Asymmetric Transfer Hydrogenation

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Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation of 1-Aryl-Substituted Dihydroisoquinolines: Access to Valuable Chiral 1-Aryl-Tetrahydroisoquinoline Scaffolds**

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The frequent occurrence of chiral 1-substituted-1,2,3,4-tetrahydroisoquinoline (THIQ) ring systems in a large number of alkaloids possessing a broad spectrum of biological and pharmaceutical properties has led to significant increasing interest in their synthesis.[1] To date, most of the traditional synthetic approaches are based on procedures employing chiral building blocks, auxiliaries, or reagents.[2] Thus, with particular emphasis on economic and ecologically valuable processes, much effort has been directed toward the development of catalytic enantioselective transformations to access enantiomerically pure 1-substituted-THIQ frameworks with a high level of selectivity.[3] Among them, the asymmetric hydrogenation[4] and asymmetric transfer hydrogenation (ATH)[5] of 1-substituted-3,4-dihydroisoquinolines (DHIQs)[6] are powerful methods because they have an intrinsic operational efficiency and are highly atom economical. However, despite the significant advances produced in these areas over the last two decades, only relatively few catalyst systems operating with high selectivity have been reported so far in the literature for the reduction of 1-alkyl-3,4-DHIQs.[6h,i,7d] Furthermore, and to the best of our knowledge, the asymmetric reduction of 1-aryl-substituted-3,4-DHIQs has only been sporadically described and still continues to be a challenge in the field of asymmetric hydrogenation.[7] To date, most of the existing catalytic systems are restricted to 1-phenyl-3,4-DHIQ as a model substrate and provide low to moderate catalytic efficiency. As far as the ATH of 1-aryl-substituted-3,4-DHIQs is concerned, only very few examples have been described. In 1999, Vedejs et al.[7c] reported the Ru^{II}-catalyzed ATH of 1-aryl-substituted-3,4-DHIQ substrates. Although high enantioselectivity was achieved (up to 98.7%), the method only tolerates a narrow range of *ortho* substituents, such as *o*-Br, *o*-NO_2, and *o*-N(R)SO_2Ar, with low to reasonable yields of 1–76%. Asymmetric hydrogenation of 1-aryl-3,4-DHIQs using iridium complexes have been recently reported by Zhang et al.[7d] and our group,[7e] with enantioselectivities higher than 90%. However, these two catalytic systems provide only moderate enantioselectivity for sterically hindered 1-(2′-substituted-aryl)-3,4-DHIQs. Therefore, the development of highly enantioselective methods that allow rapid and efficient access to the valuable 1-aryl-tetrahydroisoquinoline scaffold remains highly desirable. As part of our ongoing research program toward the use of metal-catalyzed asymmetric reduction for the synthesis of biologically relevant targets,[8] and taking in account the scarce examples of ATH of aryl-substituted-dihydroquinoline derivatives, we report herein a general and highly enantioselective Ru-catalyzed transfer hydrogenation of 1-aryl-substituted-1,2,3,4-DHIQs under mild conditions leading to the corresponding THIQ derivatives with a broad substrate scope and enantioselectivities of up to 99%.

We first examined the ATH of 1-phenyl-3,4-dihydro-6,7-dimethoxyisoquinoline **1a** in dichloromethane at 30°C for 16 h using an azeotropic 5:2 formic acid and triethylamine mixture as the hydrogen source in the presence of platinum group metal-based *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (TsDPEN) complexes (1 mol%). The results summarized in Table 1 clearly show that the stereochemical outcome of the reaction is dramatically affected by the structure of the complexes used. The reduction of **1a** under the aforementioned conditions using either Cp*Rh^{III}-TsDPEN (**3a**) or Cp*Ir^{III}-TsDPEN (**3b**) as catalysts proceeded with full conversion, but afforded only racemic product **2a** (Table 1, entries 1 and 2). Ru^{II}-TsDPEN complexes[9] **3c–g** were also tested in this transformation. Although complexes **3c–f** exhibited very poor catalytic activity, catalyst **3g**, which bears benzene as its η^6-arene, gave encouraging results in terms of both selectivity and reactivity, providing 1-phenyl-1,2,3,4-tetrahydroquinoline **2a** with an enantiomeric ratio of 87.5:12.5 and complete conversion (Table 1, entries 3–6 vs. 7).

Further examinations focused on the solvent and temperature effects. Although this asymmetric transfer hydrogenation proceeded with full conversion in all solvents tested, the best selectivity was obtained with *i*PrOH (Table 1, entry 14; e.r. = 91:9). Further, a significant drop in enantioselectivity was observed when the reaction was carried out at 50°C, whereas lowering the temperature from 30°C to 0°C led to a dramatic decrease in reactivity, resulting in only 30% conversion while maintaining good selectivity, providing **2a** in 90.5:9.5 e.r. (Table 1, entries 15 and 16).

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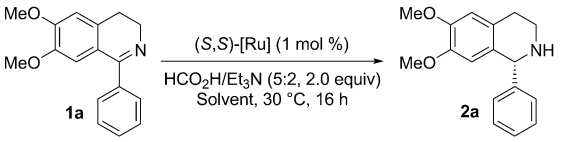
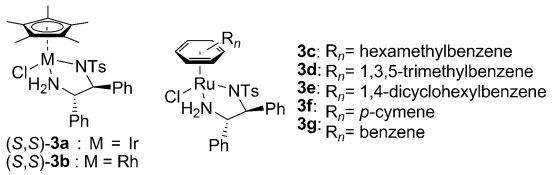
Table 1: Screening of PGM-based TsDPEN complexes.[a]



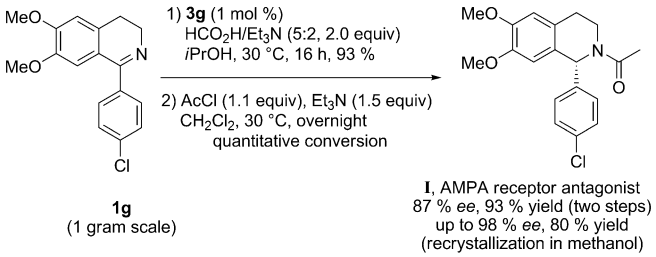
Entry	Catalyst	Solvent	Conv. [%][b]	e.r. [%][c]
1	**3a**	CH_2Cl_2	100	0
2	**3b**	CH_2Cl_2	100	0
3	**3c**	CH_2Cl_2	36	0
4	**3d**	CH_2Cl_2	13	n.d.
5	**3e**	CH_2Cl_2	9	n.d.
6	**3f**	CH_2Cl_2	15	n.d.
7	**3g**	CH_2Cl_2	100	87.5:12.5
8	**3g**	toluene	100	88.5:11.5
9	**3g**	THF	100	85:15
10	**3g**	dioxane	100	82.5:17.5
11	**3g**	DMF	100	74:26
12	**3g**	CH_3CN	100	72.5:27.5
13	**3g**	MeOH	100	83:17
14	**3g**	*i*PrOH	100	91:9
15[d]	**3g**	*i*PrOH	100	86:14
16[e]	**3g**	*i*PrOH	30	90.5:9.5

[a] Reactions were conducted at 30 °C using substrate **1** (1 mmol) and catalyst (1 mol %) for 16 h. [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 by comparison with literature data. [d] Reaction performed at 50 °C. [e] Reaction performed at 0 °C. n.d. = not determined.



A series of 1-aryl-dihydroisoquinolines **1a–z** was subjected to ATH under the optimized reaction conditions (Table 2). The reaction proceeded well in all cases, giving the corresponding THIQ derivatives **2a–z** in good to high yields (72–97 %) and good to excellent enantiomeric ratios (90.5:9.5–99.5:0.5 e.r.). The stereochemical outcome of ATH appears to be sensitive to both the nature and the position of the substituents on the aromatic rings. Methyl, bromo, and chloro substituents at the *meta* position of the 1-phenyl group of 6,7-dimethoxy substituted isoquinolines **1b–d** gave similar enantioselectivities as those obtained with compound **1a**, but products **2b–d** were isolated in significantly better yields (Table 2, entries 1–4). Moving substituents to the *para* position caused a marked increase in catalytic activity, giving **2e–g** in excellent yields (91–94 %) and high enantiomeric ratios of 93.5:6.5–95.5:4.5 (Table 2, entries 5–7). Even more impressive results were obtained with 6,7-dimethoxy substituted isoquinoline substrates **1h–p**, having either electron-donating or electron-withdrawing groups at the *ortho* position of the 1-phenyl group. These gave the desired hydrogenated products **2h–p** in high to excellent yields (83–97 %) and with consistently excellent enantioselectivities (Table 2, entries 8–16, 98:2–99.5:0.5 e.r.). These results clearly show that the enantioselectivity of the reaction gradually increases when the bulkiness of the substituents at the *ortho* position increases. These results may be a consequence of the steric effects significantly breaking the coplanarity of the 1-phenyl ring with the prochiral C=N double bond[10] in the transition state, thereby leading to high levels of enantiofacial discrimination. The data in Table 2 also indicates that substituents on the benzene ring of the isoquinoline moiety have a marked effect on the reactivity, as well as on the stereochemical outcome of the reaction (Table 2, entries 17–26). More specifically, we found that the transfer hydrogenation of imines **1q–t**, which bear no substituent ($R^1 = H$), gave consistently lower enantioselectivity and conversion (and consequently lower yield) than those obtained with the corresponding 6,7-dimethoxy analogues **1j**, **1l**, **1n**, and **1p**, even with an extended reaction time (Table 2, entries 10, 12, 14, and 16 vs. 17–20). Furthermore, when only one methoxy group is present at the 5-, 6-, or 7-position of the benzene ring of the dihydroisoquinoline core, the reaction outcome is less affected when using substrates that bear electron-withdrawing groups (Table 2, entries 14 and 15 vs. 21, 22, 25, and 26) than substrates bearing electron-donating groups (Table 2, entries 8 and 9 vs. 23 and 24), giving the desired products **2u–z** in high yields (86–90 %) and with 97.5:2.5–98:2 e.r. and 96:4 e.r., respectively.

Finally, to showcase the practicality of the process, a gram-scale synthesis of compound **I**, a potent noncompetitive AMPA receptor antagonist currently being investigated in phase III trials as an antiepileptic agent,[1d,g] was performed (Scheme 1). Under the optimized reaction conditions, DHIQ

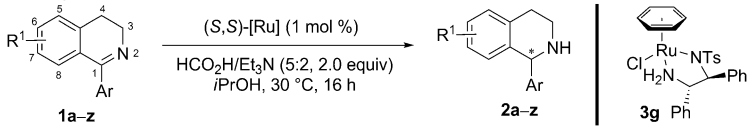


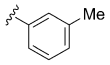
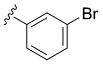
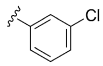
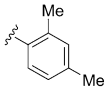
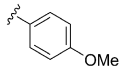
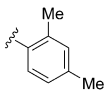
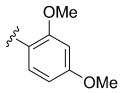
Scheme 1. Synthesis of AMPA receptor antagonist (*R*)-**I**.

1g was reduced to give **2g** in 93 % yield with a 93.5:6.5 e.r. Subsequent acetylation, followed by a single recrystallization furnished the desired compound **I**, which was isolated with up to 99:1 e.r and in 80 % yield.

In conclusion, we report a highly enantioselective Ru-catalyzed transfer hydrogenation with a broad substrate scope of readily available 1-aryl-substituted 3,4-dihydroisoquinoline derivatives. This method offers several advantages, including mild reaction conditions, low catalyst loading, and operational simplicity, which makes it a useful and attractive method for the synthesis of the valuable 1-aryl-tetrahydroisoquinoline scaffold with excellent enantioselectivities (up to 99.5:0.5 e.r.) and in high yields of isolated products. Moreover, the synthetic utility of this method for the preparation of the potent noncompetitive AMPA receptor antagonist **I** was also demonstrated on a gram scale. Application to the synthesis of

Table 2: ATH of 1-aryl substituted isoquinoline derivatives.[a]



Entry	Substrate			Yield [%][b]	e.r. [%][c]	Entry	Substrate			Yield [%][b]	e.r. [%][c]
	1	Ar	R^1				**1**	Ar	R^1		
1	**1a**		6,7-di-MeO	82	91:9 (+)	14	**1n**		6,7-di-MeO	93	99:1 (−)
2	**1b**		6,7-di-MeO	90	92:8 (+)	15	**1o**		6,7-diMeO	91	99:1 (−)
3	**1c**		6,7-di-MeO	90	91:9 (+)	16	**1p**		6,7-diMeO	92	99.5:0.5 (−)
4	**1d**		6,7-di-MeO	93	91.5:8.5 (+)	17[d]	**1q**		H	75	95:5 (+)
5	**1e**		6,7-di-MeO	92	95.5:4.5 (+)	18[d]	**1r**		H	74	95:5 (−)
6	**1f**		6,7-di-MeO	91	93.5:6.5 (−)	19[d]	**1s**		H	73	96:4 (−)
7	**1g**		6,7-di-MeO	94	93.5:6.5 (−)	20[d]	**1t**		H	72	96:4 (−)
8	**1h**		6,7-di-MeO	86	99:1 (+)	21	**1u**		5-MeO	87	97.5:2.5 (−)
9	**1i**		6,7-di-MeO	84	98:2 (+)	22	**1v**		6-MeO	90	98:2 (−)
10	**1j**		6,7-di-MeO	83	99:1 (−)	23	**1w**		7-MeO	90	96:4 (+)
11	**1k**		6,7-di-MeO	85	98:2 (+)	24	**1x**		7-MeO	86	96:4 (+)
12	**1l**		6,7-di-MeO	86	99:1 (+)	25	**1y**		7-MeO	87	98:2 (−)
13	**1m**		6,7-di-MeO	97	98:2 (+)	26	**1z**		7-MeO	89	97.5:2.5 (−)

[a] Reactions were conducted at 30 °C using substrate **1** (1 mmol) and catalyst (1 mol %) in *i*PrOH for 16 h. [b] Yield of isolated product. [c] Determined by chiral stationary phase supercritical fluid chromatography (CSP-SFC). The absolute configuration of the product is assigned by comparison of the rotation sign with literature data. [d] 80% conversion was obtained after a reaction time of 40 h.

other pharmaceutically relevant targets is currently underway in our laboratory and will be reported in due course.

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