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Enantioselective Synthesis of 1-Aryl-Substituted Tetrahydroisoquinolines Through Ru-Catalyzed Asymmetric Transfer Hydrogenation

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A convenient and general asymmetric transfer hydrogenation of a wide array of 1-aryl-3,4-dihydroisoquinoline derivatives using a [$Ru^{II}Cl(\eta^6$-benzene)TsDPEN] complex in combination with a 5:2 HCOOH–Et_3N azeotropic mixture as a hydrogen source was developed. Under mild reaction conditions, the described catalytic transformation secured a practical synthetic access to the corresponding valuable chiral 1-aryltetrahydroisoquinoline units with high atom economy, a broad substrate scope, high isolated yields (up to 97 %) and good to excellent enantioselectivities (up to 99 % *ee*). It was found that the stereochemical outcome of the reaction was strongly influenced by both the structure of the catalyst and the substituents present on the substrate. The synthetic utility of the present protocol has been demonstrated through the asymmetric synthesis of several biologically important alkaloids including the antiepileptic drug agent **1c**, as well as (–)-nor-cryptostyline alkaloids **I** and **II**.

Introduction

Chiral 1-substituted tetrahydroisoquinoline (THIQ) scaffolds are important structural units that can be found in a wide variety of naturally occurring alkaloids and synthetic analogues.[1] These compounds often exhibit significant pharmaceutical activities, including α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonistic,[2] histamine H_3 antagonist and serotonin reuptake inhibitory,[3] bradycardia,[4] multidrug resistance (MDR) reversal,[5] and antidiabetic properties.[6] Some of them are also potent cytotoxic agents with antitumoral[7] and antimicrobial activities.[8] Consequently, the incorporation of the THIQ moiety has become an important synthetic strategy in drug discovery for the development of novel chemotherapeutic agents.[9] Within this class of compounds, those bearing an aryl substituent at their C-1 positions are of particular interest because of their broad spectrum of biological and pharmaceutical properties (Figure 1). For example, synthetic solifenacin (**1a**) is a competitive muscarinic acetylcholine receptor antagonist currently used in the treatment of overactive bladder.[10] Compounds **1b** and **1c** are potent antagonists of the dopamine D_1 and AMPA receptors, respectively.[2] These receptors, which mediate dopamine and glutamate fast synaptic neurotransmission in the central nervous system, play a major role in a wide range of neurological and psychiatric disorders, including epilepsy, Huntington's, Alzheimer's and Parkinson's diseases. Cryp-

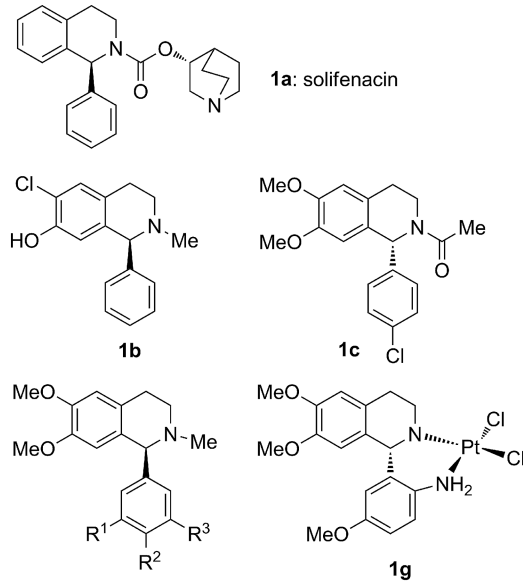

Figure 1. Selected bioactive 1-aryl-tetrahydroisoquinolines.

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tostylines **1d**–**f** have been isolated from *Cryptostylis fulva*[11] and belong to 1-aryl-*N*-methyl-THIQ alkaloids. These compounds have been used as valuable pharmacological probes for investigating and understanding the pathophysiological roles of peptides in the central and peripheral nervous systems. These peptides include the D_1 dopamine receptor, an antagonist of the substance P and a peptide neurotransmitter.[12] Another significant THIQ compound with interesting biological activity is the bicyclic chelate platinum(II) complex (**1g**) having a 1-aryl-THIQ moiety as a chelating, nonlabile ligand that displays cytotoxic activity against L1210 murine leukemia cells two times higher than the well-established antitumor *cis*-diaminedichloroplatinum(II) complex.[13]

It is therefore not surprising that during the last two decades, intense research efforts have been devoted to the development of efficient methods for the synthesis of chiral 1-substituted THIQ derivatives in both academia and industry.[14] To date, the most commonly employed synthetic routes for the preparation of such a framework rely on three main strategies: 1) the Bischler–Napieralski cyclization of β-arylethylamide followed by reduction of the resulting 3,4-dihydroisoquinoline, 2) the Pictet–Spengler reaction, which involves the condensation of β-arylethylamine with an aldehyde to form the six-membered ring, and 3) the C_1–C_α connectivity approach, which relies on the introduction of nucleophilic or electrophilic carbon units at the C-1 position of the isoquinoline core. Although these protocols have proved to be highly effective, there are some drawbacks associated with these methods, such as a limited substrate scope and the use of stoichiometric amounts of chiral sources as either substrates or reagents. Accordingly, a more general and straightforward route for the synthesis of such compounds with a high level of selectivity is still needed. With particular emphasis on economical and ecologically valuable processes, asymmetric hydrogenation (AH)[15] and asymmetric transfer hydrogenation (ATH)[16] of 1-substituted 3,4-dihydroisoquinolines (DHIQs) are among the most direct and convenient strategies to access enantiomerically pure 1-substituted THIQ frameworks. A variety of chiral metal catalysts, including Ir, Rh, Ru and Ti-based systems have been successfully used in the asymmetric reduction of 1-alkyl-3,4-DHIQs,[17,18] providing the corresponding 1-alkyl-THIQ derivatives with moderate to excellent enantioselectivities. In sharp contrast, and despite the obvious biological potential of 1-aryl-substituted THIQs, only very limited examples of AH[19a,19c,19d] and ATH[20] of challenging 1-aryl-substituted 3,4-DHIQs have been reported so far in the literature. In 2011, Zhang et al.[19a] described a general and highly enantioselective asymmetric hydrogenation of a broad range of 1-aryl-3,4-DHIQs with *ee* values ranging from 79 to 99% using [{Ir(H){(*S*,*S*)-(f)-binaphane}}$_2$(μ-I)$_3$]$_2$$^+I^-$ complex. In 2012, we showed that the (*R*)-3,5-diMe-Synphos ligand developed in our group[19b] was also an efficient ligand for the Ir-catalyzed asymmetric hydrogenation of a broad range of 1-aryl-3,4-DHIQs with *ee* values up to 94%.[19c] Ružič and Zanotti-Gerosa et al.[19d] demonstrated the feasibility of developing an efficient Ir-(*S*)-P-Phos-catalytic process for the preparation of the urinary antispasmodic drug solifenacin[10] through asymmetric hydrogenation of the hydrochloride salt of 1-phenyl-DHIQ with 95% yield and *ee* values up to 97%. Mashima et al.[19e] reported in 2013 the asymmetric hydrogenation of few isoquinolinium chloride salts using [{Ir(H){(*S*)-difluorphos}}$_2$(μ-Cl)$_3$]$_2$$^+Cl^-$ with *ee* values ranging from 96 to 99%.

As far as ATH reactions of 1-aryl-DHIQ derivatives is concerned, Noyori et al.[20a] reported in 1996 the first example of Ru/TsDPEN (TsDPEN = *N*-*p*-tolylsulfonyl-1,2-diphenylethylenediamine) catalyzed asymmetric reduction of the 1-aryl-DHIQ. Under mild reaction conditions, 1-phenyl-3,4-dihydro-6,7-dimethoxyisoquinoline was efficiently converted into the corresponding 1-phenyl-THIQ in 99% isolated yield and up to 84% *ee* using a 5:2 formic acid–triethylamine azeotropic mixture as a hydrogen source. Inspired by the research of Noyori's group, good to excellent *ee* values ranging from 84 to 99% were obtained by Vedejs et al.[20b] for the ATH reaction of a few 1-*ortho*-substituted aryl-3,4-dihydro-6,7-dimethoxyisoquinoline substrates using similar Ru/TsDPEN catalysts. Wu et al.[20c] reported in 2006 the ATH reaction of *N*-benzyl-1-phenyl-3,4-dihydro-6,7-dimethoxyisoquinolinium bromide to deliver the corresponding *N*-benzylated THIQ in 94% yield and 95% *ee* by using a water-soluble ruthenium catalyst involving a surfactant in aqueous solution in the presence of sodium formate as a hydrogen source. In 2009, a similarly high selectivity (94% *ee*) was obtained by Pihko et al.[20d] for the ATH reaction of 1-phenyl-DHIQ using the Noyori Ru/TsDPEN catalyst in the presence of water soluble Lewis acids for substrate activation. Kačer et al.[20e] developed in 2013 a ruthenium-arene complex that bears an *N*-alkylsulfonyl diamine ligand for the ATH reaction of 1-substituted 3,4-DHIQs. By employing a 5:2 HCO_2H–Et_3N azeotropic mixture, *ee* values up to 87% were obtained for the reduction of 1-alkyl-3,4-DHIQ derivatives, while significantly lower selectivities were reached using 1-phenyl-3,4-dihydro-6,7-dimethoxyisoquinoline and 1-*p*-Me-C_6H_4-3,4-DHIQ substrates, with 63% and 74% *ee*, respectively. In 2014, the group of Ward[20f] reported the asymmetric reduction of 1-phenyl-3,4-dihydroisoquinoline using an artificial imine reductase based on the biotin-streptavidin technology. Under optimized conditions, the [IrCp*^{biotin}-($_L$-ThrNH$_2$)Cl]SavWT catalyst used in combination with sodium formate as a hydride source was identified as the best catalytic system resulting in the quantitative formation of 1-phenyl-1,2,3,4-tetrahydroisoquinoline with up to 63% *ee*. Although some of the above-mentioned catalytic systems provide high selectivity, all of them suffer from a narrow substrate scope.

As a continuation of our research program dedicated to the synthesis of biologically relevant targets through metal-catalyzed asymmetric reduction,[21] and inspired by the research of Noyori[20a] and Vedejs,[20b] we recently disclosed a highly enantioselective asymmetric transfer hydrogenation of 1-aryl-substituted 3,4-DHIQs using the [Ru^{II}Cl(η^6-benzene)TsDPEN] complex in combination with a 5:2 HCO_2H–Et_3N azeotropic mixture as a hydrogen source under mild

conditions.[20f] Encouraged by the efficiency of the above mentioned ATH protocol, we report herein the full details of our investigations in finding suitable reaction conditions for the generalization of our method to a broader substrate scope. Our approach allows a rapid access to a wide variety of 1-aryl-substituted THIQ derivatives in high yields and enantioselectivities up to 99% *ee*. Additionally, the synthetic utility of the present protocol has been demonstrated through the total asymmetric synthesis of the antiepileptic drug agent **1c**, as well as (–)-nor-cryptostylines **I** and **II**.

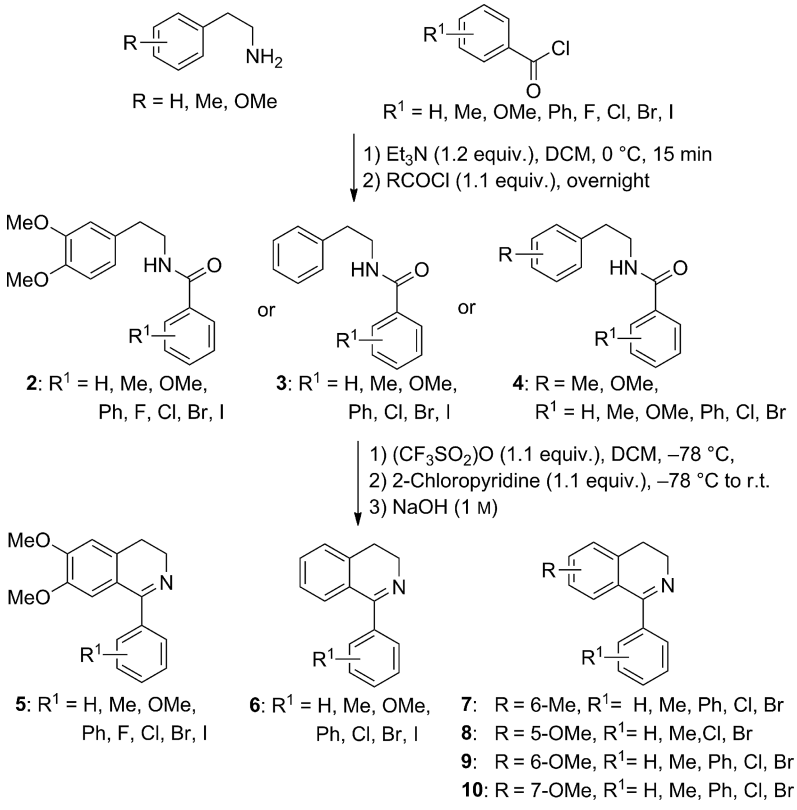
Results and Discussion

Substrate Preparation

The 1-aryl-DHIQ compounds **5**–**10** required for our study were readily prepared on large scale by using a two-step reaction sequence according to a modified procedure reported by Movassaghi.[22] As illustrated in Scheme 1, the sequence involves: 1) condensation of commercially available acyl chlorides with β-arylethylamines to give the corresponding β-arylethylamides **2**–**4**, 2) a Bischler–Napieralski type cyclization of the resulting amides **2**–**4** using trifluoromethanesulfonic anhydride and 2-chloropyridine as the base additive in refluxing CH_2Cl_2 to afford the desired 1-aryl-3,4-dihydroisoquinolines **5**–**10** in overall yields ranging from 45 to 70%.

Optimization of the Reaction Conditions

For initial optimization of the reaction conditions, the asymmetric transfer hydrogenation of 1-phenyl-3,4-dihydro-6,7-dimethoxyisoquinoline (**5a**), which resulted in the formation of THIQ **11a**, was investigated as a model reaction system. The experiments were conducted at 30 °C in dichloromethane for 16 h using a 5:2 formic acid and triethylamine azeotropic mixture as a hydrogen source in the presence of 1 mol-% of platinum group metal-based diamine complexes (**A**–**N**). As shown in Table 1, the steric and electronic properties of both the η^6-arene and the chiral diamine auxiliary ligands of the catalyst were critical factors that greatly influenced the stereochemical outcome of the process. Complete conversions were obtained when Cp*Rh^{III}-TsDPEN **A** and Cp*Ir^{III}-TsDPEN **B** catalysts were used. However, the reaction provided the desired THIQ **11a** in only racemic form (Table 1, entries 1–2). Several [$Ru^{II}Cl(\eta^6$-arene)diamine] complexes,[23] which proved to be highly efficient catalysts for the ATH reactions of various prochiral unsaturated substrates were also tested for this transformation (Table 1, entries 3–14). Almost no catalytic activity was observed when the reaction was performed with complexes **C**–**D** bearing either the TsDPEN or Ts-DACH diamine ligand in combination with the η^6-arene = mesitylene (Table 1, entries 3–4, 15 and 11% conv.). Similar results were achieved with complexes **E**–**G** possessing η^6-arene = *p*-cymene, regardless of the nature of the chiral diamine (Table 1, entries 5–7, 8–15% conv.), while the use of

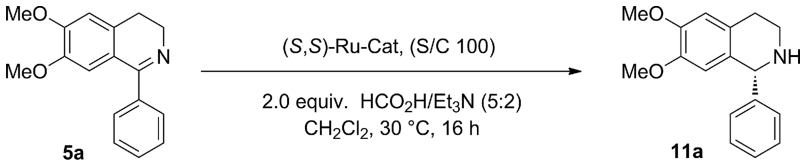


Scheme 1. Synthesis of 1-aryl-DHIQ derivatives **5**–**10** (DCM = dichloromethane).

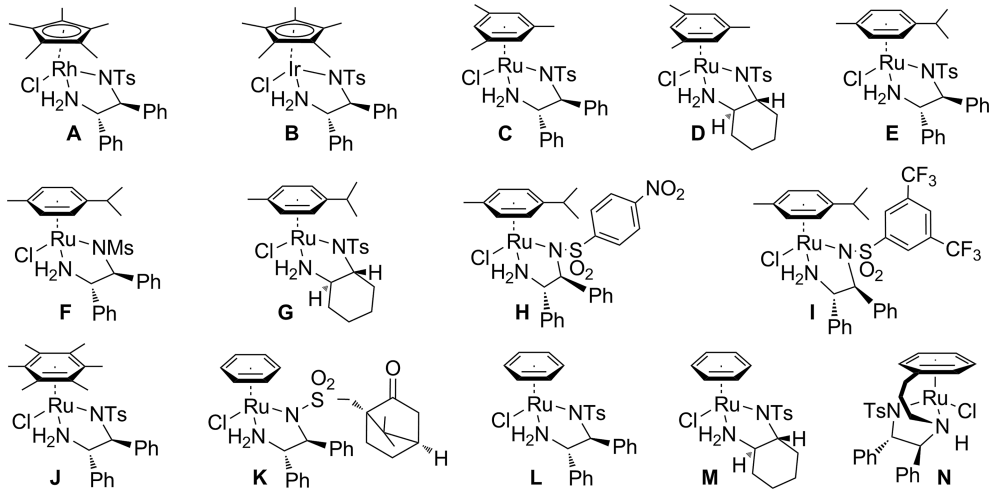
complexes bearing a more electron-withdrawing group on the TsDPEN ligand such as *p*-nitrobenzenesulfonyl (catalyst **H**) or 3,5-bis(trifluoromethyl)benzenesulfonyl (catalyst **I**) slightly improved the catalytic activity (Table 1, entries 8–9, 28–27% conv., 11–13% *ee*). A significantly higher conversion was achieved with catalyst **J** containing the hexamethylbenzene arene ring, but the desired product **11a** was delivered as a racemate (Table 1, entry 10, 71% conv.). To our delight, the use of complexes **K**–**N** having the less sterically bulky η^6-benzene as ligand led to a marked improvement in the efficiency of the reaction, providing **11a** in good to excellent conversions with enantioselectivity values ranging from 22 to 74% (Table 1, entries 11–14, 66–100% conv.).

Encouraged by these results, we further studied the impact of the solvent and the temperature on the stereochemical outcome of the reaction. The results of these experiments are summarized in Table 2. Full conversions and good isolated yields ranging from 77 to 90% were obtained in all solvents examined, but the enantiomeric excesses of the product proved to be highly solvent-dependent. Less polar solvents such as THF, toluene, and dioxane afforded THIQ **11a** with higher enantioselectivities than did polar aprotic solvents such as acetonitrile and DMF (Table 2, compare entries 2–4 vs. 5–6). The best result with respect to both selectivity and reactivity was obtained using 2-propanol as the solvent (Table 2, entry 7, 90% yield, 82% *ee*). The data presented in Table 2 also illustrates that the catalytic activity of this process was greatly affected by the reaction temperature. Lowering the temperature from 30 °C to either 20 °C or 10 °C had no repercussion on the catalytic efficiency (Table 2, compare entry 7, 90% yield, 82% *ee* vs. entries 10–11, 86 and 87% yield, 81 and 80% *ee*); and a

Table 1. Catalyst screening for ATH of **5a**.[a]



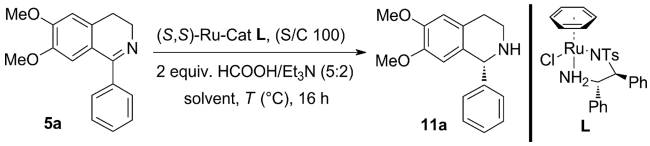
Entry	Catalyst	Conversion[b] [%]	*ee*[c] [%]
1	**A**	100	0
2	**B**	100	0
3	**C**	15	n.d.
4	**D**	11	n.d.
5	**E**	15	n.d.
6	**F**	11	n.d.
7	**G**	8	n.d.
8	**H**	28	11
9	**I**	27	13
10	**J**	71	0
11	**K**	92	22
12	**L**	100	74
13	**M**	100	71
14	**N**	66	63



[a] Reactions were conducted using 1 mmol of substrate. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC). The absolute configuration of the product was assigned to be (*R*) by comparison with literature data; n.d.: not determined.

further decrease to 0 °C or –10 °C caused a significant drop of the reaction rate while maintaining good levels of asymmetric induction (Table 2, compare entry 7, 90% yield, 82% *ee* vs. entries 12–13, 80% *ee*). Finally, performing the reaction at 50 °C provided **11a** in a good isolated yield of 87% but with a lower enantioselectivity of 72% (Table 2, compare entries 7 vs. 9). Interestingly, the catalyst loading could be reduced from 1 to 0.5 mol-% without affecting the stereochemical integrity of the new stereogenic center, although a longer reaction time (30 h) was required to reach completion (Table 1, compare entries 7 vs. 8).

Table 2. Optimization of the reaction conditions for ATH of **5a**.[a]



Entry	Solvent	*T* [°C]	Conv.[b] [%]	Yield[c] [%]	*ee*[d] [%]
1	CH_2Cl_2	30	100	87	74
2	toluene	30	100	83	77
3	THF	30	100	80	70
4	dioxane	30	100	77	65
5	DMF	30	100	77	48
6	CH_3CN	30	100	85	45
7	*i*PrOH	30	100	90	82
8[e]	*i*PrOH	30	100	83	81
9	*i*PrOH	50	100	87	72
10	*i*PrOH	20	100	86	81
11	*i*PrOH	10	100	87	80
12	*i*PrOH	0	30	28	80
13	*i*PrOH	–10	30	27	80

[a] Reactions were conducted using 1 mmol of substrate. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Isolated yields. [d] Determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC). The absolute configuration of the product was assigned to be (*R*) by comparison with literature data. [e] Reaction run for 30 h with S/C = 200.

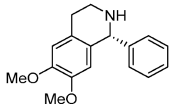
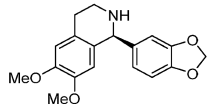
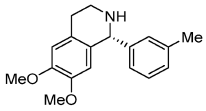
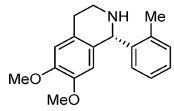
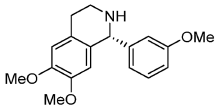
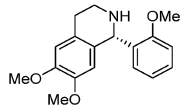
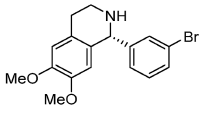
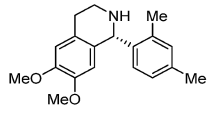
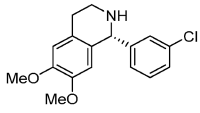
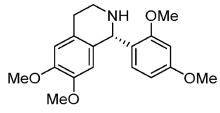
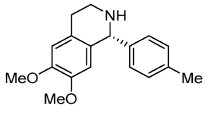
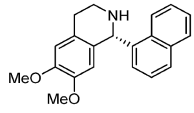
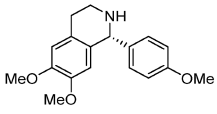
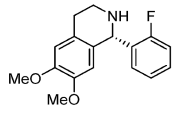
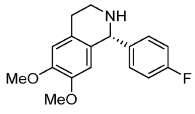
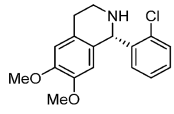
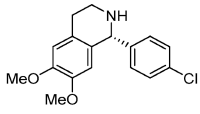
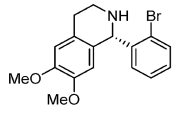
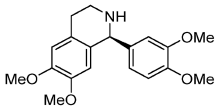
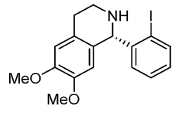
Through these screenings, the best reaction conditions for the asymmetric transfer hydrogenation of the 1-phenyl-3,4-dihydro-6,7-dimethoxyisoquinoline **5a** were therefore set as the following: 1 mol-% of [$Ru^{II}Cl(\eta^6$-benzene)-TsDPEN] catalyst **L** in combination with a 5:2 HCO_2H–Et_3N azeotropic mixture as a hydrogen source, 2-propanol as a solvent, at 30 °C for 16 h.

Scope and Limitation

With the optimized conditions for the catalytic asymmetric transfer hydrogenation reaction of **5a** in hand, the scope and limitation of the present system were investigated (Tables 3, 4, and 5). Toward this end, a full set of 1-aryl-DHIQ derivatives, diversely substituted on the aromatic rings, were synthesized (vide supra, Scheme 1). Initially, we decided to study the ATH reaction of a wide range 6,7-dimethoxy substituted isoquinoline derivatives **5a**–**t** having different substituents at the 1-phenyl ring. As outlined by the results shown in Table 3, both electron-donating or -withdrawing substituents were equally well tolerated, affording the corresponding 1-aryl-6,7-dimethoxy-tetrahydroisoquinolines **11a**–**t** in high isolated yields and good to excellent enantioinductions, varying from 69 to 99% *ee* (Table 3, entries 1–20). The data of Table 3 also reveal that the stereochemical outcome of this ATH process was strongly influenced by the substitution pattern on the pendant 1-phenyl group. For instance, DHIQ substrates possessing either an electron-donating or electron-withdrawing substituent such as methyl (**5b**), bromine (**5d**) or chlorine (**5e**) on the *meta* position led to similar results in terms of both reactivity and selectivity when compared to those achieved for the unsubstituted model substrate **5a** (Table 3, entries 1 vs. 2, 4 and 5, 90–93% yield, 82–84% *ee*). The only exception was the result obtained with the DHIQ substrate **5c**, which bears an electron-rich methoxy group. For this substrate, a lower catalytic activity was obtained, presumably due to a combination of disfavorable electronic and steric effects (Table 3, entry 3, 83% yield, 69% *ee*). Reduction of *para*-substituted DHIQ substrates **5f**–**i** uniformly gave higher selectivity, irrespective of the electronic nature of the substituents, providing the desired THIQ products **11f**–**i** in excellent yields (90–92%) and enantioselectivities (87–91% *ee*) (Table 3, entries 6–9). When the reaction was performed with *meta*- and *para*-disubstituted DHIQs **5j** and **5k**, a marked drop of the catalytic efficiency was observed (Table 3, entries 10–11, 85 and 87% yield, 75 and 82% *ee*, respectively). Finally, a wide range of *ortho*-substituted DHIQs **5l**–**t** bearing either electron-donating or electron-withdrawing groups was also examined (Table 3, entries 12–20). In all cases, the corresponding THIQ products **11l**–**t** were isolated in excellent yields (83–97%) and with high enantioselectivities ranging from 96 to 99% *ee*. These results clearly showed that steric rather than electronic effects could be invoked to explain this remarkable influence on the selectivity, as revealed by a comparison of the enantiomeric excesses obtained when the reaction was carried out with DHIQ substrates bearing a fluorine (**5q**), a chlorine (**5r**), a bromine (**5s**) and an iodine (**5t**) on the *ortho* position. Indeed, as can be seen from the data of Table 3, the selectivity of the reaction gradually increases when the size of the halogen atom increases (Table 3, entries 17–20, 96 to 99% *ee*). Obviously, the presence of an *ortho* substituent not only affected to a great extent the coplanarity between the imine functionality and the 1-aryl ring, but also efficiently hindered one C=N enantioface, favoring a specific rotamer in one of the two competing diastereomeric transition states, thereby generating an asymmetric bias.

Our next goal was to study the influence of substituents attached to the benzene ring of the isoquinoline core on the stereochemical outcome of the reaction. For this purpose, we first set out to examine the reactivity of various 1-aryl-substituted DHIQ derivatives **6a**–**l** under the optimized conditions using Ru^{II}-TsDPEN catalyst **L**. The results of these experiments are reported in Table 4. Interestingly, the ATH reaction of the unsubstituted DHIQ **6a** gave the desired THIQ **12a** in a similarly high isolated yield but with a significantly lower selectivity in comparison with the result

Table 3. ATH reaction of 1-aryl-3,4-dihydro-6,7-dimethoxyisoquinoline derivatives **5a**–**t**.[a]

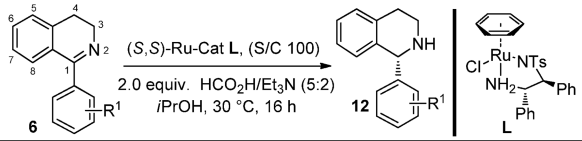
Entry		Product	Yield [%][b]	*ee* [%][c]	Entry		Product	Yield [%][b]	*ee* [%][c]
1	**11a**		90	82 (+)	11[d]	**11k**		87	82 (–)
2	**11b**		90	84 (+)	12	**11l**		86	98 (+)
3	**11c**		83	69 (+)[e]	13	**11m**		84	96 (+)
4	**11d**		90	82 (+)	14	**11n**		83	98 (–)
5	**11e**		93	83 (+)	15	**11o**		85	96 (+)
6	**11f**		90	91 (+)[e]	16	**11p**		86	98 (+)
7	**11g**		92	91 (+)	17	**11q**		97	96 (+)[e]
8	**11h**		91	87 (–)[e]	18	**11r**		93	98 (–)
9	**11i**		92	87 (–)[e]	19	**11s**		91	98 (–)
10[d]	**11j**		85	75 (–)[e]	20	**11t**		92	99 (–)

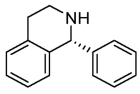
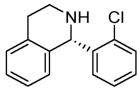
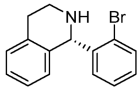
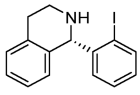
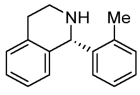
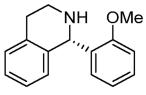
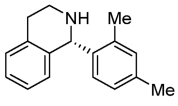
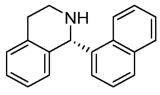
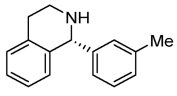
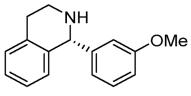
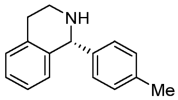
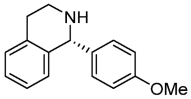
[a] Reactions were conducted using 1 mmol of substrate. [b] Isolated yields. [c] Determined by chiral stationary phase supercritical-fluid chromatography (CSP-SFC). [d] The (*R*,*R*)-Ru catalyst was used, giving the corresponding (*S*)-hydrogenated product. [e] Determined by CSP-SFC on the *N*-tosylated product.

obtained for the reduction of 1-phenyl-3,4-dihydro-6,7-dimethoxyisoquinoline (**5a**, Table 4, entry 1, 90% yield, 29% *ee* vs. Table 3, entry 1, 90% yield, 82% *ee*).

This considerable difference in selectivity could presumably be attributed to the electron-releasing effect of the two methoxy groups, which increases the C=N double bond

Table 4. ATH reactions of 1-aryl-3,4-dihydroisoquinoline derivatives **6a**–**l**.[a]



Entry		Product	Yield [%][b]	*ee* [%][c]
1	**12a**		90	29 (–)
2[d]	**12b**		73	92 (–)
3[d]	**12c**		71	94 (–)
4[d]	**12d**		72	92 (–)
5	**12e**		77	84 (–)
6	**12f**		78	79 (+)
7	**12g**		75	90 (+)
8	**12h**		74	90 (–)
9	**12i**		88	36 (–)
10	**12j**		93	33 (+)
11	**12k**		87	36 (–)
12	**12l**		89	39 (+)

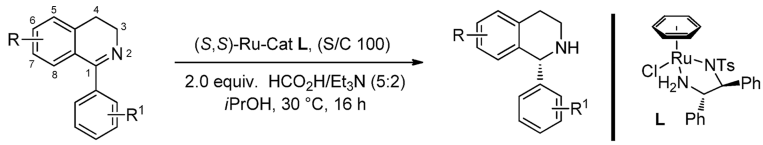
[a] Reactions were conducted using 1 mmol of substrate. [b] Isolated yields. [c] Determined by chiral stationary phase supercritical-fluid chromatography (CSP-SFC). [d] 80% conversion after 40 h of reaction.

electron density and allows stronger C(sp^2)H/π interactions between the aromatic ring of the isoquinoline skeleton and a hydrogen atom on the η^6-benzene ligand, thus improving C=N enantiofacial discrimination by the Ru^{II} catalyst (see Figure 2, vide infra). A similar trend was observed for all 1-aryl-substituted DHIQ derivatives **6b**–**l** tested irrespective of the nature and position of the substituents present on the pendant 1-phenyl ring. For instance, the ATH reaction of substrates **6b**–**h** having either electron-donating or electron-withdrawing substituents at the *ortho* position uniformly provided the corresponding 1-aryl THIQs **12b**–**h** with lower chemical and optical yields (Table 4, entries 2–8, 71–78% yield, 79–94% *ee* vs. Table 3 entries 12–20, 83–97% yield, 96–99% *ee*). This effect was even more pronounced along the series of DHIQs **6i**–**l** possessing *meta* and *para* substituents, although the desired reduced products **12i**–**l** were isolated in comparably high yields (Table 4, entries 9–12, 87–93% yield, 33–39% *ee* vs. Table 3 entries 2–11, 83–93% yield, 69–91% *ee*).

To establish the effects of electron-rich substituents present on the isoquinoline unit on the course of the reaction, we subsequently applied our catalytic system to the ATH reaction of a wide range of 1-aryl-substituted DHIQ derivatives **7**–**10** bearing a methoxy or a methyl group at the 5-, 6-, or 7-position of the benzene ring of the isoquinoline moiety. As outlined in Table 5, all substrates were efficiently converted into the corresponding THIQ derivatives **13**–**16** in good yields ranging from 80 to 93%. It was found, however, that the position of the substituents greatly influenced the selectivity of the reaction. As expected, substrates **7a**–**c**, **8a**–**e**, **9a**–**d** and **10a**–**f** bearing either electron-donating or electron-withdrawing groups at the *ortho* position of the 1-phenyl ring generally displayed good to excellent enantiofacial discrimination, leading to the targeted products **13a**–**c**, **14a**–**e**, **15a**–**d** and **16a**–**f** with good to excellent *ee* values in the range of 84 to 95%, 91 to 96%, 79 to 93% and 92 to 96%, respectively (Table 5, entries 1–3, 8–12, 17–20, and 25–30). This result clearly confirmed that the presence of *ortho*-substituents on the 1-phenyl ring is an essential and sufficient parameter to achieve high levels of selectivity, as previously observed for compounds **5l**–**t** (Table 3, entries 12–20) and **6b**–**h** (Table 4, entries 2–8), regardless of the substitution pattern on the benzene ring of the isoquinoline moiety. The data presented in Table 5 also show that the presence of a methoxy group at the 5-position considerably altered the selectivity of the reaction, because *ee* values ranging from 3 to 34% were obtained for the reduction of DHIQ derivatives **7d**–**g** (Table 5, entries 4–7). For compounds **14f**–**i** and **15e**–**h** that bear a methoxy or a methyl groups at the 6-position, enantiomeric excesses ranging from 33 to 60% and 27 to 53%, respectively, were obtained (Table 5, entries 13–16 and 21–24). Finally, a higher selectivity was restored for the THIQ derivatives **16g**–**j** having a methoxy substituent at the 7-position of the benzene ring of the isoquinoline scaffold (Table 5, entries 31–34, 54–80% *ee*).

Based on the above results, it appears that the catalytic efficiency of the process for this series of monosubstituted

Table 5. ATH reactions of 1-aryl-3,4-dihydro-monosubstituted isoquinoline derivatives **7**–**10**.[a]



7: R = 5-MeO
8: R = 6-MeO
9: R = 6-Me
10: R = 7-MeO

13: R = 5-MeO
14: R = 6-MeO
15: R = 6-Me
16: R = 7-MeO

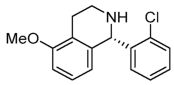
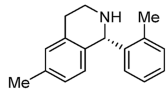
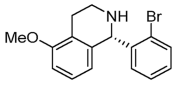
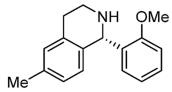
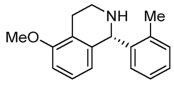
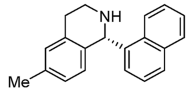
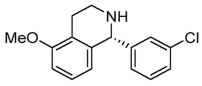
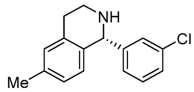
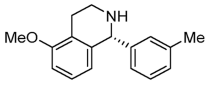
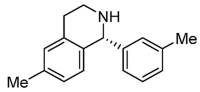
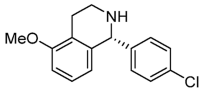
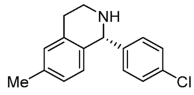
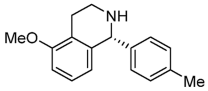
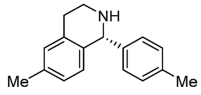
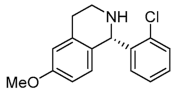
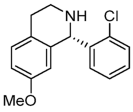
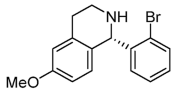
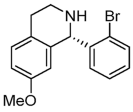
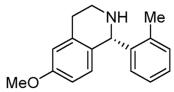
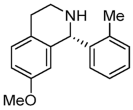
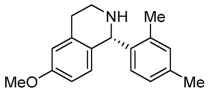
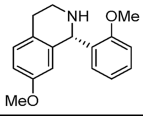
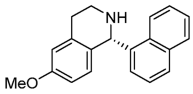
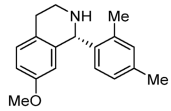
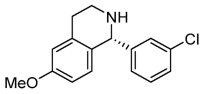
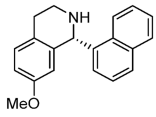
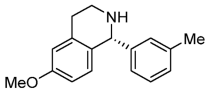
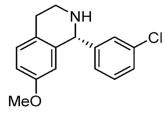
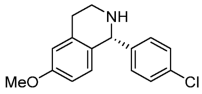
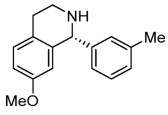
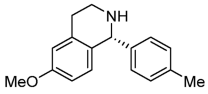
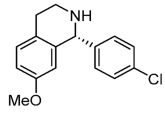
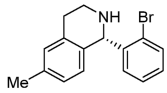
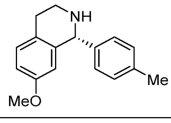
Entry		Product	Yield [%][b]	*ee* [%][c]	Entry		Product	Yield [%][b]	*ee* [%][c]
1	**13a**		85	92 (–)	18	**15b**		90	93 (–)
2	**13b**		87	95 (–)	19	**15c**		82	79 (–)
3	**13c**		87	84 (–)	20	**15d**		92	93 (–)
4	**13d**		88	3 (–)[d]	21	**15e**		90	27 (–)
5	**13e**		86	17 (–)[d]	22	**15f**		85	39 (–)
6	**13f**		82	34 (–)[d]	23	**15g**		86	53 (–)[d]
7	**13g**		84	15 (–)[d]	24	**15h**		93	50 (–)[d]
8	**14a**		90	96 (–)	25	**16a**		87	96 (–)
9	**14b**		84	95 (–)	26	**16b**		89	95 (–)
10	**14c**		92	92 (–)	27	**16c**		90	92 (+)
11	**14d**		90	91 (–)	28	**16d**		86	92 (+)

Table 5. *(Continued)*

Entry		Product	Yield [%][b]	*ee* [%][c]	Entry		Product	Yield [%][b]	*ee* [%][c]
12	**14e**		87	95 (–)	29	**16e**		90	96 (–)
13	**14f**		85	33 (–)	30	**16f**		91	96 (–)
14	**14g**		88	46 (–)	31	**16g**		86	54 (–)
15	**14h**		80	60 (–)[d]	32	**16h**		90	63 (–)
16	**14i**		86	54 (–)[d]	33	**16i**		83	80 (–)[d]
17	**15a**		87	93 (–)	34	**16j**		89	59 (–)[d]

[a] Reactions were conducted using 1 mmol of substrate. [b] Isolated yields. [c] Determined by chiral stationary phase supercritical-fluid chromatography (CSP-SFC). [d] Determined by CSP-SFC on the *N*-tosylated product.

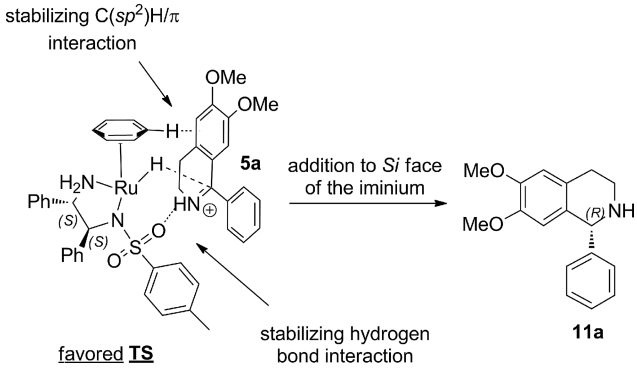


Figure 2. Origin of the enantioselectivity for the ATH reaction of DHIQ **5a** using the (*S*,*S*)-Ru catalyst.

DHIQs **7**–**10** was most likely due to increased steric hindrance near the reactive center during the approach of the Ru catalyst rather than electronic effects.

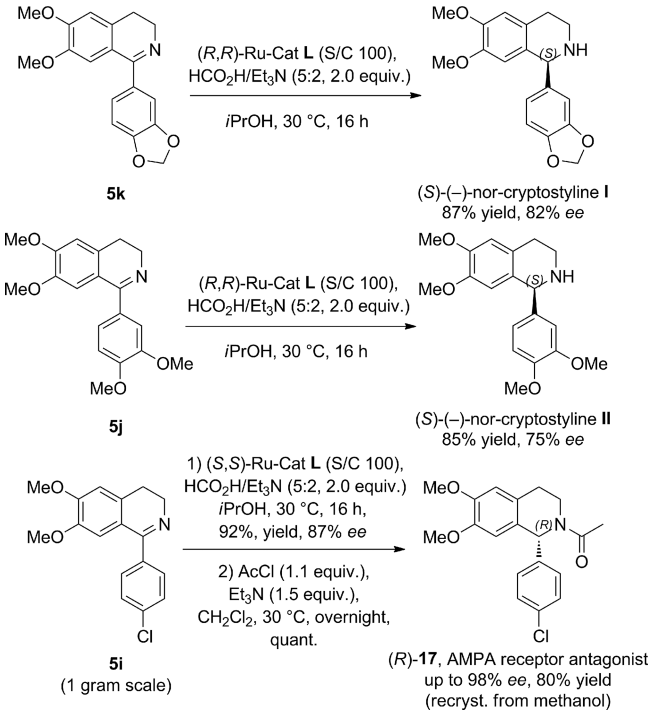
Origin of the Enantioselectivity

Based on mechanistic and computational studies, the concerted outer-sphere mechanism of hydrogen transfer from [$Ru^{II}H(\eta^6$-arene)diamine] intermediate to ketones via a cyclic six-membered transition state is now relatively well established and generally accepted.[24] In sharp contrast, the mechanism for the ATH reaction of imines using the same Noyori-type catalyst has been much less explored.[25] Until recently, it has merely been assumed that both classes of compounds (e.g., ketones and imines) follow the same mechanistic pathway. Based upon several experiments, Bäckvall et al.[25a] in 2006 and Wills et al.[25c,25d] in 2009 demonstrated that the mechanism for the reduction of imines is different than the one that operates for ketones. They suggested that an ionic, rather than a concerted mechanism, wherein the imine is protonated prior to hydrogen transfer is involved in the ATH reaction of imines. In 2011, this ionic mechanism was supported by the contributions of Kačer et al.[25f,25g] using DFT calculations. As a result, the selectivity observed in the ATH reaction of the 1-phenyl-3,4-dihydro-6,7-dimethoxyisoquinoline **5a** using [$Ru^{II}Cl(\eta^6$-benzene)(*S*,*S*)-TsDPEN] as catalyst could be explained through the transition state model depicted in Figure 2. In the proposed favored **TS**, the metal hydride is delivered to the *Si* face of the DHIQ after acidic activation in which the C=N bond of the iminium cation is not coordinated to the NH_2 group of the TsDPEN ligand, leading to the (*R*)-THIQ **11a** as a major product enantiomer, as is observed experimentally. Additionally, these DFT calcula-

tions also reveal that two attractive interactions which retain the substrate at the active site of the ruthenium complex and stabilize the **TS** appear to be crucial to the control of the absolute product stereochemistry: 1) a C(sp^2)H/π interaction between the aromatic ring of the isoquinoline skeleton and a hydrogen atom on the η^6-benzene ligand and 2) a hydrogen bonding interaction between the C=NH^+ group of the substrate and an oxygen of the SO_2 fragment of the TsDPEN ligand.

Synthetic Applications

To demonstrate the utility of our process, several 1-aryl-THIQ derivatives of pharmaceutical interest have been prepared (Scheme 2).



Scheme 2. Synthesis of (*S*)-(–)-norcryptostylines **I**, **II** and AMPA receptor antagonist (*R*)-**17**.

For example, natural (*S*)-(–)-norcryptostylines **I** and **II**, which are known to modulate glutamate neurotransmission in the central nervous system,[11,12] were obtained in good yields and enantioselectivities (Scheme 2, 87% and 85% yields, 82% and 75% *ee*, respectively) through the ATH reaction of the corresponding DHIQ derivatives **5k** and **5j** (vide supra, Table 2, entries 10 and 11). The above protocol also provided an efficient and straightforward access to compound (*R*)-**17**, which is a potent noncompetitive AMPA receptor antagonist investigated in phase III trials as an antiepileptic agent.[2] The targeted THIQ (*R*)-**17** has been prepared on gram-scale using a two-step sequence depicted in Scheme 2. Under the optimized reaction conditions, DHIQ **5i** was smoothly transformed to the corresponding THIQ **11i** (not shown) in excellent yield and good enantioselectivity (Scheme 2, 92% yield, 87% *ee*). Subsequent acetylation, followed by a single recrystallization in methanol afforded the desired product **17** in 80% isolated yield and with an excellent enantiopurity up to 98% *ee*.

Conclusions

A general, efficient and highly enantioselective asymmetric transfer hydrogenation reaction of a wide range of readily available 1-aryl-3,4-dihydroisoquinoline derivatives has been developed using a 5:2 formic acid and triethylamine azeotropic mixture as a hydrogen source in the presence of the [Ru^{II}Cl(η^6-benzene)(*S*,*S*)-TsDPEN] catalyst. Several general tendencies emerged from these results. The reaction has been found to accommodate a remarkably broad substrate scope, providing the corresponding 1-aryl-tetrahydroisoquinoline scaffolds, which are versatile building blocks of high utility to both organic and medicinal chemists, in good to excellent yields and with unprecedented high levels of enantioselectivity and wide scope. Our study also revealed that the stereochemical outcome of the reaction was strongly influenced by both the structure of the catalyst and the position and nature of the substituents present on the aromatic rings of the substrate. In particular, it was found that the ATH reaction of substrates having two, rather than one, electron-rich methoxy groups provided significantly higher chemical yields (up to 97%) and enantioselectivities (up to 99%). This can be explained through the existence of stronger C-H/π attractive interactions between a C(sp^2)-H substituent on the η^6-benzene ligand of the Ru complex and the aromatic ring of the isoquinoline skeleton that greatly stabilized the **TS** (see Figure 2, vide supra). In sharp contrast, for 1-aryl-substituted DHIQs that bear only one substituent on the benzene ring of the isoquinoline moiety, it can be concluded that the selectivity of the reaction depends mainly on steric interactions, rather than electronic effects. Finally, the mild reaction conditions, high yields, operational simplicity and practicability render this process an attractive and straightforward approach to the asymmetric synthesis of 1-aryl-THIQ derivatives of pharmaceutical interest.

Experimental Section

All reactions were run under an atmosphere of argon. Reaction vessels were dried under vacuum and cooled under a stream of argon. Dichloromethane and tetrahydrofuran were distilled prior to use from calcium hydride and sodium/benzophenone, respectively. Solvents, reagents and chemicals were purchased from Sigma–Aldrich, Alfa Aesar, TCI and Acros Organic and were used as purchased unless stated otherwise. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using a Bruker AVANCE 300 (300 MHz). Chemical shifts are reported in delta (δ) units, part per million (ppm) downfield from tetramethylsilane (TMS) relative to the singlet at δ = 7.26 ppm for deuterated chloroform. Coupling constants are reported in Hertz (Hz). The following abbreviations are used: s singlet, d doublet, t triplet, q quartet, m multiplet, br. broad. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded using a Bruker AVANCE 300 (75 MHz). Chemical

shifts are reported in delta (δ) units, part per million (ppm) relative to the center line of the triplet at δ = 77.0 ppm for deuterated chloroform. ^{13}C NMR spectra were routinely run with broadband decoupling. High-resolution mass spectra were performed by the Groupe de Spectrométrie de masse de l'Université Pierre et Marie Curie (Paris). Enantiomeric excesses were determined by chiral supercritical fluid chromatography (SFC), on a BERGER instrument equipped with a UV detector or by chiral stationary phase high performance liquid chromatography (HPLC), on a Waters e2695 instrument equipped with a UV detector. Those analyses were performed using Chiralcel columns and eluting with the solvent mixture as indicated. Optical rotation values were recorded with a Perkin–Elmer 241 polarimeter at 589 nm (sodium lamp) and are given in deg cm^2 g^{-1}.

General Procedure for Asymmetric Transfer Hydrogenation of DHIQs: The 3,4-dihydroisoquinoline (1 mmol, 1 equiv.) and Ru catalyst (0.010 mmol, 0.010 equiv.) were placed in a glass tube fitted with a septum, outlet needle, and magnetic stirring bar. 2-Propanol was then added, followed by the formic acid–triethylamine 5:2 azeotrope (2 mmol, 170 μL, 2 equiv.). The reaction mixture was stirred at 30 °C until all the starting material had been consumed (TLC monitoring). The reaction mixture was then neutralized by careful addition of saturated $NaHCO_3$ (10 mL) (vigorous gas evolution). After being stirred for an additional 10 min, dichloromethane (10 mL) was added. After decantation, the resulting mixture was extracted twice with dichloromethane (2 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was filtered through a pad of silica gel using ethyl acetate as eluent. The solvent was removed under reduced pressure, and the residue obtained was dried in vacuo to give the desired chiral THIQ.

Supporting Information (see footnote on the first page of this article): Supporting information for this article containing experimental procedures and characterization data for all new compounds is available.

Acknowledgments

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