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Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201701094

Link to VoR: http://dx.doi.org/10.1002/ejoc.201701094

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10.1002/ejoc.201701094

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Asymmetric Transfer Hydrogenation of 1-Aryl-3,4-Dihydroisoquinolines Using a Cp*Ir(TsDPEN) Complex

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Abstract: We report herein a simple alternative method for the asymmetric transfer hydrogenation of 1-aryl-3,4-dihydroisoquinolines (1-Ar-DHIQs) that are known to be challenging substrates owing to their poor reactivity. The hydrogenation protocol employs the readily available Cp*Ir(TsDPEN) (where Cp* = pentamethylcyclopentadienyl and TsDPEN = (*S*,*S*)-HNCHPhCHPhNTs^{2-}) catalytic complex, 2-propanol and HCOOH/triethylamine mixture as the solvent and hydrogen donor, and anhydrous phosphoric acid as an inexpensive additive. The series of examined substrates shows a favourable tolerance to various functional groups. Unlike 1-alkyl-DHIQs, where the enantiomeric excess (*ee*) starkly changes during the course of hydrogenation, 1-Ar-DHIQs exhibit a constant *ee* value, which makes the method practical and useful for the production of fine chemicals containing the 1,2,3,4-tetrahydroisoquinoline motif.

Optically pure chiral compounds are abundant among active pharmaceutical ingredients, agrochemicals, and fragrances. As their interaction with chiral receptors in living organisms is enantiospecific, each of the two enantiomers can provoke strikingly different effects. Efficient methods for the production of single enantiomers are thus highly sought-after and as a result, asymmetric synthesis, where the desired stereoisomer is formed directly, has been intensively investigated in the past decades. Among those methods, catalytic asymmetric transfer hydrogenation (ATH) of ketones and imines, pioneered by Noyori *et al.*,[1] is now very well established.[2–10] Still, this catalytic system has certain limitations, such as the poor reactivity of 1-aryl-3,4-dihydroisoquinolines (1-Ar-DHIQs) as precursors of the chiral 1-aryl-1,2,3,4-tetrahydroisoquinoline (1-Ar-THIQ) motif present in naturally-occurring alkaloids (Cryptostylines) and drugs (*e.g.*, Solifenacin[11] or Gantacurium[12]). Efficient asymmetric hydrogenation protocols for 1-Ar-DHIQs have been reported with iridium-phosphine complexes.[11,13–16] However, the corresponding ligands are oxygen sensitive and the complexes may not be readily available. For those reasons, protocols toward 1-Ar-THIQs employing the Noyori-Ikariya complexes are highly attractive.

Noyori and co-workers originally showed that complex **1a** (Figure 1), bearing η^6-benzene and naphthalene-1-sulfonamide ligands, could catalyse the ATH of 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline (**2a**) with 84% enantiomeric excess (*ee*).[17] The use of **1a** in the synthesis of muscle relaxant Gantacurium was shown by the group of Boros.[12] However, Vedejs *et al.*[18] observed irreproducible results with **1a** and found that complex **1b** (Figure 1), featuring the classic TsDPEN (*N*-*p*-toluenesulfonyl-1,2-diphenylethylene-1,2-diamine) ligand, was significantly more soluble under the reaction conditions and provided reproducible results in ATH of 1-aryl-DHIQs. Enantioselective reduction of **2a** with the most popular catalyst **1c**, containing *p*-cymene as the η^6-arene (Figure 1), was tackled by converting the substrate to an iminium salt *via* alkylation.[19] **2a** underwent **1c** catalysed ATH in aqueous methanol with $AgSbF_6$/$La(OTf)_3$ activation.[20] We previously contributed to this topic with a borneolsulfonyl-based ruthenium catalyst, achieving reactivity comparable to that of **1a** in the ATH of 1-Ar-DHIQs and **1c** with 1-alkyl-DHIQs.[21] While the Cp*RhCl(TsDPEN) complex (**1d**, Figure 1) provides excellent reactivity due to the rhodium metal centre, the enantioselectivity achieved with 1-Ar-DHIQs is close to zero.[22] The field has been developed further by the group of Ratovelomanana-Vidal who disclosed conditions for efficient ATH of 1-Ar-DHIQs using the **1b** catalyst.[23,24] They also reported that rhodium complex **1d** and its iridium analogue **1e** (Figure 1) display good reactivity with substrate **2a**, but the product is formed as a racemate.

We wish to demonstrate here a simple and efficient method for the ATH of 1-Ar-DHIQs employing the readily available iridium complex in its 16e$^-$ form (**1e′**, Figure 1) and anhydrous phosphoric acid as an additive.

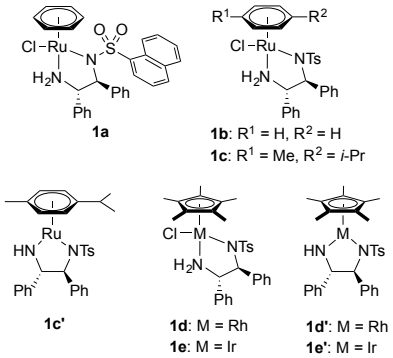

Figure 1. Structures of complexes discussed or investigated in this study.

Our initial investigations started with ATH of the simplest substrate, 1-phenyl-3,4-dihydroisoquinoline (**2b**), using the HCOOH/triethylamine (HCOOH/TEA) hydrogen-donor mixture. As ruthenium complexes (**1a**–**c**) have been examined thoroughly

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[+] CF Plus Chemicals s.r.o. (www.cfplus.cz), an ETH Zurich spin-off, commercializes the 1-aryl-3,4-dihydroisoquinolines reported here.

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by others (*vide supra*), we turned our attention to Rh- and Ir-based complexes. Adopting the reaction conditions previously established on 1-methyl-DHIQs,[25] complex **1d**, as well as its 16e⁻ congener **1d′** (Figure 1), afforded only trace amounts of the THIQ product **3b** (Table 1, entries 1 and 2). Changing the solvent to anhydrous 2-propanol (*i*-PrOH) provided 64–66% conversion, but only 3% *ee* (Table 1, entries 3 and 4), which is consistent with previous findings made for **1d** in dichloromethane (DCM).[22,23]

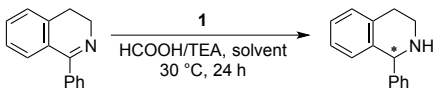
Applying the synthetic procedure for the preparation of complex **1d**[22] in the synthesis of **1e**, we arrived directly at its 16e⁻ form **1e′**. Under the same ATH conditions, **1e′** provided the product **3b** in 83% conversion and 60% *ee* (Table 1, entry 5). Leaving out TEA caused lower reactivity (Table 1, entries 6 and 8). Test experiments without HCOOH (Table 1, entries 7 and 8) resulted in practically zero conversion, excluding the possibility that *i*-PrOH might serve as the reductant. Likewise, other solvents tested (acetonitrile, DCM, DMSO, hexafluoro-2-propanol) did not lead to further improvements (Table 1, entries 9–12).

Optimization of the ratios of HCOOH, TEA and **2b** (Table S1) enabled us to find two optimal ratios of HCOOH:TEA. While with the molar ratio of 2.5:1 we obtained **3b** in 80% conversion and 71% *ee* (Table S1, entry 5), equimolar ratio of HCOOH:TEA gave 72% conversion, but a higher *ee* value of 77% (Table S1, entry 12) after 24 h. The latter combination was selected for further refinement.

Various additives were tested in order to enhance the reactivity and/or enantioselectivity (Table S2). L-Proline as a chiral additive caused a notable decrease of *ee* (Table S2, entries 1 and 2). Lewis-acidic aluminium chloride led to lower reactivity (Table S2, entries 3 and 4). Out of the Brønsted acids tested (trifluoroacetic acid, tetrafluoroboric acid, and 85% aq. orthophosphoric acid – Table S2, entries 5–15), the 85% aq. solution of orthophosphoric acid helped increase the *ee* to 82% (Table S2, entry 14). Therefore, orthophosphoric acid was investigated further, including the anhydrous phosphoric acid (APA)[11] prepared by mixing the 85% H_3PO_4 with stoichiometric amounts of phosphorus pentoxide (Table S2, entries 16–28). With this additive and anhydrous *i*-PrOH as a solvent, the *ee* was increased to 86% at full conversion (Table S2, entry 26 and Table 2, entry 1). Interestingly, APA obtained from a commercial source gave consistently lower reactivity (Table S2, entries 22 and 24).

Test experiment without APA (Table 2, entry 2) gave 65% conversion and 77% *ee*. Reactions without HCOOH (Table 2,

Table 1. Screening of complexes **1d**, **1d′** and **1e′** in the ATH of imine **2b** in various solvents.[a]

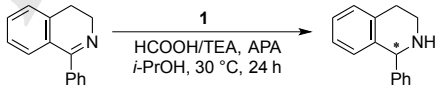


2b **3b**

Entry	1	Solvent	Conversion [%][b]	*ee* [%][c]
1	**1d**	MeCN	3	n.d.[d]
2	**1d′**	MeCN	2	n.d.[d]
3	**1d**	*i*-PrOH	64	3
4	**1d′**	*i*-PrOH	66	3
5	**1e′**	*i*-PrOH	83	60
6[e]	**1e′**	*i*-PrOH	54	34
7[f]	**1e′**	*i*-PrOH	1	n.d.[d]
8[g]	**1e′**	*i*-PrOH	0	n.d.[d]
9	**1e′**	MeCN	87	10
10	**1e′**	DCM	57	7
11	**1e′**	DMSO	4	n.d.[d]
12[h]	**1e′**	HFIP[i]	0	n.d.[d]

[a] Conditions: **2b** (0.15 mmol), **1** (0.0015 mmol, 1 mol% vs. **2b**), HCOOH (36 μL, 0.95 mmol), TEA (53 μL, 0.38 mmol), HCOOH:TEA = 2.5, total volume: 2 mL, 30 °C, 24 h. Amine product was obtained by alkalization and extraction. [b] Determined by GC. [c] Determined by GC using pre-column derivatization.[25] [d] Not determined due to low conversion. [e] Without TEA. [f] Without HCOOH. [g] Without HCOOH and TEA. [h] Reaction time of 3 h. [i] HFIP = hexafluoro-2-propanol.

Table 2. Screening of complexes **1c**, **1c′**, **1d**, **1d′**, and **1e′** in the ATH of imine **2b** with APA as additive.[a]



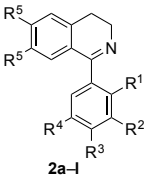
2b **3b**

Entry	1	Conversion [%][b]	*ee* [%][c]
1	**1e′**	>99	86
2[d]	**1e′**	65	77
3[e]	**1e′**	4	6
4[f]	**1e′**	0	n.d.[g]
5[h]	**1e′**	0	n.d.[g]
6	**1c**	1	n.d.[g]
7	**1c′**	1	n.d.[g]
8	**1d**	8	3
9	**1d′**	11	3

[a] Conditions: **2b** (0.15 mmol), **1** (0.0015 mmol, 1 mol% vs. **2b**), HCOOH (11 μL, 0.3 mmol), TEA (41 μL, 0.3 mmol), HCOOH:TEA = 1, APA (2 equiv to **2b**), *i*-PrOH, total volume: 2 mL, 30 °C, 24 h. Amine product was obtained by basification and extraction. [b] Determined by GC. [c] Determined by GC using pre-column derivatization.[26] [d] Without APA. [e] Without HCOOH. [f] Without TEA. [g] Not determined due to low conversion. [h] Without HCOOH and TEA.

entry 3), TEA (Table 2, entry 4) or both HCOOH and TEA (Table 2, entry 5) did not proceed. Other catalysts (**1c**, its 16e$^-$ complex **1c′**, **1d**, and **1d′**) exhibited poor activity (Table 2, entry 6–9). This shows that the reaction conditions were indeed tailored for the iridium-based **1e′**.

Next, we set out to explore the structure-activity trends by hydrogenating imines **2a**–**l** with the same basic scaffold that differ by position and type of various functional groups (Figure 2). As an extension, we also incorporated 3,4-dihydro-*β*-carboline **2m** from the family of harmala alkaloids.



	R^1	R^2	R^3	R^4	R^5
2a	H	H	H	H	OMe
2b	H	H	H	H	H
2c	H	H	NO_2	H	H
2d	H	H	CF_3	H	H
2e	H	H	OMe	H	H
2f	H	H	Me	H	H
2g	H	H	Br	H	H
2h	H	H	CO_2Me	H	H
2i	H	CF_3	H	H	H
2j	Me	H	H	H	H
2k	H	OMe	OMe	OMe	H
2l	OMe	OMe	OMe	OMe	OMe

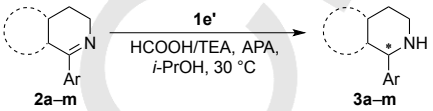
Figure 2. Structures of substrates **2a**–**m** tested in ATH catalysed by **1e′**.

The substrate scope study (Table 3) started with imine **2a** bearing two methoxy groups in positions 6 and 7. After 3 h, the conversion to amine **3a** was 88% (Table 3, entry 1) and the reaction did not proceed any further after 24 h. Such a suppressed reactivity (compared to **2b** in Table 3, entry 2) was surprising to us since in the 1-methyl-DHIQ series, the 6,7-dimethoxy derivatives are known to be more reactive.[27] In contrast, varying the *para*-substitution of the 1-phenyl moiety did not alter the reactivity to a significant extent as seen from high conversions of **2c**–**h** (Table 3, entries 3–8). Trifluoromethyl group in the *meta*-position (substrate **2i**) caused slightly diminished catalytic activity (Table 3, entry 9) and *ortho*-methyl-substituted derivative (**2j**) showed poor reactivity (Table 3, entry 10), consistent with findings of Perez *et al.*[24] in ATH of *ortho*-halogenated substrates with complex **1b**. Derivative **2k** bearing 3,4,5-trimethoxyphenyl group also required longer time for complete reaction compared with **2b** (Table 3, entries 2 and 11). Moreover, the highly methoxylated substrate **2l** showed a stark decrease in reactivity (Table 3, entry 12), similarly as in the case of **2a** (Table 3, entry 1). Therefore, these two structural features, *i.e.*, 6,7-dimethoxy substitution of the DHIQ core together with *ortho*-substitution of the 1-phenyl substituent, can be considered key factors inhibiting the ATH reaction under given conditions.

Additionally, 3,4-dihydro-*β*-carboline **2m** was tested (Table 3, entry 13), giving excellent reactivity but mediocre *ee* – unlike DHIQs **2a**–**l** that were hydrogenated with fair to good enantioselectivity (Table 3, entries 1–12). Remarkably, using this catalytic system, substrates **2b**, **2e** and **2f** (79–86% *ee*) were hydrogenated with higher *ee*s than using the Ru-based complex **1b**, where only 29–39% *ee* was achieved.[24]

Stirling *et al.* have recently demonstrated that when performing the ATH of a 1-alkyl-substituted DHIQ (6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline **4**) catalysed by **1e**, the *ee* decreases in the course of the reaction, sometimes even leading to enantionselectivity reversal at higher conversions. The authors explain this unusual phenomenon by different kinetics of formation of each enantiomer – while the (*R*) isomer is formed in a first-order reaction with reaction rates decreasing exponentially, the formation of the opposite *(S)* enantiomer follows a zero order kinetics.[28]

Table 3. ATH of substrates **2a**–**m** catalysed by complex **1e′**.[a]



Entry	Substrate	Time [h]	Conversion [%][b]	Yield [%][c]	*ee* [%][d]
1[e]	**2a**	3	88[g]	–[h]	72 (+)
2	**2b**	3	>99	90	86[i] (–)
3	**2c**	3	98	90	64 (–)
4	**2d**	6	95	79	73[i] (–)
5	**2e**	3	97	92	79[i] (–)
6	**2f**	3	97	87	83[i] (–)
7	**2g**	3	96	86	76[i] (–)
8	**2h**	3	97	90	77[i] (–)
9	**2i**	18	93	77	80 (–)
10[f]	**2j**	6	55[g]	–[h]	77[i] (–)
11	**2k**	6	96	90	84 (–)
12[f]	**2l**	6	46[g]	–[h]	76 (+)
13	**2m**	3	>99	92	50 (–)

[a] Conditions: substrate **2** (0.15 mmol), **1e′** (0.0015 mmol, 1 mol% vs. substrate), HCOOH (11 μL, 0.3 mmol), TEA (41 μL, 0.3 mmol), HCOOH:TEA = 1, APA (2 equiv to substrate), total volume: 2 mL, 30 °C. Amine product was obtained by basification and extraction. [b] Determined by ^{1}H NMR. [c] Isolated yield taking into account conversion as purity. [d] Determined by HPLC. [e] Loading of **1e′**: 2 mol%. [f] Loading of **1e′**: 5 mol%. [g] The same value observed after 24 h. [h] Not isolated due to incomplete conversion. [i] Determined by GC using pre-column derivatization.[26]

We observed the same behaviour with **4** and **1e′** under optimized conditions, although the effect was even more pronounced in some cases (Figure 3). In fact, the other isomer of the product **5** can be formed depending on the reaction conditions. For instance, in acetonitrile with APA, the *ee* of **5** changed from –14 to –45% (*i.e.*, the (*S*)-THIQ isomer was formed) in 2 h. Leaving out the APA led to attenuated reactivity and also less pronounced *ee* changes during the course of reaction, decreasing from +77% *ee* to +58% *ee* with (*R*)-isomer formed. Similar experiments in anhydrous *i*-PrOH revealed a dramatic change from +43% *ee* to –56% *ee* with APA and only +80% *ee* to +74% *ee* without APA (Figure 3).

Remarkably, however, this phenomenon was virtually absent when identical experiments were performed with 1-Ph-DHIQ **2b** – the *ee* was more or less constant in the course of the reaction (Figure S1). On the contrary, the absence of APA led to either no (acetonitrile) or sluggish (*i*-PrOH) reactivity. These experiments thus further confirmed the necessity of an acid additive.

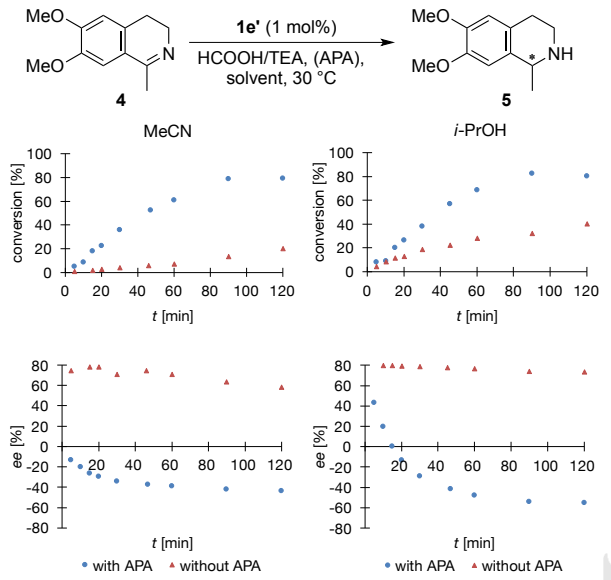


Figure 3. Time-conversion and time-*ee* plots of ATH of imine **4** in acetonitrile and *i*-PrOH catalysed by **1e′**.

To sum up, we have developed a simple protocol for the ATH of 1-aryl-substituted DHIQs using anhydrous phosphoric acid as the key additive and a readily available iridium catalytic complex. The method very well tolerates various functional groups, following a relatively simple structure-activity pattern. Although with a 1-alkyl-substituted substrate the enantioselectivity rapidly changes and can even be reversed during the course of the reaction, 1-aryl-DHIQs are hydrogenated with a practically constant *ee*. The Ir-based anhydrous phosphoric acid promoted system thus represents an attractive and practical alternative to the few other existing methods for ATH of 1-aryl-DHIQs.

Acknowledgements

The work was financially supported by the Czech Science Foundation (GA15-08992S), specific university research (MSMT No 20-SVV/2017), the Operational Programme Prague – Competitiveness (CZ.2.16/3.1.00/24501), and National Program of Sustainability (NPU I LO1613, MSMT-43760/2015). We thank Prof. Dr. Antonio Togni (ETH Zürich) and Dr. Petr Beier (IOCB CAS Prague) for providing their laboratories and Dr. Jiří Rybáček (IOCB CAS Prague) for providing the HPLC instrument.

Keywords: 1-aryl-3,4-dihydroisoquinolines • asymmetric synthesis • hydrogenation • iridium • phosphoric acid

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10.1002/ejoc.201701094

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Layout 2:

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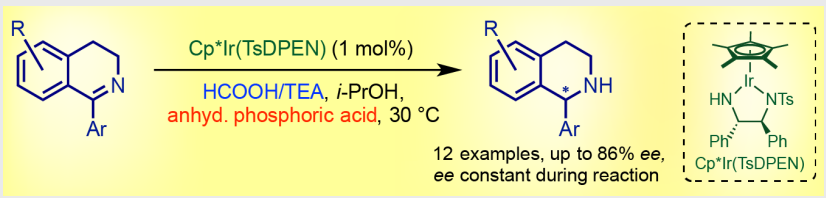

A method for the asymmetric transfer hydrogenation of 1-aryl-3,4-dihydroisoquinolines is reported. Employing the Cp*Ir(TsDPEN) catalytic complex with anhydrous phosphoric acid additive, high yields and good-to-high enantiomeric excess (*ee*) can be achieved. The *ee* is constant during the reaction, unlike in the case of 1-alkyl-3,4-dihydroisoquinolines where it changes dramatically.

Asymmetric Hydrogenation

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Asymmetric Transfer Hydrogenation of 1-Aryl-3,4-Dihydroisoquinolines Using a Cp*Ir(TsDPEN) Complex