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A One-Pot Process for the Enantioselective Synthesis of Tetrahydroquinolines and Tetrahydroisoquinolines *via* Asymmetric Reductive Amination (ARA)

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Asymmetric reductive amination for the synthesis of both chiral tetrahydroquinolines (THQs) and tetrahydroisoquinolines (THIQs) has been realized with an Ir/ZhaoPhos catalytic system *via* a one-pot *N*-Boc deprotection/intramolecular asymmetric reductive amination (ARA) sequence. Control experiments reveal that HCl plays a vital role to the success of this transformation. The HCl acid assists the removal the *N*-Boc protecting group and also provides chloride ion to interact with the thiourea moiety in ZhaoPhos, thus leading to excellent reaction enantiocontrol.

Chiral tetrahydroquinolines (THQs) and tetrahydroisoquinolines (THIQs) are universal structural units in a large number of biologically active molecules, including natural alkaloids and pharmaceuticals.[1] For instance, chiral 2-substituted THQ units exist in naturally occurring (-)-angustrureine,[2a] (-)-galipinine[2b] and (-)-cuspareine,[2c] and 1-substituted THIQ motifs are present in (+)-cryptostyline II,[2d] drug molecule Solifenacin[2e] as well as an AMPA receptor antagonist.[2f] Due to their significance, extensive efforts have been devoted to the development of high efficient methods toward chiral THQs and THIQs.

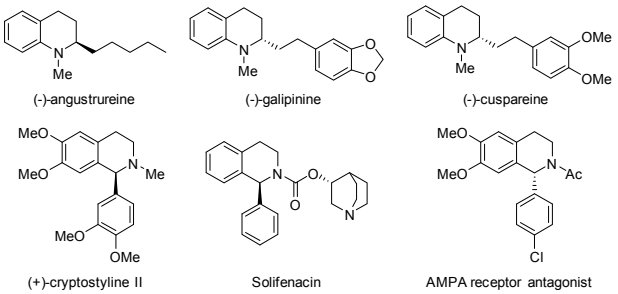
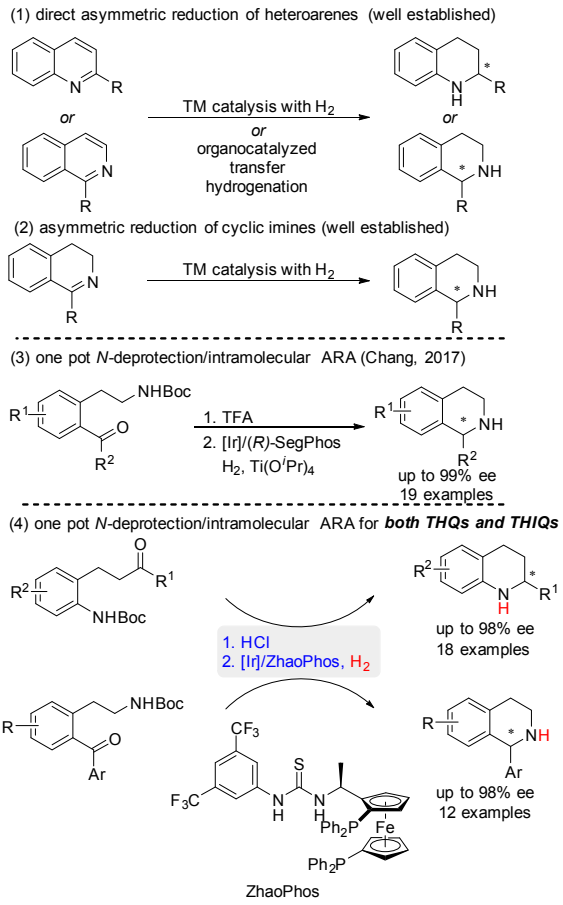


Fig. 1. Selected natural alkaloids and pharmaceuticals containing a chiral THQs or THIQs unit



Scheme 1. Strategies toward chiral THQs and THIQs

Direct asymmetric reduction of easily accessed quinoline or isoquinoline derivatives represents the most straightforward route to achieve enantioenriched THQs and THIQs. To this end, transition metal (TM) catalysis with molecular H_2[3] and organocatalysis with hydrogen transfer reagents have been well established (Eq 1, Scheme 1).[4] TM-catalyzed asymmetric reduction of benzo-fused cyclic

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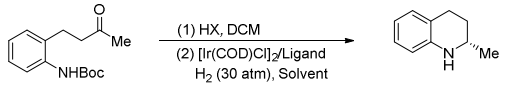
imines is an alternative strategy and several efficient catalytic systems have been identified (Eq 2, Scheme 1)[5]. Besides, intramolecular ARA,[6] an approach which avoids the presynthesis of the imines, provides another facile and efficient route towards chiral THIQs. Remarkably, based on Wills's original contribution regarding a one-pot deprotection/cyclization/asymmetric transfer hydrogenation for the synthesis of chiral amines,[7a] Chang recently unveiled an elegant one-pot *N*-Boc deprotection and Ir-catalyzed ARA sequence for the preparation of chiral THIQs (Eq 3, Scheme 1).[7b] Despite remarkable advances, high efficient catalytic systems capable of furnishing both chiral THQs and THIQs remain rare and thus highly desirable.

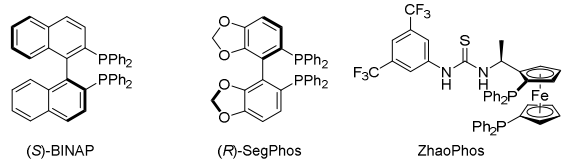
Recently we have developed a kind of novel ligand, ZhaoPhos, comprising a chiral ferrocenyl bisphosphine scaffold and a tunable thiourea subunit.[8] By taking advantage of the anion bonding interaction between the thiourea moiety in the ligand and chloride counterion from the substrates, we have successfully realized the asymmetric hydrogenation of unprotected NH imines,[9a] isoquinolines and quinolones,[9b] as well as indoles.[9c] We envisaged that in situ formed cyclic iminium ion, paired with a suitable counteranion (such as Cl^-), could be stereoselectively reduced through similar working models (Eq 4, Scheme 1). We herein report a unified strategy for asymmetric synthesis of both chiral THQs and THIQs *via* a one-pot *N*-Boc deprotection and Ir-catalyzed ARA sequence.

Table 1. Optimization of Reaction Conditions[a]

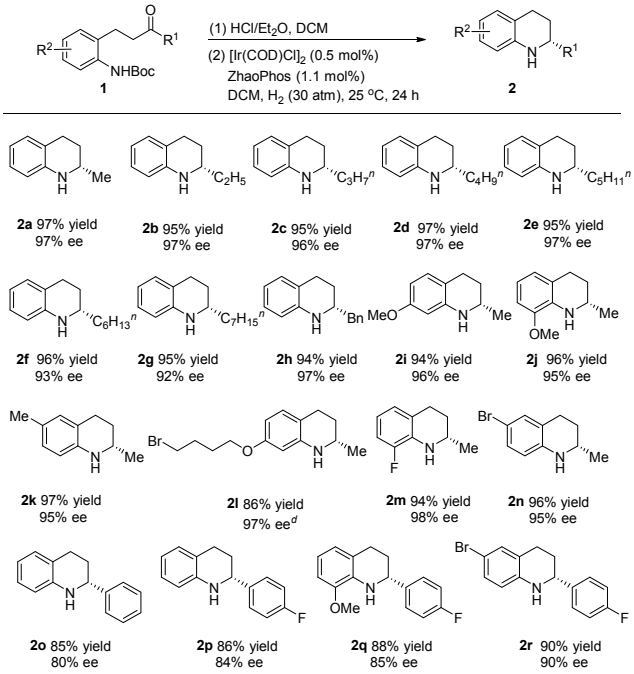


Entry	Ligand	Solvent	HX	Conversion (%)[b]	ee (%)[c]
1	ZhaoPhos	DCM	CF_3CO_2H	>95%	64%
2	**ZhaoPhos**	**DCM**	**HCl/Et$_2$O**	**>95%**	**97%**
3	(*S*)-BINAP	DCM	HCl/Et$_2$O	>95%	65%
4	(*R*)-SegPhos	DCM	HCl/Et$_2$O	>95%	86%
5	ZhaoPhos	THF	HCl/Et$_2$O	>95%	92%
6	ZhaoPhos	^{i}PrOH	HCl/Et$_2$O	>95%	89%
7	ZhaoPhos	EtOAc	HCl/Et$_2$O	>95%	93%
8	ZhaoPhos	toluene	HCl/Et$_2$O	>95%	95%
9[d]	ZhaoPhos	DCM	HCl/Et$_2$O	>95%	90%
10[e]	ZhaoPhos	DCM	HCl/Et$_2$O	>95%	93%
11	ZhaoPhos	DCM	HCl/HOAc	>95%	96%

[a]Reaction conditions: **1a** (0.1 mmol), $[Ir(cod)Cl]_2$ (0.5 mol%), ligand (1.1 mol%), HX (4.0 equiv.), solvent (0.6 mL); [b]Determined by ^{1}H NMR; [c]Determined by HPLC; [d]$[Rh(cod)Cl]_2$ was used; [e]$Rh(NBD)_2BF_4$ was used.



We began our study by exploring the reductive amination conditions for the synthesis of chiral THQs with model substrate **1a**. Since the removal of the Boc protecting group on *N* atom is essential to the subsequent cyclization, CF_3COOH (TFA), as an obvious choice, was first tried. With all volatile components removed, the resulting mixture underwent smoothly asymmetric reductive amination in the presence of a catalyst combination of $[Ir(cod)Cl]_2$ and ZhaoPhos, however, with only moderate enantiocontrol (entry 1, Table 1). We speculated that the poor asymmetric induction was due to a very weak interaction between the anion of TFA and the thiourea subunit in ZhaoPhos. TFA was thus replaced with HCl/Et$_2$O to remove the *N*-Boc protecting group. As expected, benefiting from the strong anion bonding interaction between the thiourea moiety and the chloride ion,[9a,10] the asymmetric induction of the cyclization step enhanced remarkably, affording the desired product **2a** with 97% ee (entry 2). Commercially available chiral phosphine ligands BINAP and SegPhos were also investigated, but both displayed inferior results (entries 3-4). Screening of other solvents, such as THF, ^{i}PrOH, toluene and EtOAc, demonstrated that dichloromethane remained the most efficient one (entries 5-8). In addition, rhodium precatalyst proved to be also efficient, giving full conversions albeit with slightly decreased enantiocontrol (entries 9-10). Further attempt to use other HCl source did not provide superior results (entry 11). Therefore, the optimal condition was identified as follows: employing HCl/Et$_2$O to remove the *N*-Boc protecting group, $[Ir(cod)Cl]_2$ and ZhaoPhos as the catalyst, and dichloromethane as the solvent at 25 °C with a hydrogen pressure of 30 atm.



[a]Reaction conditions: **1** (0.2 mmol), $[Ir(cod)Cl]_2$ (0.5 mol%), ZhaoPhos (1.1 mol%), HCl (4.0 equiv.), DCM (0.6 mL); [b]Isolated yield; [c]Determined by HPLC; [d]Determined by UPLC

Scheme 2. Substrate scope for the synthesis of chiral THQs[a-c]

With the optimal conditions in hand, the scope of the reductive amination for the synthesis of chiral THQs was then studied, as depicted in Scheme 2. Alkyl substituents (**1b-1h**) with various chain lengths attached to the carbonyl moiety had only small influence to the outcome of enantiocontrol, and excellent enantioselectivities of the desired THQs were generally obtained (92-97% ee). Substituent effect on the bridged benzene ring is not obvious in terms of reactivity or enantioselectivity, and the enantiocontrol was excellent throughout, regardless of the position and electronic property of the substituents (**2i-2n**). Remarkably, a bromo-containing alkyl side chain on the phenyl ring was well tolerated (**2l**). Besides alkyl

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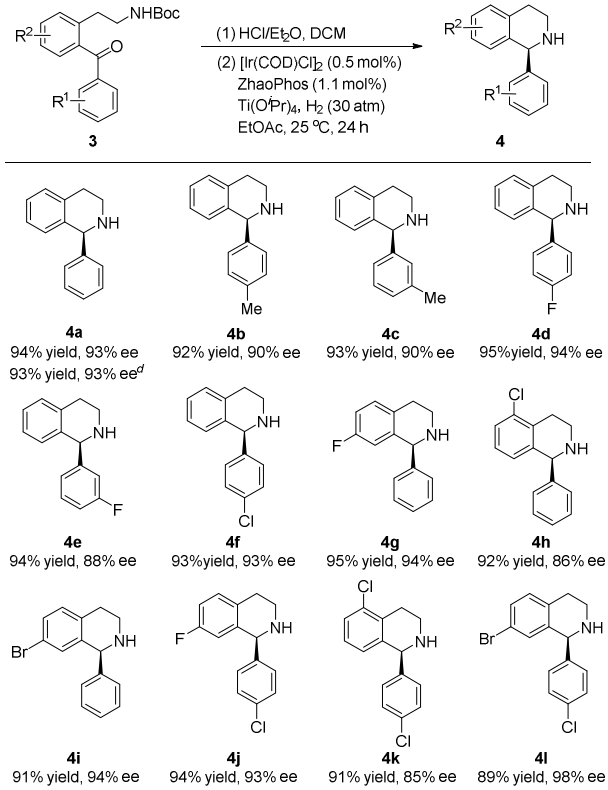
substituents, different aryl substituents attached to the carbonyl moiety were also investigated. In general, these substrates output slightly inferior results regarding conversions and enantioselectivity (**2o-2r**, 80-90% ee).

Encouraged by the success towards the synthesis of chiral THQs with Ir/ZhaoPhos catalytic system, we then copied the optimal reaction conditions for the synthesis chiral THIQs. Unfortunately, the reaction was totally shut down for **3a** at the second step. We were glad to find that addition of $Ti(OiPr)_4$ over the reductive amination step could overcome the obstacle.[11] The ARA step of **3a** processed smoothly to give desired product **4a** in a high yield albeit moderate ee value (75% ee). Solvent effect was then evaluated to improve the enantiocontrol, revealing that EtOAc was the optimal solvent which afforded **4a** with 94% yield and 93% ee (for details see the Supporting Information).



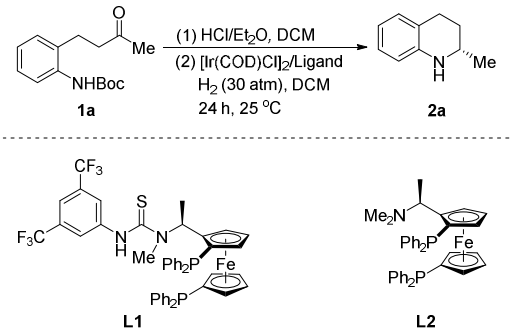
[a] Reaction conditions: **3** (0.2 mmol), [Ir(cod)Cl]$_2$ (0.5 mol%), ZhaoPhos (1.1 mol%), $Ti(OiPr)_4$ (1.0 equiv.), EtOAc 0.6 mL; [b] Isolated yield; [c] Determined by HPLC for the corresponding benzamides; [d] S/C = 500.

Scheme 3. Substrate scope for the synthesis of chiral THIQs[a-c]

Under slightly revised reaction conditions, we explored the generality of the protocol for the synthesis of chiral THIQs, as summarized in Scheme 3. A variety of 1-aryl substituted THIQs were effectively prepared with up to 98% ee and 95% yield (**4a-4l**). The substituent position on both benzene rings of the THIQ has little influence on the outcome of enantioselectivity. Notably, the transformation went smoothly even with a catalyst loading of 0.2 mol% to efficiently give product **4a**, a key intermediate to the drug molecule Solifenacin[2e] and biologically active molecule (+)-FR115427.[12]

To obtain insight into the efficacy of the catalytic system, **L1** and **L2** were tested under otherwise standard conditions, and the results were summarized in Table 2. The *N*-methylated ligand **L1** displayed comparable activity and slightly diminished enantiocontrol, possibly due to the reason that there is only one acidic N-H proton available to interact with the counterion (entry 2, 92% ee). Further, the ligand **L2** which has no thiourea subunit exhibited high activity but with much worse asymmetric induction (entry 3, 55% ee). These results suggest the importance of hydrogen bonds in this reaction and that the thiourea motif could efficiently help to form a better chiral environment.

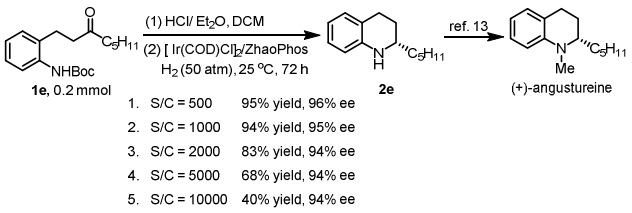
Table 2. Investigation of Structure-Activity Relationship of ZhaoPhos



Entry	Ligand	Conversion (%)[b]	ee (%)[c]
1	**ZhaoPhos**	>95%	98%
2	**L1**	>95%	92%
3	**L2**	80%	55%

[a]All reactions were carried out with a [Ir(cod)Cl]$_2$/ligand/**1a** (0.2 mmol) ratio of 1 : 2.2 : 200 in 0.6 mL of DCM under hydrogen (30 atm) for 24 h; [b]Determined by ^{1}H NMR; [c]Determined by HPLC analysis.

To showcase the practicality of this protocol, TON experiments were conducted. **1e** was selected because its corresponding product **2e** was a key intermediate to natural product angustureine.[13] Although the transformation remained highly efficient with a catalyst loading of 0.1 mol% (TON= 1000), further decrease of the catalyst loading resulted in an obvious drop of the reactivity (94% to 40% yield, entries 1-5, Scheme 4).



1. S/C = 500 95% yield, 96% ee
2. S/C = 1000 94% yield, 95% ee
3. S/C = 2000 83% yield, 94% ee
4. S/C = 5000 68% yield, 94% ee
5. S/C = 10000 40% yield, 94% ee

Scheme 4. TON experiments of **1e**

In summary, we have developed a highly efficient catalytic system for asymmetric synthesis of both chiral THQs and chiral THIQs. The strong Brønsted acid HCl plays a critical role in this transformation, not only facilitating the removal the *N*-Boc protecting group, but also providing chloride ion to interact with the thiourea moiety in ZhaoPhos, thereby offering excellent enantiocontrol. Control experiments revealed the superiority of ZhaoPhos against several commercially available bisphosphine ligands.

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Conflicts of interest

There are no conflicts to declare

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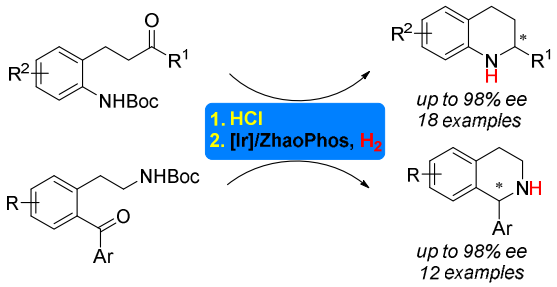

Asymmetric reductive amination for the synthesis of both chiral tetrahydroquinolines and tetrahydroisoquinolines has been realized with an Ir/ZhaoPhos catalytic system *via* a one-pot *N*-Boc deprotection/intramolecular asymmetric reductive amination (ARA) sequence.