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A Highly Enantioselective Access to Tetrahydroisoquinoline and β-Carboline Alkaloids with Simple Noyori-Type Catalysts in Aqueous Media

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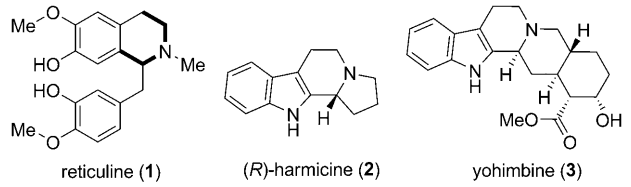
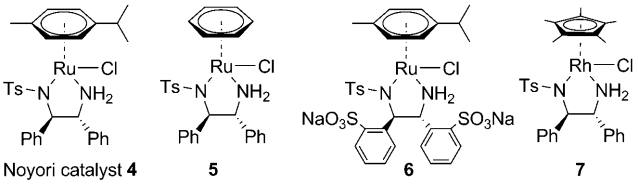
The asymmetric synthesis of enantiomerically pure tetrahydroisoquinolines and tetrahydro-β-carbolines remains a challenge in organic synthesis. This skeleton is shared by a number of biologically active compounds,[1] such as reticuline (**1**), (R)-harmicine (**2**), yohimbine (**3**) and reserpine (not depicted) (Scheme 1). Currently, the state-of-the-art method for accessing this skeleton is asymmetric reduction[2] by using the Ru catalysts described by the Noyori group (Scheme 2).[3] Typically, an azeotropic mixture of Et_3N and HCOOH (ca. 5:2 ratio) is used as a source of hydrogen. The need for an excess of triethylamine and the possibility of formation of carbon monoxide in this system[4] renders it less attractive for scale up.



Scheme 1. Alkaloids containing the tetrahydroisoquinoline system.



Scheme 2. The Noyori catalyst and selected variants.

Since the seminal publication by the Noyori group on asymmetric transfer hydrogenation with the HCOOH–Et_3N azeotropic mixture,[3] a number of variants of the original monotosylated diamine ligand and the ruthenium catalyst have been reported. The modifications have addressed the role of the metal (Ru, Ir, Rh),[5,6,7] the diamine ligand,[8] and the π-complexed aromatic ring.[3,9,10,11] The hydride-transfer catalyst system has generally been very tolerant to all of those modifications, affording typically good to excellent enantioselectivities. However, the use of alternative conditions that might allow water soluble or otherwise recalcitrant substrates to be reduced has received relatively little attention. For reactions in aqueous solution, Süss-Fink and co-workers reported the use of a catalyst based on *trans*-1,2-diaminocyclohexane[8a] and (aminomethyl)pyrrolidine[8b] chiral ligands. Zhu and co-workers have also described a highly interesting sulfonated variant **6**[12] (Scheme 2) of the original Noyori ligand.

Herein, we report a very convenient protocol for asymmetric hydrogen-transfer reductions of dihydroisoquinoline skeletons with simple unmodified, commercially available diamine ligands under aqueous conditions using sodium formate as the hydride source.[13] In addition, for substrates resistant to the standard conditions, we also present an experimentally simple solution in which the reaction is accelerated by increasing the activity of the catalyst with silver salts as well as activation of the substrate with lanthanide triflates.

Initially, we focused on the reduction of simple alkyl-substituted dihydroisoquinolines and β-carbolines (**8a,b** and **10a,b**, Scheme 3 and Table 1) using aqueous sodium formate as the hydride source and cetyltrimethylammonium bromide (CTAB) as a cationic surfactant.[5a,14] To our delight, using the simple Noyori-type catalyst **4**, we obtained the products in excellent yields (87% or higher) and enantiomeric excess (99% *ee* or higher).

The aqueous conditions might be highly useful for the reduction of fused iminium ions of the type **12** and **13**

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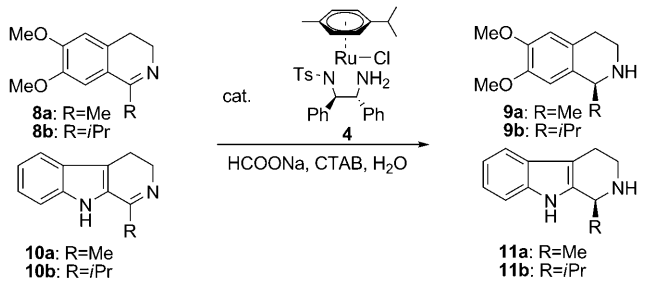


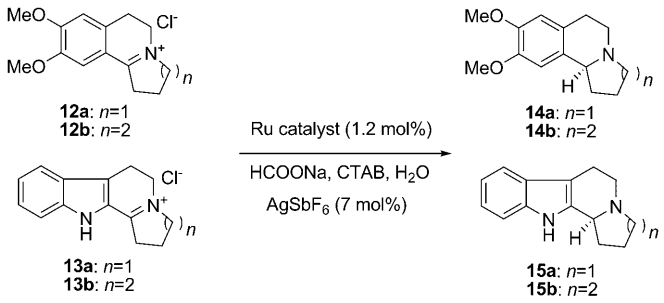
Scheme 3. Asymmetric transfer hydrogenation of alkyl imines.

Table 1. Asymmetric transfer hydrogenation of alkyl-substituted imines in aqueous media.

Entry	Substrate	*T*	Yield[a] [%]	*ee*[b] [%]	Configuration
1	**8a**	RT	90	99	*S*
2	**8b**	40 °C	87	99.5	*S*
3	**10a**	RT	90	>99	*S*
4	**10b**	40 °C	92	>99	*S*

[a] Isolated yields. Reaction time: 16 h. See the Experimental Section for conditions (0.25 mmol scale, 0.6 mol % catalyst). [b] The *ee* value was determined by HPLC (Daicel-OD column).

(Scheme 4). Their reduction affords a direct route to indole alkaloid skeletons. As an alternative, the acyl-Pictet–Spengler reaction also allows the catalytic asymmetric synthesis



Scheme 4. Asymmetric transfer hydrogenation of polycyclic iminium salts.

of similar ring systems.[15] Unfortunately, the acyl-Pictet–Spengler approach appears to be limited to β-carbolines with an indole ring system, and all attempts to expand the scope to the enantioselective synthesis of isoquinolines have failed.

Our first experiments with polycyclic iminium systems were not very encouraging and less than 5% conversions were observed after 24 h under the initial conditions. Fortunately, a solution was easily found by the addition of $AgSbF_6$ to generate an in situ modification of the catalyst[16] to increase the turnover of the catalyst. With complex **4**, polycyclic iminiums **12a** and **12b** were reduced with fair selectivity, although in modest yields (37 and 50% respectively), thus creating compounds **14a** and **14b**. However, a significant improvement was obtained by switching to the corresponding benzene complex **5**. The silver-modified method was particularly suitable for the hydrogenation of the iminium salts **13a** and **13b**, which are only sparingly soluble in organic solvents. Their reduction allows a very short synthesis of the indoloquinolizidine alkaloid (−)-(*S*)-harmicine **15a** and its homologue **15b** (Table 2, entries 7 and 8). It is worth

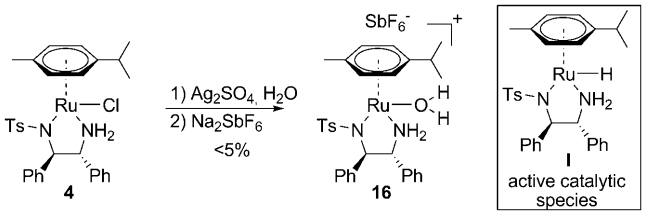
Table 2. Asymmetric transfer hydrogenation of polycyclic iminium salts.

Entry	Substrate	Cat.	Additive	Yield [%]	*ee*[a] [%]	Configuration
1	**12a**	**4**	–	<5	ND[b]	–
2	**12a**	**4**	$AgSbF_6$	37[c]	87	*S*
3	**12a**	**5**	$AgSbF_6$	45[c]	94	*S*
4	**12a**	**7**	$AgSbF_6$	85[c]	58	*S*
6	**12b**	**5**	$AgSbF_6$	65	96	*S*
7	**13a**	**4**	$AgSbF_6$	94[c]	98	*S*
8	**13b**	**4**	$AgSbF_6$	85	98	*S*

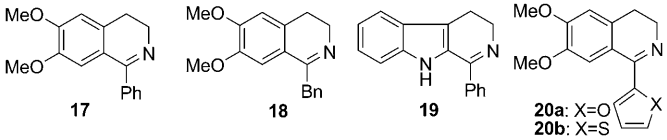
[a] The *ee* value was determined by HPLC (Daicel-OD column). [b] ND = not determined. [c] Isolated as a hydrochloride salt.

noting that hydrogenation-transfer methods provide the shortest enantioselective routes published so far for crispine[17] and harmicine;[18] furthermore, our protocol also allows a significant improvement to the enantioselectivity compared with previous reports.[19]

To shed light on the mechanism of the activation with silver, we attempted to isolate the active catalyst by a two-step process (Scheme 5).[8a] Although only a very low yield of the catalyst was obtained (mainly due to the low solubility of **4** in water), the isolated complex exhibited NMR spectroscopy and HRMS data that were consistent with structure **16**. To test the activity of this catalyst, we selected benzyl-substituted substrate **18** (Scheme 6), which gave only 40% conversion with the original Noyori catalyst **4** (Table 3, entries 1–3). The isolated complex turned out to be just as active in the reduction of **18** as our original catalyst system (compare Table 4, entry 1), affording the reduction product in 88% yield. Taken together, these two experiments strong-



Scheme 5. Isolation of the active catalyst.



Scheme 6. Substrates bearing aromatic or benzylic substituents.

Table 3. Optimization experiments for substrates **17** and **18**, resistant to standard conditions.[a]

Entry	Substrate	Additive	Conv.[b] [%]	*ee*[c] [%]	Configuration[d]
1	**18**	none	40	ND[e]	*S*
2	**18**	$AgSbF_6$	90[f]	98.5	*S*
3	**18**	none, cat. **16**	88[f]	99	*S*
4	**17**	none	5	ND[e]	–
5	**17**	$AgSbF_6$	27	97	*S*
6	**17**	$La(OTf)_3$	20	ND[e]	–
7	**17**	$AgSbF_6/Sc(OTf)_3$	31	90	*S*
8	**17**	$AgSbF_6/Y(OTf)_3$	60	92	*S*
9	**17**	$AgSbF_6/La(OTf)_3$	80	94	*S*
10	**17**	$AgSbF_6/Ce(OTf)_3$	72	93.5	*S*
11	**17**	$AgSbF_6/Yb(OTf)_3$	54	94.5	*S*
12	**17**	$AgSbF_6/Bi(OTf)_3$	87	94	*S*

[a] Reaction time: 16 h. See the Experimental Section for conditions. (0.125 mmol scale, 1.3 mol% catalyst, 2.4 mol% $AgSbF_6$) [b] Conv. = conversion, as determined by crude NMR spectroscopy. [c] The *ee* value was determined by HPLC (Daicel-OD column). [d] Hydrogenation products are levorotary. [e] ND = not determined. [f] Isolated yield.

Table 4. Optimization of the Ag-Lewis acid activated transfer hydrogenations in aqueous conditions and comparison with H_2O/MeOH conditions.[a]

Entry	Substrate	Conditions	Additive	Yield (conv.)[b] [%]	*ee*[d,e] [%]
1	**18**	H_2O/CTAB	$AgSbF_6$	90 (99)	98
2	**19**[f]	H_2O/CTAB	$AgSbF_6/La(OTf)_3$	(94)[c]	99
3	**19**[f]	H_2O/CTAB	$AgSbF_6/Bi(OTf)_3$	(99)[c]	99
4	**20a**	H_2O/CTAB	$AgSbF_6$	(40)[b]	87
5	**20a**	H_2O/CTAB	$AgSbF_6/La(OTf)_3$	(99)[c]	70
6	**20a**	H_2O/CTAB	$AgSbF_6/Bi(OTf)_3$	(99)[c]	60
7	**20b**	H_2O/CTAB	$AgSbF_6/La(OTf)_3$	(27)	90
8	**20b**	H_2O/CTAB	$AgSbF_6/Bi(OTf)_3$	(22)	94
9	**8a**	H_2O/MeOH	$AgSbF_6$	59 (99)	99
10	**13b**	H_2O/MeOH	$AgSbF_6$	90 (99)	95
11	**17**	H_2O/MeOH	$AgSbF_6/La(OTf)_3$	80 (99)	93
12	**19**	H_2O/MeOH	$AgSbF_6/La(OTf)_3$	78 (99)	98
13	**20b**	H_2O/MeOH	$AgSbF_6/La(OTf)_3$	50 (54)	94

[a] Reaction time: 16 h. See the Experimental Section for conditions. [b] Conv. = conversion, as determined by NMR spectroscopy. [c] The isolated yields in these cases were generally 20–30% lower due to difficulties in removing the CTAB residues. [d] The *ee* value was determined by HPLC (Daicel-OD column). [e] All hydrogenation products are levorotary and are likely to have the same configuration. [f] Reaction time 40 h.

ly suggest the in situ generation of cationic intermediate **16**. Interestingly, the less bulky BF_4^- and PF_6^- salts were not effective and even decreased the catalytic activity.

Although benzyl-substituted substrate **18** (Scheme 6) was readily reduced under the micelle conditions, substrates with aryl substituents conjugated to the imine system (e.g., **17**, **19**, **20a**, and **20b**; Scheme 6) turned out to be more challenging. For the asymmetric reduction of **17**, a work-around based on the reduction of *N*-benzyl iminium derivatives has been proposed.[12b]

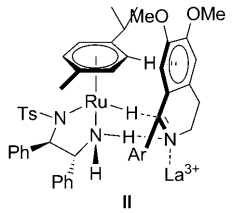
It has previously been established that under the original Noyori conditions the reduction proceeds via a protonated iminium species.[20] We hypothesized that activation of the imine with water-soluble Lewis acids might be possible. Lanthanide and bismuth(III) triflates are known to accelerate reactions with imines.[21] The best results were obtained when silver and Lewis acid activation were used together (Table 3, entries 7–12). Increasing the size of the cation in the series $Sc^{3+} < Y^{3+} < La^{3+}$ afforded better conversions (compare Table 3, entries 7–9);[.22] the use of bismuth also gave good results (Table 3, entry 12) and good enantioselectivities.

The results of the application of the double activation method to the reduction of other aromatic/benzylic substrates are presented in Table 4 (entries 1–13). To summarize the results (compare Tables 1, 2, and 3), imines with alkyl substituents could be reduced without any additive, but for aromatic substituents both Lewis acid activation and catalyst activation ($AgSbF_6$) were indispensable. The benzyl-substituted substrates and the fused iminium salts represent intermediate cases in which only the catalyst needs to be activated with silver salts.

Although the conversions with the surfactant method were typically excellent, purification of the products from the surfactant residues was more problematic with aromatic substrates (especially **17** and **20a**). In addition, thiophenyl-substituted **20b** was surprisingly unreactive (Table 4, entries 7 and 8). For these cases, we found that aqueous methanol (2:1 H_2O/MeOH) could be used (Table 4, entries 9–13) as a simple alternative to the surfactant conditions.[23] Of the solvent mixtures tested (mixtures of water with methanol, ethanol, acetonitrile, and THF), aqueous methanol (2:1 H_2O/MeOH) afforded the highest rates. This protocol was especially useful for lipophilic substrates with aromatic substituents, such as **17**, **19**, and **20b**. The optimized procedures are summarized in Table 4. The H_2O/MeOH system allows for easier purification and this procedure is more convenient to scale up. However, for the alkyl-substituted imines, such as **8a** (Table 4, entry 9) and most polycyclic iminium salts (see Table 2), the CTAB method afforded better results (only the reduction of **13b** proceeded with a higher yield in aqueous methanol).[24]

Although it has been established that the reductions proceed through protonated substrates, it is interesting to note that the reductions of alkyl-substituted imines do proceed under our (slightly basic) aqueous conditions. Blackmond et al. have suggested that reductions of imines with Rh–diamine catalysts might proceed via the unprotonated imine.[25] However, to explain the observed rate enhancement effect of metal triflates, we suggest that these reductions proceed by the ionic "anti" mechanism proposed by Wills et al.[25b] Although the N−H bond of the catalyst already activates the imine, the Lewis acid may provide additional activation (Scheme 7). In most cases this extra activation does not appear to disturb the enantioselectivity of the catalyst; however, in the case of furan **20a**, the enantioselectivity was clearly eroded (compare entries 4–6, Table 4), possibly due to complexation of the furan ring with lanthanum.

In summary, we have developed two alternative modifications to the original Noyori reduction procedure by performing the reaction under aqueous conditions and using



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Scheme 7. The Wills' anti ionic mechanism allows dual activation of the substrate by the catalyst and lanthanum.

sodium formate as the hydrogen donor. The use of $AgSbF_6$ to boost the activity of the ruthenium catalyst, as well as the optional use of lanthanide Lewis acids and aqueous methanol, allowed the reactions to proceed at good rates and good-to-excellent enantioselectivities, and substrates normally resistant to hydrogenation could also be used. The method is also applicable to the reduction of polycyclic iminium salts, allowing for a very short synthesis of the alkaloids crispine and harmicine. Applications of the method to the total synthesis of more complex targets will be reported in due course.

Experimental Section

Typical procedure for asymmetric transfer hydrogenation of imines in aqueous media by yusing Lewis acids and CTAB: In a GC vial, imine (0.125 mmol, 100 mol%), (*R*,*R*)-Noyori catalyst, (1.0 mg, 0.0016 mmol, 1.3 mol%), $AgSbF_6$ (1.0 mg, 0.0030 mmol, 2.4 mol%), Lewis acid $M(OTf)_3$ (0.041 mmol, 33 mol%), CTAB (46 mg, 0.13 mmol, 100 mol%) and sodium formate (130 mg, 1.9 mmol, 1500 mol%) were mixed with 0.75 mL of degassed water and vigorously stirred for 16 h at 40 °C under inert atmosphere. The reaction mixture was allowed to cool to RT and then extracted with CH_2Cl_2 (2×2 mL). The combined extracts were dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (1–10% MeOH in CH_2Cl_2) afforded the desired products.

Typical procedure for asymmetric transfer hydrogenation of imines in water/methanol mixture using lanthanum(III) triflate: In a small vial, imine (0.125 mmol, 100 mol%), (*R*,*R*)-Noyori catalyst, (1.0 mg, 0.0016 mmol, 1.3 mol%), $AgSbF_6$ (3.0 mg, 0.009 mmol, 2.4 mol%), sodium formate (130 mg, 1.9 mmol, 1500 mol%), lanthanum triflate (24 mg, 0.041 mmol, 33 mol%) were dissolved in water-methanol mixture (2:1 v/v, 0.75 mL) and vigorously stirred for 16 h at 40 °C under inert atmosphere. The mixture was allowed to cool to RT and extracted by CH_2Cl_2 (2×3 mL). The combined extracts were dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (silica gel, 1–10% MeOH in CH_2Cl_2) afforded the desired products.

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Keywords: alkaloids · asymmetric synthesis · catalysis · imines · lanthanides · transfer hydrogenation

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[24] The polycyclic iminium salts **12a**, **12b**, and **13a** afforded only poor-to-moderate results under these conditions; see the Supporting Information for details.

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