] in 1973 and developed by Maruoka as promising 1,3-dipoles to undergo 1,3-dipolar cycloaddition[8] with α,β-unsaturated aldehydes catalyzed by a BINOL–Ti (BINOL = 1,1′-bi-2-naphthol) complex, leading to the formation of a chiral tetrahydroisoquinoline scaffold.[9a] Since then, several catalytic asymmetric reactions of *C*,*N*-cyclic azomethine imines with different reagents, such as vinyl ether,[9b] alkynes,[9c] cyclopropanes,[10] δ-substituted allenoates,[11] aldehydes,[12] Morita–Baylis–Hillman carbonates,[13] unsaturated nitriles[14] and vinyl aziridines[15], have been developed in the past few years, and *C*,*N*-cyclic azomethine imines have emerged as important precursors for the formation of various enantio-enriched C1-substituted tetrahydroisoquinoline derivatives. However, despite these impressive achievements, there are some drawbacks such as long reaction time, unsatisfactory stereoselectivity and high catalyst loading. Therefore, the development of new efficient catalytic asymmetric methods to access chiral C1-substituted tetrahydroisoquinoline derivatives is still in high demand.

As a continuation of our interest in the development of chiral-at-metal Rh(III) complexes[16] as chiral Lewis acids in catalytic asymmetric reactions,[17] herein we report an enantioselective [3+2] cycloaddition of *C*,*N*-cyclic azomethine imines with α,β-unsaturated 2-acyl imidazoles catalyzed by a chiral-at-metal Rh(III) complex, affording enantio-enriched C1-substituted tetrahydroisoquinolines with a fused five member ring, which contains three contiguous tertiary stereocenters.

Key results in the search for a suitable chiral-at-metal complex and optimal reaction conditions are shown in Table 1.

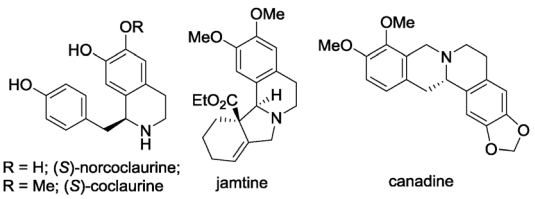

Fig. 1 Examples of important chiral tetrahydroquinoline derivatives.

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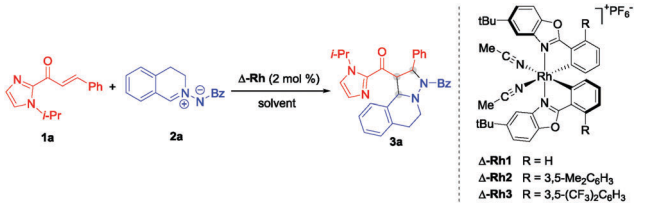
Table 1 Optimization of the reaction conditions[a]

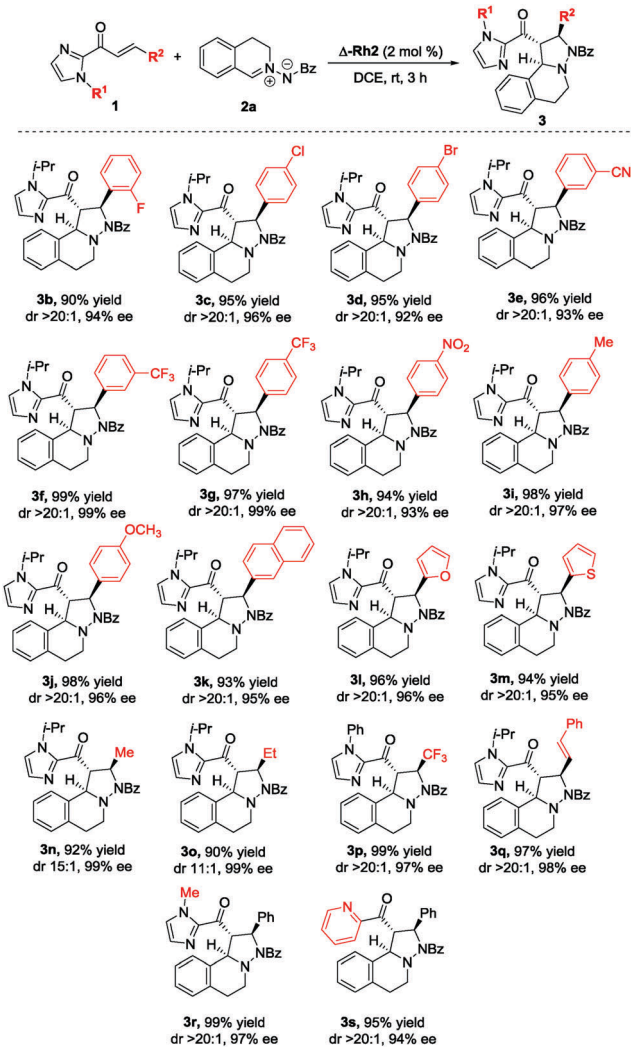


Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**Δ-Rh1**	DCE	3	94	>20:1	93
2	**Δ-Rh2**	DCE	3	99	>20:1	98
3	**Δ-Rh3**	DCE	3	93	>20:1	91
4	**Δ-Rh2**	DCM	3	96	>20:1	93
5	**Δ-Rh2**	THF	3	91	>20:1	94
6	**Δ-Rh2**	Toluene	3	95	>20:1	94
7[e]	**Δ-Rh2**	DCE	7	95	>20:1	96
8	None	DCE	—	NR	—	—

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.12 mmol) and a catalyst (2.0 mol%) in a solvent (0.2 mL) under an argon atmosphere. [b] Isolated yield. [c] Diastereomeric ratio, determined *via* the ^{1}H NMR analysis of the crude reaction mixture. [d] Enantiomeric excess, determined *via* chiral HPLC analysis. [e] 1.0 mol% catalyst loading.

α,β-Unsaturated 2-acyl imidazole **1a** and *C*,*N*-cyclic azomethine imine **2a** were chosen as the model substrates to react in the presence of 2 mol% **Δ-Rh1** developed by Meggers' group[16a] in 1,2-dichloroethane (DCE) at room temperature. To our delight, the reaction proceeded smoothly for 3 hours to afford the corresponding product **3a** in 94% yield with >20:1 dr and 93% ee (Table 1, entry 1). An evaluation of the chiral-at-metal complexes (entries 1–3) showed that the catalyst **Δ-Rh2**[17a,c] is the superior one in terms of reactivity and stereoselectivity, mediating the formation of **3a** in 99% yield with >20:1 dr and 98% ee (entry 2). Various solvents such as DCM, THF and toluene provided comparable results (entries 4–6). A further decrease in the loading of **Δ-Rh2** to 1 mol% under similar reaction conditions (entry 2) led to **3a** with a prolonged reaction time (7 hours, entry 7). A control experiment in the absence of the catalyst failed to provide any product, thereby demonstrating that this reaction crucially depends on the catalysis by chiral-at-metal Rh(III) complexes (entry 8).

With the optimal conditions in hand (Table 1, entry 2), the scope of this chiral Rh(III) complex catalyzed [3+2] cycloaddition reaction was then examined. We first studied the cycloaddition of *C*,*N*-cyclic azomethine imine **2a** with α,β-unsaturated 2-acyl imidazoles **1** bearing a β-aryl substituent. The results are summarized in Scheme 1. The use of substrate **1** with an electron-withdrawing moiety at the *ortho*, *meta* or *para*-position of the β-aryl substituent led to high yields of the desired products (Scheme 1, **3b–h**). Placing electron-donating groups on the β-aryl substituent was also well tolerated (**3i–3j**), and the β-naphthyl-substituted substrate and heteroaryl (*e.g.*, furyl, thienyl) analogues worked fine as well (**3k–m**). These reactions gave high yields (>90%), excellent values of diastereoselectivity (dr >20:1) and enantioselectivity (up to 99% ee). α,β-Unsaturated 2-acyl imidazoles **1** with a β-alkyl substituent (*e.g.*, methyl, ethyl, trifluoromethyl and styryl) also worked well under the optimal reaction conditions,

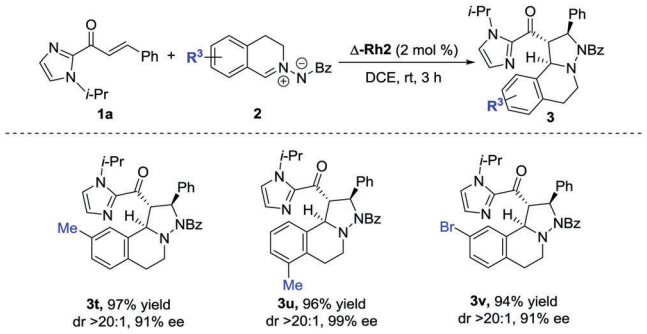


Scheme 1 Substrate scope of α,β-unsaturated 2-acyl imidazoles. Reaction conditions: **1** (0.10 mmol), **2a** (0.12 mmol) and **Δ-Rh2** (2.0 mol%) in DCE (0.2 mL) at room temperature under an argon atmosphere. All isolated yields are based on substrate **1**. The ee values were determined by HPLC analysis using a chiral stationary phase. The dr values were detected by crude ^{1}H NMR.

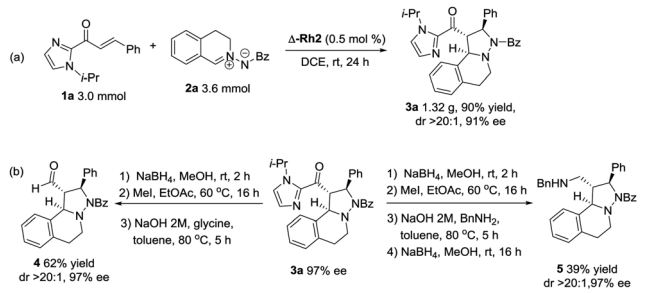
providing products **3n** to **3q** in high yields (>90%) with excellent stereoselectivities (up to 99% ee and >20:1 dr). The *N*-isopropylimidazole group on substrate **1** was further replaced with *N*-methylimidazole and 2-pyridyl, and no significant influence on the reactivity and selectivity was observed, delivering the desired products (**3r** and **3s**) in high yields (>95%) with excellent stereoselectivities (dr >20:1, ee ≥94%).

Cycloaddition of α,β-unsaturated 2-acyl imidazole **1a** with substituted *C*,*N*-cyclic azomethine imines **2** was also investigated (Scheme 2). No matter electron-rich or -deficient phenyl substituted 1,3-dipoles **2**, all substrates reacted smoothly to deliver the corresponding products (**3t–v**) in high yields (>94%) with excellent stereoselectivities (dr >20:1, up to 99% ee).

To verify the synthetic potential of the current protocol, a gram-scale reaction with **1a** (3.0 mmol) was conducted at a lower catalyst loading (0.5 mol%). The reaction completed in 24 hours,



Scheme 2 Substrate scope of *C,N*-cyclic azomethine imines. Reaction conditions: **1a** (0.10 mmol), **2** (0.12 mmol) and **Δ-Rh2** (2.0 mol%) in DCE (0.2 mL) at room temperature under an argon atmosphere. All isolated yields are based on substrate **1a**. The ee values were determined by HPLC analysis using a chiral stationary phase. The dr values were detected by crude ^{1}H NMR.



Scheme 3 Gram-scale experiment and synthetic transformations.

and product **3a** was obtained in 90% yield, with a little erosion of the enantioselectivity (91% ee) and excellent diastereoselectivity (dr >20:1, Scheme 3a). On the other hand, the acyl imidazole moiety of product **3a** could be converted into optically active aldehyde **4** by reduction and further removal of the imidazole moiety without any loss in the enantiomeric excess (Scheme 3b), and then it would be easy for the aldehyde to transform into other substituents, for example, amine **5** (Scheme 3b).

Based on the previous investigations, the proposed model of stereoselective control is shown in Fig. 2. The α,β-unsaturated 2-acyl imidazole can be activated by the rhodium catalyst through bidentate *N,O*-coordination. An asymmetric induction of the catalyst could be attributed to its high steric bulk around the Rh center. The *Si*-face of the coordinated substrate is effectively shielded by one of the *tert*-butyl groups. Then *C,N*-cyclic azomethine imines can attack in a highly selective approach from the *Re*-face of the coordinated substrate, meanwhile, the *exo*-selectivity should be adopted to minimize steric repulsion, leading to the desired five member ring with (1*S*, 2*S*, 3*R*) configuration, which is consistent with the observed absolute configuration of **3i** determined by X-ray crystallographic analysis (Fig. 2, for details, see the ESI†).[18] Other products were assigned by analogy.

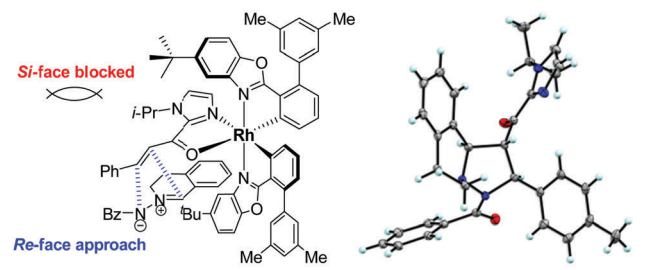


Fig. 2 Proposed model and the X-ray structure of **3i** with thermal ellipsoids shown at the 35% probability level.

In conclusion, we have developed a highly efficient asymmetric [3+2] cycloaddition of α,β-unsaturated 2-acyl imidazoles with *C,N*-cyclic azomethine imines catalyzed by chiral-at-metal rhodium complexes, affording enantio-enriched C1-substituted tetrahydroisoquinoline derivatives in high yields (>90%) with excellent stereoselectivities (up to 99% ee and >20:1 dr). Remarkably, this protocol has extraordinary advantages in terms of reactivity and stereoselectivity, given the fact that as low as 0.5 mol% **Δ-Rh2** can realize the title reaction on a gram scale, yielding the desired product with high stereoselectivity.

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Conflicts of interest

There are no conflicts to declare.

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