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Enantioselective Synthesis of 1-Aryl-tetrahydroisoquinolines through Iridium Catalyzed Asymmetric Hydrogenation

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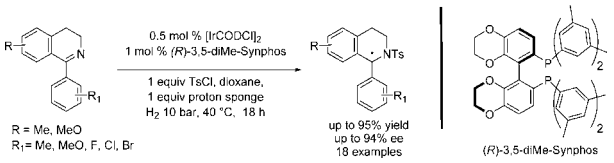
ABSTRACT



Asymmetric hydrogenation of 1-aryl-3,4-dihydroisoquinolines using the [IrCODCl]$_2$/(*R*)-3,5-diMe-Synphos catalyst is reported. Under mild reaction conditions, this atom-economical process provides easy access to a variety of enantioenriched 1-aryl-1,2,3,4-tetrahydroisoquinoline derivatives, which are important pharmacophores found in several pharmaceutical drug candidates, in high yields and enantiomeric excesses up to 99% after a single crystallization.

Isoquinoline derivatives, widely present in plants and several tissues in mammalian alkaloids, play an important role in the field of medicinal chemistry due to their remarkable pharmacological potential.[1] Among the members of this family, 1-aryl-substituted-1,2,3,4-tetrahydroisoquinoline derivatives (THIQs) constitute a major group in this class of alkaloids. For example, compound **I** (Solifenacin, YM-905) is a competitive muscarinic acetylcholine receptor antagonist currently used in the treatment of overactive bladders.[2] 1-Phenyl-tetrahydroisoquinoline **II** originally developed as a general anesthetic agent shows phencyclidine-like stereotype behavior and ataxia,[3] whereas compound **III** is a potent noncompetitive AMPA receptor antagonist currently being investigated in phase III trials as an antiepileptic agent[4] (Figure 1). In view of their high potential as pharmaceutical drug candidates, the synthesis of 1-substituted-THIQs has attracted much attention, and various efficient methods have been developed during the past decades.

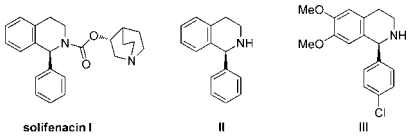


Figure 1. Bioactive 1-aryl-tetrahydroisoquinolines.

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However, most of these methods, involve the use of chiral starting building blocks or rely on diastereoselective reactions using a stoichiometric amount of chiral sources.[5] Consequently, the development of new efficient catalytic enantioselective methods to give 1-substituted-THIQ frameworks is required. To date, only a few approaches are based on catalytic asymmetric reactions.[5,6] Among them, asymmetric hydrogenation of 1-substituted 3,4-dihydroisoquinoline derivatives (DHIQs) constitutes one of the most direct and viable strategies for the synthesis of such compounds. Over the past two decades, significant progress in the development of transition-metal catalyzed asymmetric hydrogenation[7] and asymmetric transfer hydrogenation[8] has been done in this area. However, since the seminal work of Buchwald et al.[9] and Noyori et al.,[10] using a chiral *ansa*-titanocene catalyst and a Ru/TsDPEN catalyst for the asymmetric reduction of the 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline (95 and 96% ee, respectively), only a few efficient catalytic systems have been reported to give 1-alkyl-THIQs in high enantioselectivity.[11h,k,l] Surprisingly, most of the catalytic systems provide low to moderate selectivity for the hydrogenation of more challenging 1-aryl-substituted-DHIQs, which has been attributed to greater steric hindrance arising from the adjacent aromatic ring. So far, only two examples of catalytic enantioselective reduction of 1-aryl-substituted-3,4-dihydroisoquinolines have been described in the literature. Vedejs et al.[11m] reported excellent ee values, ranging from 94 to 99%, via asymmetric transfer hydrogenation using the Noyori Ru/TsDPEN catalyst with the substrate scope limited to a few 1-*ortho*-substituted aryl-3,4-dihydro-7,8-dimethoxyisoquinolines. In 2011, Zhang et al.[11k] described the asymmetric hydrogenation of 1-alkyl- and 1-aryl-3,4-dihydroisoquinolines with excellent conversions and high enantioselectivities using the iodine-bridged dimeric iridium complex $[\{Ir(H)[(S,S)\text{-}(f)\text{-binaphane}]\}_2\text{-}(\mu\text{-}I)_3]^+I^-$. We report herein the efficient enantioselective synthesis of various 1-aryl-THIQ derivatives **2** through Ir/(*R*)-3,5-diMe-Synphos catalyzed asymmetric hydrogenation of the corresponding 1-aryl-DHIQs **1**.

Initial investigations began with the hydrogenation of 1-phenyl-DHIQ **1a** as a standard substrate using 0.5 mol % of $[IrCODCl]_2$ in the presence of various diphosphines **L1**−**L8** at 40 °C in THF under 30 bar of H_2 for 18 h (Table 1). In all cases, the hydrogenation product **2a** was isolated in good to excellent yields. The use of Difluorphos ligand **L1**[12] and the Sunphos family of ligands **L2**−**L4**,[13] which both share similar dihedral angles but opposite electronic profiles, gave moderate enantioselectivities ranging from 35 to 39% (Table 1, entries 1−4). The data in Table 1 clearly showed that the steric properties of the diphosphine, in particular the substituents at the phosphorus atom, greatly influenced the stereochemical outcome of the reaction. This steric effect was revealed by a comparison of the selectivity of the reaction carried out with catalysts bearing the Synphos family of ligands[14] (Table 1, entries 5−8). The Synphos ligand **L5** and the corresponding 4-Me-C_6H_4 substituted diphosphine **L6** afforded slightly better selectivities compared to ligands **L1**−**L4**, with 46 and 42% ee, respectively (Table 1, entries 5 and 6), while ligands **L7** and **L8** having 3,5-dialkyl-substituents on the P-phenyl rings led to a significant increase in

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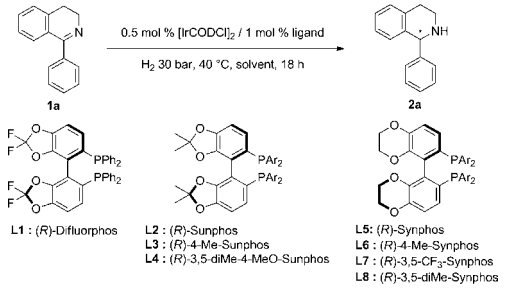
Table 1. Ligand Screening for Asymmetric Hydrogenation of **1a**[a]



entry	ligand	solvent	yield (%)[b]	ee (%)[c]
1	**L1**	THF	97	38
2	**L2**	THF	90	35
3	**L3**	THF	89	39
4	**L4**	THF	75	39
5	**L5**	THF	95	46
6	**L6**	THF	93	42
7	**L7**	THF	91	69
8	**L8**	THF	95	71
9	**L8**	toluene	93	55
10	**L8**	Et_2O	92	65
11	**L8**	dioxane	95	73
12	**L8**	CH_2Cl_2	89	41
13	**L8**	$ClCH_2CH_2Cl$	90	38
14	**L8**	EtOAc	89	65
15	**L8**	MeOH	87	18

[a] All reactions were performed using 1 mmol of substrate **1a** with 1 mol % of Ir-catalyst. [b] After flash column chromatography. [c] Determined by chiral stationary phase-supercritical fluid chromatography.

enantioselectivity regardless of the electronic nature of the substituents (Table 1, entries 7 and 8, 69 and 71% ee). This result is another manifestation of what Pregosin et al.[15] have named the "3,5-*meta*-dialkyl effect".

Further examinations focused on the solvent employed (Table 1, entries 8–15). Although the hydrogenation could be performed in all tested solvents, the best results with regard to both selectivity and reactivity were achieved in ethereal solvents, and dioxane was found to be the solvent of choice, giving **2a** in 95% isolated yield and 73% ee (Table 1, entry 11).

It is well-known that the presence of a second coordinating group attached to the nitrogen atom is a critical element for achieving both high reactivity and selectivity in the asymmetric hydrogenation of C=N bonds.[7] We thus decided to evaluate the effect of various activating reagents for the hydrogenation of **1a**. The results of these experiments are reported in Table 2. With the exception of $(PhCO)_2O$, the reduction of **1a** under 30 bar of H_2 at 40 °C using dioxane in the presence of anhydride derivatives (1 equiv) proceeded smoothly to afford the desired product **3a** in excellent yield and with significant higher enantioselectivity than those obtained when the reaction is performed without an activator (Table 2, entries 1–4, 70–84% ee). To our delight, the enantiomeric excess of **3a**

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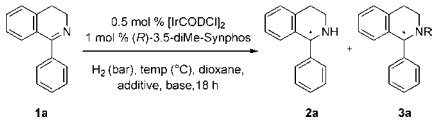
Table 2. Optimization of the Reaction Conditions for Asymmetric Hydrogenation of **1a**[a]



				yield (%)[b]		
entry	additive/ base	temp (°C)	P (bar)	**2a**	**3a**	ee **3a** (%)[c]
1	$(Boc)_2O$/none	40	30	0	94	84
2	$(Ac)_2O$/none	40	30	0	92	83
3	$(PhCO)_2O$/none	40	30	0	94	70
4	$(EtOCO)_2O$/none	40	30	0	96	81
5	TsCl/none	40	30	46	45	92
6	TsCl/K_2CO_3	40	30	30	65	84
7	TsCl/DIPEA	40	30	20	77	84
8	TsCl/Et_3N	40	30	20	75	84
9	TsCl/proton sponge	40	30	0	95	92
10	TsCl/proton sponge	60	30	0	95	92
11	TsCl/proton sponge	20	30	0	92	87
12	TsCl/proton sponge	40	50	0	94	92
13	TsCl/proton sponge	40	10	0	95	94

[a] All reactions were performed using 1 mmol of substrate **1a** with 1 mol % of Ir-catalyst. [b] After flash column chromatography. [c] Determined by chiral stationary phase-supercritical fluid chromatography.

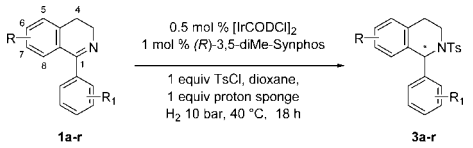
increased remarkably to 92% ee when TsCl (1 equiv) was used. However, **3a** was obtained in only 45% yield along with the nonprotected THIQ compound **2a** in similar yield (Table 2, entry 5). To avoid the formation of **2a**, which probably resulted from the reduction of the hydrogen chloride salt of **1a** produced during the reaction, as previously observed by Zhou et al.[11j] for the asymmetric hydrogenation of quinolines activated by chloroformates, we studied the effect of several bases (Table 2, entries 6–9). Gratifyingly, the amount of **2a** was completely suppressed when the sequestering proton sponge was used, giving the desired product **3a** in 95% yield and 92% ee.[16]

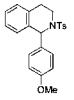
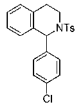
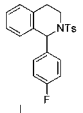
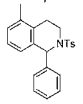
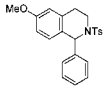
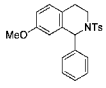
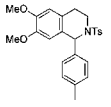
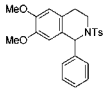
Finally, variation of the hydrogen pressure and reaction temperature has only little effect on the catalytic activity (Table 2, entries 9–13).

To assess the substrate scope, a full set of 1-aryl- DHIQ derivatives **1a**–**r** were synthesized and hydrogenated under the optimized reaction conditions (Table 3). High yields were obtained for all substrates, with good to excellent enantioselectivities ranging from 81% to 94%. The stereochemical outcome of the reaction was largely influenced by the substitution pattern on the aromatic rings. For example, compounds **1** with an *ortho* substituent on the 1-phenyl group gave uniformly lower enantioselectivities compared to the nonsubstituted DHIQ **1a**, probably due to the unfavorable steric hindrance between the *ortho*-substituted group of the substrate and the catalyst during the reaction (Table 3, compare entry 1 vs entries 2, 5, and 8, 80–83% ee). Similar results were obtained with substrates possessing an electron-withdrawing group (Table 3,

(16) For mechanism discussion, see Supporting Information.

Table 3. Asymmetric Hydrogenation of 1-Aryl-Substituted 3,4-Dihydroisoquinolines **1a**–**r**[a]



entry		product	yield (%)[b]	ee (%)[c]
1	**3a**		94	94 (96)[d]
2	**3b**		88	83 (99)
3	**3c**		86	83 (99)
4	**3d**		95	90 (99)
5	**3e**		62	80 (97)
6	**3f**		93	90 (97)
7	**3g**		91	90 (99)
8	**3h**		85	82 (90)
9	**3i**		92	82 (98)
10	**3j**		88	81 (96)
11	**3k**		90	84 (99)
12	**3l**		88	84 (98.5)
13	**3m**		85	84 (92)
14	**3n**		85	88 (95)
15	**3o**		80	88 (99)
16	**3p**		77	89 (97)
17	**3q**		77	88 (99)
18	**3r**		81	92 (99)

[a] All reactions were performed using 1 mmol of substrate **1** with 1 mol % of Ir-catalyst. [b] After flash chromatography. [c] Determined by chiral stationary phase-supercritical fluid chromatography. Absolute configuration was determined to be *R* by comparison of the specific rotation with reported data. [d] Number ee values after a single crystallization.

entries 9–11, 81–84% ee), whereas compounds with an electron-donating group tend to give significantly better selectivity (Table 3, entries 4, 6, and 7, 90% ee). When the benzene ring of the dihydroisoquinoline moiety was substituted by a methyl group, enantioselectivities between 84 to 88% ee were obtained (Table 3, entries 12–14), whereas the presence of one or two methoxy groups gave higher enantiofacial discrimination (Table 3, entries 15–18, 88–92% ee). It is also worth noting that the enantiomeric excesses of all hydrogenated products **3a**–**r** could be easily upgraded to 90–99% after a single crystallization, as outlined in Table 3. Moreover, the tosyl protecting group of **3a** was easily removed without affecting the stereochemical integrity, giving **2a** in quantitative yield and with 94% ee.[17]

In summary, we have demonstrated that the (*R*)-3,5-diMe-Synphos is an efficient ligand for the Ir-catalyzed asymmetric hydrogenation of challenging 1-aryl-3,4-dihydroisoquinolines under mild reaction conditions. This method provides an atom economical and attractive route to pharmaceutically relevant chiral 1-aryl-THIQ compounds in high yields and excellent enantioselectivities up to >99%, after a single crystallization.

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Supporting Information Available. Full experimental details and characterization data. This material is available free of charge via Internet at http://pubs.acs.org.

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