Asymmetric Catalysis

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A Highly Efficient and Enantioselective Access to Tetrahydroisoquinoline Alkaloids: Asymmetric Hydrogenation with an Iridium Catalyst**

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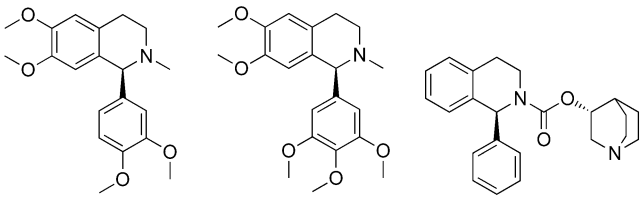
Tetrahydroisoquinolines are an important class of alkaloids displaying high bioactivities.[1] They are present in numerous natural products, and in pharmaceutical drugs and drug candidates, for example, (+)-cryptostyline II,[2a] (+)-cryptostyline III,[2a] and solifenacin (Scheme 1).[2b] Among the

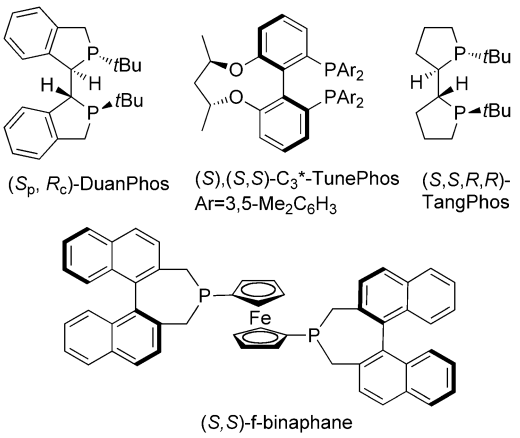


Scheme 1. Structures of (+)-cryptostyline II, (+)-cryptostyline III, and solifenacin.

various synthetic methods developed in recent decades to afford enantiomerically pure tetrahydroisoquinolines,[1,3] catalytic asymmetric hydrogenation of the corresponding imines shows most promise as a highly efficient and straightforward approach.[4]

During the past two decades, a number of catalytic systems for asymmetric hydrogenation[5] and asymmetric transfer hydrogenation[6] of this class of imines have been invented. Using the chiral titanocene developed by Buchwald and Willoughby, 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline was hydrogenated with 98% *ee*.[5a] Noyori and coworkers initiated research into the Ru^{II}/TsDPEN complex for the highly enantioselective transfer hydrogenation of 3,4-dihydroisoquinolines.[6a] This system was successfully applied in the reduction of 1-(2′-NHR/$NO_2C_6H_4$)-3,4-dihydroisoquinoline.[6b] Since then, intense research has been focused on this system and modifications have taken place on all components of this catalytic complex, such as, the diamine ligand, the transition metal center, the coordinating η-arene, and the counterion.[5h,6c–j] Although these titanocene, Ru/DPEN and Rh/DPEN systems addressed the reduction of 1-alkyl-3,4-dihydroisoquinolines effectively, the asymmetric hydrogenation to enantiomerically pure 1-aryl-tetrahydroisoquinolines remains a challenge, probably owing to the relatively rigid and space-demanding spatial features of these imines. For example, there is no report on the asymmetric hydrogenation of 1-phenyl-3,4-dihydroisoquinoline, a reaction which would lead to the pharmaceutical drug solifenacin (Scheme 1), and the industrial production of this particular tetrahydroisoquinoline depends on an optical resolution of the racemic mixture using tartaric acid.[7]

Herein, we report the highly efficient asymmetric hydrogenation of 1-substituted 3,4-dihydroisoquinolines catalyzed by an iridium/f-binaphane complex with excellent reactivity and enantioselectivities (up to 99% *ee* and TONs of up to 10000). The combination of iridium and f-binaphane (Scheme 2) was chosen based on their outstanding performance in asymmetric hydrogenation of a variety of imines



Scheme 2. Structures of chiral phosphine ligands.

from our research.[8] Iridium/diphosphine complexes show more potential for imine reduction in the presence of various additives and possess better activities than other transition metals.[9] At the same time, f-binaphane, which is a strong electron donor and features a flexible ferrocene-based backbone, thus allowing the accommodation of a wide range of substrates around the transition metal center, has been

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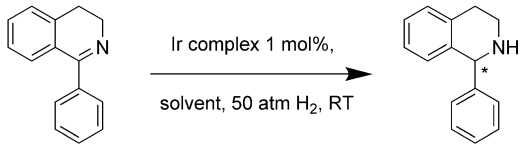
deployed successfully in asymmetric imine reduction[8] and in reductive amination.[10]

Initially two iridium precursors were explored along with (*S*,*S*)-f-binaphane for the asymmetric hydrogenation of the standard substrate 1-phenyl-3,4-dihydroisoquinoline (**1a**). The neutral $[\{Ir(cod)Cl\}_2]$ (cod = 1,5-cyclooctadiene) gave better conversion yet with limited enantioselectivity (Table 1, entries 1 and 2). From the solvent screening (Table 1, entries 3–7), CH_2Cl_2 afforded the best enantioselectivity and a good conversion. With the addition of 10 mol% of I_2[11a] the enantiomeric excess was enhanced to 88% and a full conversion was achieved (Table 1, entry 8). When the amount of I_2 was reduced to 1 mol%, the *ee* value dropped to 81% (Table 1, entry 9). Other common additives,[11] such as potassium carbonate, triethylamine, phthylamide, and trifluoroacetic acid were also investigated and proved to have no positive effect on this hydrogenation. In a control study, a brief screening of other diphosphines was carried out. As expected, none of these ligands yielded comparable results to f-binaphane (Table 1, entries 10–12). The iodine-bridged dimeric iridium complexes, initially reported by Genet et al,[12] have shown excellent reactivity in our previous research on asymmetric hydrogenation of cyclic imines.[8d] Therefore, complex $[\{Ir(H)[(S,S)\text{-(f)-binaphane}]\}_2(\mu\text{-}I)_3]^+I^-$ (**A**) was also applied in our study. To our delight, the enantiomeric excess was further improved to 95% with a complete conversion (Table 1, entry 13). Using 0.05 mol% of this Ir catalyst, the reaction still preceded smoothly without compromising the enantioselectivity; when the catalyst loading was further decreased to 0.005 mol%, a slightly lower conversion and *ee* value were obtained (Table 1, entries 14 and 15).

To explore the scope and limitations of this Ir/f-binaphane catalytic system, a range of 1-substituted 3,4-dihydroisoquinoline imines (**1a**–**1p**) were synthesized and hydrogenated under the optimized reaction conditions. The results are summarized in Table 2. This iridium complex reduced both 1-alkyl- (Table 2; entries 2, 3, and 14) and 1-aryl-3,4-dihydroisoquinolines effectively with excellent enantioselectivities. As for 1-aryl-3,4-dihydroisoquinoline imines, whether the substituents are at the *para* (**1d**–**1g**) or *meta* (**1h**–**1i**) position of the phenyl ring, all substrates afforded the corresponding tetrahydroisoquinoline alkaloids with high enantioselectivities (*ee* values range from 94% to 99%), regardless of the electronic properties of the substituents; interestingly, when the imines bear a 1-*ortho*-substituted phenyl ring (**1j** and **1k**), the hydrogenation results vary dramatically, and a higher catalyst loading was required (Table 2, entries 10 and 11). The high *ee* value for 1-(2′-$OMeC_6H_4$) imine is probably attributed to the coordination effect of the oxygen to the transition metal center, while the poor result for 1-(2′-MeC_6H_4) imine stems from steric reasons. This catalytic system also worked quite well for 1-heteroaromatic imine **1l**, giving 96% *ee* with a full conversion (Table 2, entry 12). It is worth mentioning that both enantiomerically pure (*S*)-(−)-norcryptostyline II (**2o**) and (*S*)-(−)-norcryptostyline III (**2p**) were obtained in over 99% *ee* (Table 2, entries 15 and 16).

In summary, the highly effective iodine-bridged dimeric $[\{Ir(H)[(S,S)\text{-(f)-binaphane}]\}_2(\mu\text{-}I)_3]^+I^-$ complex has been applied in the asymmetric hydrogenation of a wide range of 3,4-dihydroisoquinolines with excellent enantioselectivities and high turnover numbers (up to 10000). The use of I_2 as an additive enhanced the performance of this catalyst. This catalytic system offers an efficient access to various enantiomerically pure tetrahydroisoquinoline alkaloids, including the substructure of the pharmaceutical drug of solifenacin. Further applications of this complex for the asymmetric hydrogenation of 3,4-dihydroquinolines and other cyclic imines are in progress.

Table 1: Asymmetric hydrogenation of 1-phenyl-3,4-dihydroisoquinoline.[a]



1a **2a**

Entry	Ir precursor	Ligand	Solvent	Additive	Conv. [%][b]	*ee* [%][b]
1	$[Ir(cod)_2BF_4]$	f-binaphane	EtOAc/CH_2Cl_2 (1:1)	–	30	22
2	$[\{Ir(cod)Cl\}_2]$	f-binaphane	EtOAc/CH_2Cl_2 (1:1)	–	52	23
3	$[\{Ir(cod)Cl\}_2]$	f-binaphane	EtOAc	–	98	32
4	$[\{Ir(cod)Cl\}_2]$	f-binaphane	CH_2Cl_2	–	86	46
5	$[\{Ir(cod)Cl\}_2]$	f-binaphane	THF	–	99	22
6	$[\{Ir(cod)Cl\}_2]$	f-binaphane	toluene	–	84	20
7	$[\{Ir(cod)Cl\}_2]$	f-binaphane	MeOH/CH_2Cl_2 (6:1)	–	11	35
8	$[\{Ir(cod)Cl\}_2]$	f-binaphane	CH_2Cl_2	I_2 (10 mol%)	>99	88
9	$[\{Ir(cod)Cl\}_2]$	f-binaphane	CH_2Cl_2	I_2 (1 mol%)	>99	81
10	$[\{Ir(cod)Cl\}_2]$	TangPhos	CH_2Cl_2	I_2 (10 mol%)	70	34
11	$[\{Ir(cod)Cl\}_2]$	DuanPhos	CH_2Cl_2	I_2 (10 mol%)	<5	–
12	$[\{Ir(cod)Cl\}_2]$	C_3*-TunePhos	CH_2Cl_2	I_2 (10 mol%)	<5	–
13[c,d]	$[\{Ir(cod)Cl\}_2]$	f-binaphane	CH_2Cl_2	I_2/HI	>99	95
14[c,e]	$[\{Ir(cod)Cl\}_2]$	f-binaphane	CH_2Cl_2	I_2/HI	>99	95
15[c,f]	$[\{Ir(cod)Cl\}_2]$	f-binaphane	CH_2Cl_2	I_2/HI	93	93

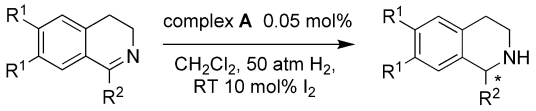
[a] Reaction conditions: [Ir]/ligand/substrate = 1:1:100, ligand/metal 1:1, 50 atm of H_2, RT, 24 h. [b] Reaction conversions and enantiomeric excess were determined by HPLC on a chiral stationary phase after the amine products were converted into the corresponding acetamides. [c] HI was used for preparation of the iodine-bridged dimeric iridium complex $[\{Ir(H)[(S,S)\text{-(f)-binaphane}]\}_2(\mu\text{-}I)_3]^+I^-$ (**A**) according to references [8d], [12] [d] Complex **A** loading is 0.5 mol%. [e] Complex **A** loading is 0.05 mol%. [f] Complex **A** loading is 0.005 mol%.

Experimental Section

Substrate preparation: All substrates were prepared from the corresponding 2-arylethyl amine and alkyl- or arylcarbonyl chloride in two steps according to literature reports.[13]

Catalyst preparation: Complex **A** was prepared according to literature reports.[8d,12] $[\{Ir(cod)Cl\}_2]$ (26.9 mg, 40 mmol) and (*S*,*S*)-f-binaphane (71.0 mg, 88 mmol) in toluene (6 mL) were stirred at room temperature for 2 h. Then an excess of aqueous HI (55%, 34 μL) was added via a syringe. The resulting mixture was stirred overnight, and all volatiles were removed under reduced pressure. The residue was dissolved in dichloromethane, and hex-

Table 2: Asymmetric hydrogenation of 3,4-dihydroisoquinolines by Ir/f-binaphane.[a]



1 **2**

Entry	R^1	R^2	Product	Conv. [%][b]	*ee* [%][b]
1	H (**1a**)	C_6H_5	**2a**	>99	95 (*S*)
2	H (**1b**)	*i*Pr	**2b**	>99	96 (−)
3	H (**1c**)	Cy	**2c**	>99	95 (−)
4	H (**1d**)	4-MeC_6H_4	**2d**	>99	94 (+)
5	H (**1e**)	4-ClC_6H_4	**2e**	>99	96 (*S*)
6	H (**1f**)	4-$MeOC_6H_4$	**2f**	>99	95 (*S*)
7	H (**1g**)	4-$CF_3C_6H_4$	**2g**	>99	97 (+)
8	H (**1h**)	3-MeC_6H_4	**2h**	>99	95 (+)
9	H (**1i**)	3-ClC_6H_4	**2i**	>99	98 (+)
10[c]	H (**1j**)	2-MeC_6H_4	**2j**	98	79 (+)
11[c]	H (**1k**)	2-$MeOC_6H_4$	**2k**	>99	98 (−)
12	H (**1l**)	2-furoyl	**2l**	>99	96 (+)
13	OMe (**1m**)	C_6H_5	**2m**	>99	97 (*S*)
14	OMe (**1n**)	*i*Pr	**2n**	>99	95 (*S*)
15	OMe (**1o**)	3,4-$(MeO)_2C_6H_3$	**2o**	99	>99 (*S*)
16	OMe (**1p**)	3,4,5-$(MeO)_3C_6H_2$	**2p**	99	>99 (*S*)

[a] Reaction conditions: complex **A**/I_2/substrate = 0.05:10:100, 50 atm of H_2, RT, 24 h. [b] Conversions and enantiomeric excesses were determined by HPLC and GC on a chiral stationary phase after the products were converted into the corresponding acetamides. The absolute configuration of the product is shown in brackets and is assigned by comparison of the rotation sign with literature data.[3b,6b] [c] Complex **A**/substrate = 0.25:100. Cy = cyclohexyl.

anes were added to precipitate the complex (85.0 mg, 83% yield) as a pale yellow powder.

Hydrogenation: In a nitrogen-filled glovebox, complex **A** (2.5 mg, 0.001 mmol) was dissolved in anhydrous CH_2Cl_2 (1.0 mL) and equally divided into 10 vials charged with imine substrates (0.2 mmol) in anhydrous CH_2Cl_2 solution (1.0 mL). Then I_2 (5.1 mg, 0.02 mmol) was added and the total solution was made to 2.0 mL for each vial. The resulting vials were transferred to an autoclave, which was charged with 50 atm of H_2, and the reaction mixtures were stirred at room temperature for 24 h. The hydrogen gas was released slowly and the solution was concentrated and passed through a short column of silica gel to remove the metal complex. The chiral amine products reacted with acetic anhydride to yield the corresponding acetamides, which were then analyzed by HPLC and GC on a chiral stationary phase to determine the enantiomeric excesses.

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