OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

Josiphos-Type Binaphane Ligands for Iridium-Catalyzed Enantioselective Hydrogenation of 1-Aryl-Substituted Dihydroisoquinolines

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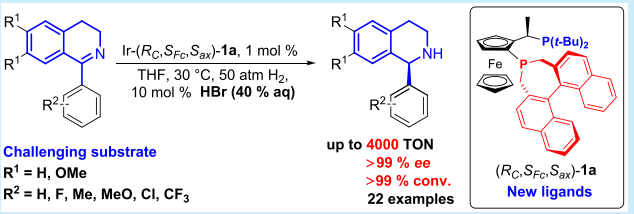
Supporting Information

ABSTRACT: Convenient synthesis and useful application of a series of Josiphos-type binaphane ligands were described. The iridium complexes of these chiral diphosphines displayed excellent enantioselectivity and good reactivity in the asymmetric hydrogenation of challenging 1-aryl-substituted dihydroisoquinoline substrates (full conversions, up to >99% *ee*, 4000 TON). The use of 40% HBr (aqueous solution) as an additive dramatically improved the asymmetric induction of these catalysts. This transformation provided a highly efficient and enantioselective access to chiral 1-aryl-substituted tetrahydroisoquinolines, which were of great importance and common in natural products and biologically active molecules.



1,2,3,4-Tetrahydroisoquinolines (THIQs) and their analogues are a class of highly important biological active compounds.[1] Their pharmacological activities usually involve multidrug resistance reversal, antidiabetic properties, or central nervous system (CNS) activities and so on.[2] Thus, constant efforts have been extensively devoted to the development of efficient synthetic methods of THIQs. In particular, chiral 1-substituted THIQs scaffolds are present ubiquitously in natural products, pharmaceuticals, and bioactive compounds (Figure 1), such as (*S*)-salsolidine,[3a] (*S*)-carnegine,[3b] (*S*)-norlaudanosine,[3c] solifenacin,[3d] AMPA receptor antagonist I,[3e] (*S*)-cryptostyline II,[3f] (*S*)-cryptostyline III,[3f] TRPM8 channel receptor antagonist IV and V,[3g,h] etc. Among various synthetic approaches to afford chiral 1-substituted THIQs,[2a,4] catalytic asymmetric hydrogenation (AH) of 1-substituted 3,4-dihydroisoquinolines (DHIQs) has been recognized as one of the most straightforward, efficient, environmental-friendly, and cost-effective approaches.

During the past two decades, considerable progress has been made in the AH of 1-alkyl-3,4-DHIQs.[5] However, the enantioselective hydrogenation of 1-aryl-3,4-DHIQs still remains a great challenge, which has been attributed to greater steric hindrance arising from the adjacent aromatic ring.[5d,6] To the best of our knowledge, there have been only very few successful examples reported in literature. The first breakthrough in the AH of 1-aryl-3,4-DHIQs was reported by Zhang's group in 2011. Excellent enantioselectivities (up to 99% *ee*) and high turnover numbers (up to 10 000) were obtained using the iodine-bridged dimeric $[\{Ir(H)[(S,S)\text{-(f)-binaphane}]\}_2(\mu\text{-I})_3]^+I^-$ complex as the catalyst (Scheme 1).[7] However, the enantioselectivities varied dramatically with the substrates bearing a 1-*ortho*-substituted phenyl ring. Subsequently, the $[IrCODCl]_2$/(*R*)-3,5-diMe-Synphos catalyst

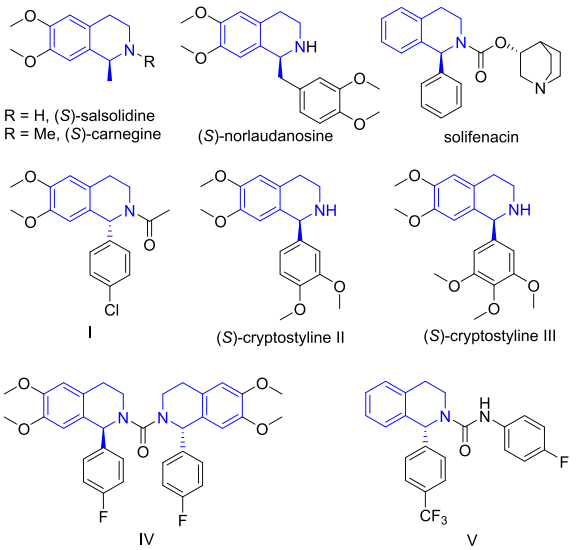


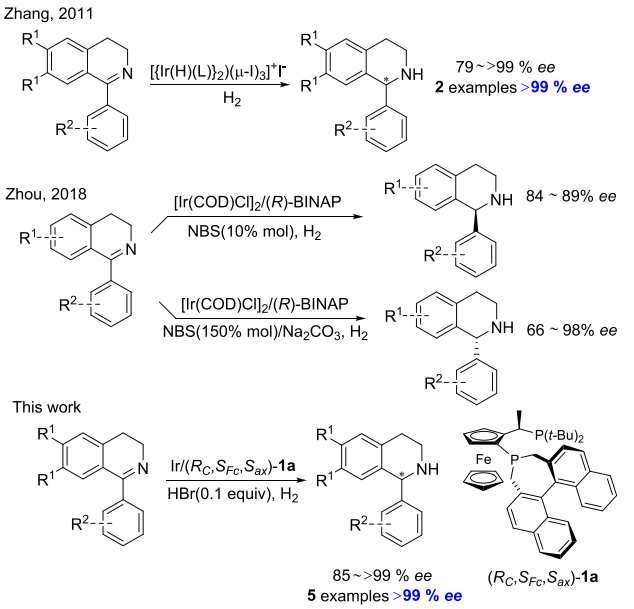
Figure 1. Bioactive chiral 1-substituted THIQs. (*S*)-Salsolidine, (*S*)-carnegine, (*S*)-norlaudanosine, AMPA receptor antagonist I, solifenacin, (*S*)-cryptostyline II, (*S*)-cryptostyline III, TRPM8 channel receptor antagonist IV and V.

was used for the process by Ratovelomanana-Vidal et al. via activating the nitrogen atom of the dihydroisoquinoline ring. Similarly, this catalytic system provided only moderate enantioselectivities for sterically hindered 1-(2′-substituted-aryl)-3,4-DHIQs.[6b] Then, Zanotti-Gerosa's group successfully

Received: September 14, 2019

DOI: 10.1021/acs.orglett.9b03251
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Asymmetric Hydrogenation of 1-Aryl-3,4-DHIQs



prepared the key intermediate of (*S*)-salsolidine by AH of 1-phenyl-3,4-DHIQ hydrochloride on a 200 g scale (95% yield, 98% *ee*).[6c] Togni et al. also applied *P*-trifluoromethyl ligands to the AH of 1-substituted-3,4-DHIQ hydrochlorides at 55−60 °C and 100 atm of H_2, and a 96% *ee* value was obtained.[6d] Recently, a dual stereocontrolled catalytic system in AH of 1-substituted-3,4-DHIQs was established by Zhou's group, and both enantiomers of hydrogenation products were obtained respectively by tuning the amount of NBS using the BINAP ligand of the single configuration.[8] Unfortunately, this catalytic system seemed only to be effective in less sterically hindered 1-(3′- or 4′-substituted-aryl)-3,4-DHIQs. Therefore, developing additional enantioselective catalysts for the efficient construction of chiral 1-aryl-substituted THIQ frameworks through enantioselective hydrogenation is highly welcomed.

As part of our ongoing research toward the development of metal-catalyzed asymmetric synthesis of biologically relevant targets,[9] we hope to develop an efficient catalytic system to prepare the chiral 1-aryl-THIQs. Currently, the state-of-the-art ligand for this transformation is (*S*,*S*)-f-binaphane explored by Zhang et al. in 2001, which possesses strongly electron-donating ability and backbone rigidity.[10] As we all know, the Josiphos ligands are a kind of privileged ligands and have already been used in a wide variety of transformations, often with high enantioselectivities and generally good to very high s/c ratios.[11] The two phosphine groups of Josiphos ligands could be introduced separately, allowing the easy preparation of numerous chiral ligands with diverse steric and electronic properties. We then designed a new type of chiral ligand combining the privileged skeleton of Josiphos and the axial chiral phosphine moiety of f-binaphane, hoping to produce new ligands with higher modularity and more convenient modification (Figure 2). Herein, we report our efforts toward the synthesis of this Josiphos-type binaphane ligands **1** and their application in Ir-catalyzed AH of 1-aryl-3,4-DHIQs (Scheme 1).

As illustrated in Scheme 2, the synthesis of Josiphos-type binaphane ligands **1** is quite simple and straightforward starting from commercially available (*R*)-Ugi's amine (**2**) and optically pure binol (**3**). (*S*)-**3** was first converted to corresponding

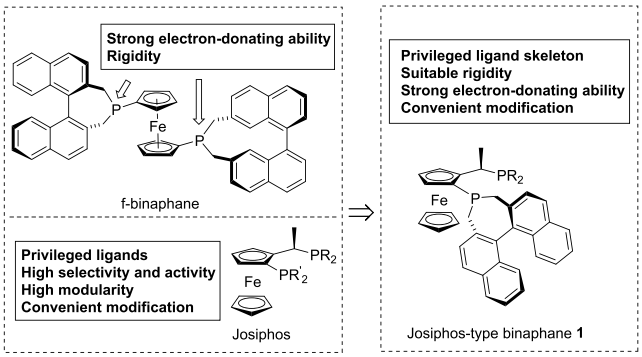
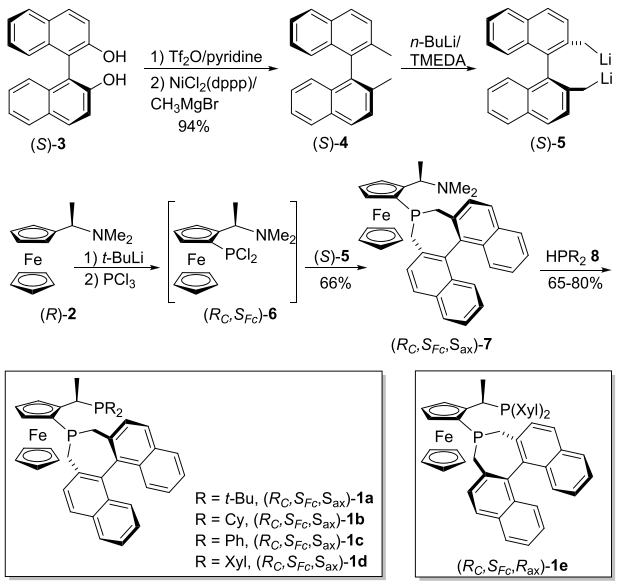


Figure 2. Design of the Josiphos-type binaphane ligands **1**.

Scheme 2. Synthesis of Josiphos-Type binaphane ligands 1

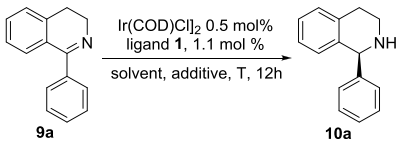


sulfonate ester in quantitative yield, and subsequent nickel-catalyzed Kumada coupling with methyl magnesium bromide led to 2,2′-dimethylbinaphthalene **4** in 94% yield.[12a] The dilithium salt **5** was easily obtained by reaction of **4** with *n*-butyl lithium in the presence of TMEDA.[12b] Then, according to our published procedures,[12c] highly diastereoselective *ortho*-lithiation of (*R*)-**2** followed by treatment with PCl_3 gave **6**, which was further transformed into monophosphine (R_C,S_{Fc},S_{ax})-**7** by reaction with dilithium salt **5** in 66% isolated yield. Finally, the second phosphino group was introduced by a stereospecific S_N1-type reaction, of which the dimethylamino moiety was substituted with retention of configuration in moderate to good yields (65−80%).[13] In addition, we synthesized ligand (R_C,S_{Fc},R_{ax})-**1e**, which is the diasteroisomer of ligand (R_C,S_{Fc},S_{ax})-**1d**, to investigate the chirality matching between different chiral sources in the ligand.

Initial investigations began with the hydrogenation of the standard substrate 1-phenyl-3,4-DHIQ (**9a**) using standard conditions. The reaction proceeded smoothly when employing (R_C,S_{Fc},S_{ax})-**1a**−**1d** and (R_C,S_{Fc},R_{ax})-**1e** as ligands to afford (*S*)-1-phenyl-THIQ **10a** in high yields (Table 1, entries 1−5). It is noteworthy that the axial chirality at the binaphthalene backbone of **1** had a pronounced influence on the stereoinduction, and the chiralities with S_{ax}, R_{Fc}, and R_C were more matched (entries 4 vs 5). With regard to the effect of the P-substituents, the *t*-Bu group was highly beneficial in terms of

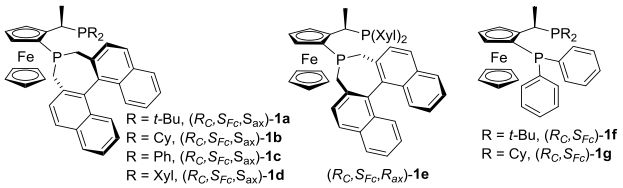
DOI: 10.1021/acs.orglett.9b03251
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Asymmetric Hydrogenation of 1-Phenyl-3,4-DHIQ by Ir-1[a]



Entry	Ligand	Solvent	Additive	T (°C)	Conv[b] (%)	ee[c] (%)
1	(R_C,S_{Fc},S_{ax})-**1a**	toluene	I_2, TFA	30	>99	81
2	(R_C,S_{Fc},S_{ax})-**1b**	toluene	I_2, TFA	30	>99	60
3	(R_C,S_{Fc},S_{ax})-**1c**	toluene	I_2, TFA	30	>99	22
4	(R_C,S_{Fc},S_{ax})-**1d**	toluene	I_2, TFA	30	>99	65
5	(R_C,S_{Fc},R_{ax})-**1e**	toluene	I_2, TFA	30	>99	15
6	(R_C,S_{Fc})-**1f**	toluene	I_2, TFA	30	65	35
7	(R_C,S_{Fc})-**1g**	toluene	I_2, TFA	30	60	21
8	(R_C,S_{Fc},S_{ax})-**1a**	THF	I_2, TFA	30	>99	84
9	(R_C,S_{Fc},S_{ax})-**1a**	THF	none	30	>99	74
10	(R_C,S_{Fc},S_{ax})-**1a**	THF	I_2	30	>99	75
11	(R_C,S_{Fc},S_{ax})-**1a**	THF	TFA	30	>99	85
12	(R_C,S_{Fc},S_{ax})-**1a**	THF	40% HBr	30	>99	>99
13[d]	(R_C,S_{Fc},S_{ax})-**1a**	THF	40% HBr	50	98	99
14[e]	(R_C,S_{Fc},S_{ax})-**1a**	THF	40% HBr	50	85	98

[a]Reaction conditions: Ir/ligand/additive/substrate = 1:2.2:20:200, (substrate) = 0.25 M, 50 atm H_2, 30 °C, 12 h. [b]Conversions were determined by ^{1}H NMR. [c]Enantiomeric excesses were determined by chiral HPLC after the products were converted into the corresponding acetamides. The absolute configuration is assigned by comparison of the rotation sign with literature[7] data. [d]Catalyst loading is 0.1 mol %. [e]Catalyst loading is 0.02 mol %.



enantioselectivity and catalytic activity (entry 1). For comparison, two classic Josiphos ligands (R_C,S_{Fc})-**1f** and (R_C,S_{Fc})-**1g** were tested in the hydrogenation of **9a**, but lower enantioselectivities and yields were obtained (entries 6 vs 7). After screening for solvent, iridium precursor, additive, temperature, and hydrogen pressure (see the Supporting Information, Table S1), the transformation catalyzed by Ir-(R_C,S_{Fc},S_{ax})-**1a** in THF at 30 °C and 50 atm H_2 in the presence of 40% HBr (aqueous solution) turned out to be optimal, providing (*S*)-**10a** in quantitative yield and up to >99% *ee* (entry 12). To the best of our knowledge, this is the best result in AH of 1-phenyl-3,4-DHIQ compared with previous reports. Combined with these results and the related mechanistic research,[8,14] we proposed that HBr was used not only to activate the imine substrate through hydrogen bromide but also to improve the performance of the catalyst via a six-membered cyclic transition state due to the formation of salts between the substrate and the hydrogen bromide (Figure 3).

To explore the substrate scope of this catalytic system, a wide range of 1-aryl-3,4-DHIQs (**9a**–**9v**) were synthesized and

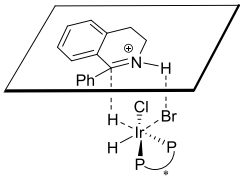


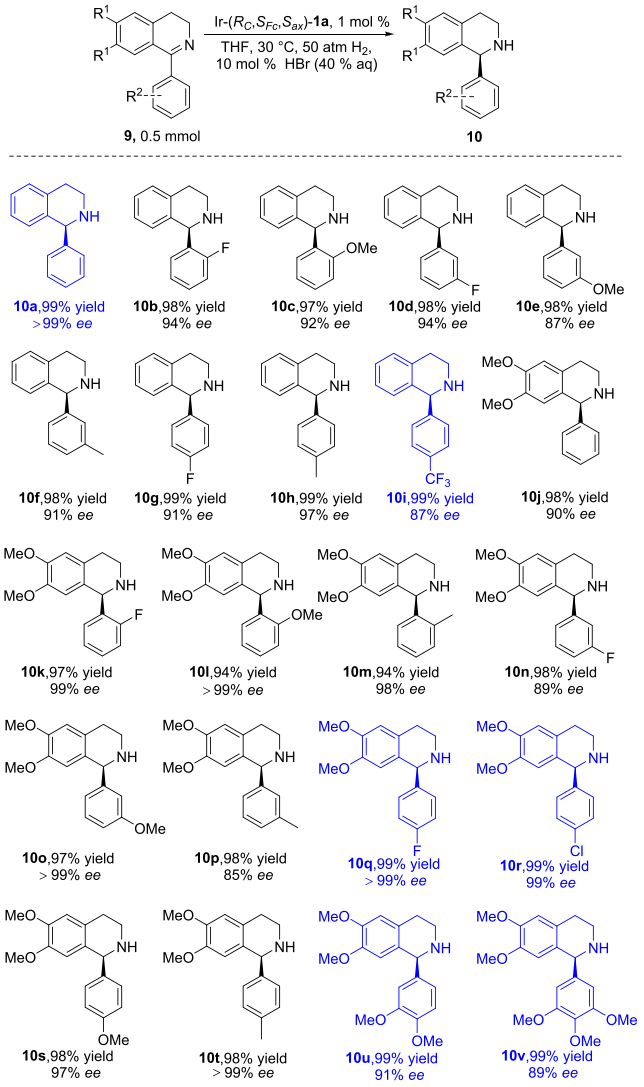
Figure 3. Probable transition state of hydrogenation.

hydrogenated under the optimized reaction conditions. High yields were obtained for all substrates, with good to excellent enantioselectivities ranging from 85% to >99% *ee* (Scheme 3). The stereochemical outcome of the substrates **9b**–**9i** appears to be insensitive to the nature and position of the substituents present on the 1-phenyl ring, affording adducts with similar enantioselectivities. A remarkable increase in enantioselectivities was observed when 6,7-dimethoxy was introduced in the benzene ring of the dihydroisoquinoline core (**9k**–**9m**, **9o**, **9q**–**9t**), especially for the substrates bearing either electron-donating or electron-withdrawing groups at the *ortho* (**9k**–**9m**) or *para* position (**9q**–**9t**) of the pendant 1-phenyl ring. It was worth mentioning that this catalytic system performed very well in the asymmetric synthesis of several important intermediates (**10a**, **10u**, **10v**, and **10q**) of pharmaceuticals or biological active compounds, for example, solifenacin, (*S*)-cryptostyline II, (*S*)-cryptostyline III, and TRPM8 channel receptor antagonist IV. In addition, (*R*)-**10i** and (*R*)-**10r** would be conveniently obtained with the enantiomer of the ligand (R_C,S_{Fc},S_{ax})-**1a**, which were the important intermediates of the TRPM8 channel receptor antagonist V and AMPA receptor antagonist I. Furthermore, the catalytic system was also applied to the AH of 1-alkyl-3,4-DHIQs (**9w**, **9x**), but the results were disappointing. Lower enantioselectivities and yields were obtained for both 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (47% *ee*, 56% yield) and 1-ethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (38% *ee*, 60% yield).

Encouraged by the remarkable enantioselectivity, catalytic activity, and easily availability of these new ligands, we carried out the application of this catalytic system in the large-scale

DOI: 10.1021/acs.orglett.9b03251
Org. Lett. XXXX, XXX, XXX−XXX

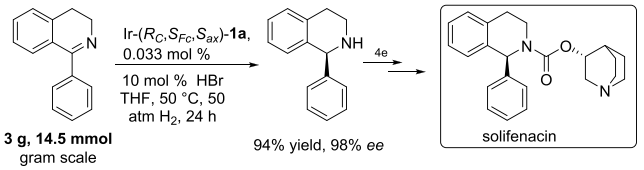
Scheme 3. Asymmetric Hydrogenation of 1-Aryl-3,4-DHIQs by Ir-(R_C,S_{Fc},S_{ax})-1a



synthesis of the prescription drug solifenacin.[4e] A scaled-up catalytic hydrogenation was subsequently conducted, and (*S*)-1-phenyl-1,2,3,4-THIQ (**10a**) was obtained in 98% *ee* with a substrate to catalyst ratio of 3000. The chiral amine **10a** was simply transformed to solifenacin in two classical and high yield reactions (Scheme 4).

In conclusion, a new class of chiral diphosphine ligands (Josiphos-type binaphane **1**) has been synthesized and applied in the Ir-catalyzed AH of challenging 1-aryl-3,4-DHIQ substrates with excellent enantioselectivities and high turnover numbers (up to 4000). The use of 40% HBr (aqueous solution) as an additive dramatically enhanced the asymmetric induction of this catalyst. This catalytic system provides an atom-economic and efficient access to enantiomerically pure 1-aryl-THIQs derivatives, including the substructure of the pharmaceutical drug solifenacin. Further applications of these diphosphine ligands are in progress and will be reported in due course.

Scheme 4. Gram-Scale Asymmetric Hydrogenation of 1-Phenyl-3,4-DHIQ



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03251.

Procedures, NMR and HPLC spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21372259, 21472240) and Fourth Military Medical University (2018XA009) for financial support.

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DOI: 10.1021/acs.orglett.9b03251
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