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Asymmetric Transfer Hydrogenation of 3-Nitroquinolines: Facile Access to Cyclic Nitro Compounds with Two Contiguous Stereocenters

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Enantiopure nitro compounds are versatile building blocks in organic synthesis because they can be easily transformed into a vast array of important chiral compounds, such as amines, aldehydes, acids or denitrated compounds.[1] To date, many elegant catalytic methods have been developed for the synthesis of enantiopure nitro compounds, such as enantioselective conjugate additions to nitroalkenes,[2] asymmetric Henry reaction,[3] and asymmetric reduction of prochiral unsaturated nitro compounds.[4] In view of the ready availability and easy preparation of the aromatic nitro compounds, the asymmetric reduction of such compounds would provide efficient and straightforward access to the corresponding chiral cyclic saturated and partially saturated nitro compounds. However, because of their resonance stability and special electron-withdrawing and coordination properties, there is little information available in literature about the asymmetric reduction of aromatic nitro compounds, despite the fact that catalytic asymmetric hydrogenation of heteroarenes/arenes has been well documented.[5–7] Given the significance of the intriguing chiral cyclic nitro compounds, the development of asymmetric reduction of aromatic nitro compounds is challenging but highly desirable. Herein, we report an efficient asymmetric transfer hydrogenation of aromatic nitro compounds, 3-nitroquinolines, with excellent enantio- and diastereoselectivities, and both epimers of a biologically active compound were synthesized using this protocol as the key step.

We began our studies using the readily available 2-phenyl-3-nitroquinoline (**1a**)[8] as a model substrate. The [{Ir(cod)Cl}$_2$]/bisphosphine/I$_2$ catalyst system has been successfully applied in enantioselective hydrogenation of imines[9] and heteroaromatic compounds.[5] The original experiment was conducted on the hydrogenation of **1a** by employing [{Ir(cod)Cl}$_2$]/(*S*)-MeO-Biphep/I$_2$ [(*S*)-MeO-Biphep = (*S*)-(2,2′-dimethoxybiphenyl-6,6′-diyl)bis(diphenylphosphine)].[6a] Unfortunately, the desired product 2-phenyl-3-nitro-1,2,3,4-tetrahydroquinoline (**4a**) was obtained in poor yield and with poor enantioselectivity (16% yield and 19% *ee*), the main reasons for which may be the strong aromaticity of aromatic nitro compounds and the interaction of the nitro group with the iridium catalyst. Chiral organocatalysts with high functional-group tolerance have been successfully applied in asymmetric transfer hydrogenation of C=O, C=N, and C=C bonds and heteroaromatic compounds using Hantzsch ester as the hydrogen source.[10] So, our further studies changed to explore organocatalyzed asymmetric transfer hydrogenation. Chiral phosphoric acid (CPA)[11] **3a** was employed as the catalyst with Hantzsch ester **2a** as the hydrogen source. When the reaction was carried out in toluene at room temperature, **4a** was obtained with 97% yield and 28% *ee* (Table 1, entry 1). Next, the effect of the reaction medium was tested (Table 1, entries 2–5). A dramatic influence was observed, and benzene was found to be the best choice with regard to both yield and enantioselectivity (97% yield, 35% *ee*; Table 1, entry 5). Then, various commercially available chiral H$_8$-BINOL-derived phosphoric acids (*S*)-**3** were tested (Table 1, entries 6–12). From this survey the more sterically congested catalysts, such as **3b** and **3c**, were less reactive (Table 1, entries 6 and 7), the best result (99% yield, 85% *ee*; Table 1, entry 11) was obtained when **3g** bearing the 2-methoxyphenyl substituent was employed.

Once the best organocatalyst **3g** was confirmed, we conducted further investigation of the effect of several common Hantzsch esters (**2a**, **2b**, and **2c**). There appears to be a trend toward declined enantiocontrol as the relative size of the ester moieties at the 3,5-dihydropyridine site increases (R = OMe, 86% *ee*; R = OEt, 85% *ee*; R = O*t*Bu, 74%

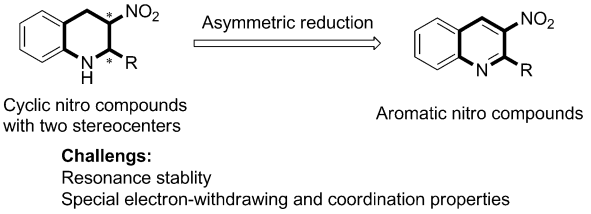

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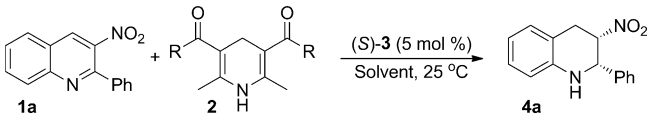
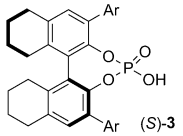
Table 1. Evaluation of reaction parameters.[a]





3a: Ar = Ph
3b: Ar = $SiPh_3$
3c: Ar = 3,5-$(CF_3)_2C_6H_3$
3d: Ar = 2-Naphthyl
3e: Ar = 2-MeC_6H_4
3f: Ar = 4-$MeOC_6H_4$
3g: Ar = 2-$MeOC_6H_4$
3h: Ar = 2-ClC_6H_4

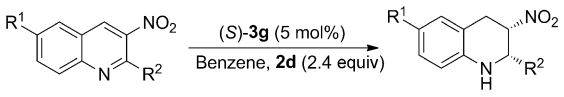
Entry	Solvent	**2**	(*S*)-**3**	Yield [%][b]	*ee* [%][c]
1	toluene	**2a**	**3a**	97	28
2	THF	**2a**	**3a**	13	−23
3	1,4-dioxane	**2a**	**3a**	13	<1
4	CH_2Cl_2	**2a**	**3a**	47	21
5	benzene	**2a**	**3a**	97	35
6	benzene	**2a**	**3b**	9	39
7	benzene	**2a**	**3c**	34	9
8	benzene	**2a**	**3d**	99	50
9	benzene	**2a**	**3e**	99	73
10	benzene	**2a**	**3f**	94	36
11	benzene	**2a**	**3g**	99	85
12	benzene	**2a**	**3h**	97	81
13	benzene	**2b**	**3g**	99	86
14	benzene	**2c**	**3g**	47	74
15	benzene	**2d**	**3g**	97	94

[a] Reactions were performed with **1a** (0.125 mmol) and **2** (2.4 equiv) in solvent (5.0 mL) at 25 °C with catalyst (*S*)-**3** (5 mol %). The d.r. values of products were determined by ^{1}H NMR spectroscopy. In all cases, d.r. > 20:1. [b] Yield of isolated product based on **1a**. [c] Determined by HPLC analysis.

ee; Table 1, entries 11, 13–14). So, a smaller-sized dihydropyridine **2d** bearing acetyl groups was synthesized[12] and tested. As expected, a much better enantioselectivity was obtained (94% *ee*; Table 1, entry 15). Thus, the optimized conditions were established as: chiral phosphoric acid **3g** (5 mol%), dihydropyridine **2d** (2.4 equiv), benzene, 25 °C.

In order to probe the generality of the catalytic system, a series of 3-nitroquinolines were subjected to transfer hydrogenation under the optimized conditions, and the results were summarized in Table 2. All the 2-aryl substituted substrates were smoothly converted to the corresponding products in high yields. Notably, the electronic property of the phenyl group on C2-position had a great influence on the enantioselectivity (Table 2, entries 1–8 and 10). Substrates bearing electron-withdrawing groups gave much higher *ee* values than those with electron-donating groups. Especially, substrate **1h** with a 4-CF_3 group on the phenyl ring gave the best enantioselectivity (99% *ee*; Table 2, entry 8), although it required a much longer reaction time. This method was also successfully applied to the 2-(furan-2-yl) substituted substrate **3i** with 80% *ee* (Table 2, entry 9), which might be a consequence of its electron-rich nature. High enantioselectivities were also observed in the hydrogenation of 2,6-disubstituted substrates **1k** and **1l** (92% *ee* and 92% *ee*; Table 2, entries 11 and 12). Using this catalyst system, the

Table 2. Catalytic asymmetric transfer hydrogenation of **1**.[a]

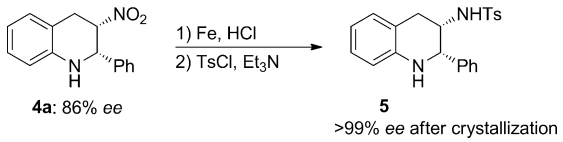


Entry	R^1	R^2	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	H	C_6H_5	25	97 (**4a**)	94 (*S,S*)
2	H	3-MeC_6H_4	25	99 (**4b**)	97 (−)
3	H	4-MeC_6H_4	25	99 (**4c**)	98 (−)
4	H	4-$MeOC_6H_4$	25	97 (**4d**)	88 (−)
5	H	4-ClC_6H_4	45	97 (**4e**)	96 (−)
6	H	4-BrC_6H_4	45	99 (**4f**)	96 (−)
7	H	4-FC_6H_4	45	97 (**4g**)	95 (−)
8	H	4-$CF_3C_6H_4$	45	95 (**4h**)	99 (−)
9	H	2-furanyl	25	99 (**4i**)	80 (−)
10	H	2-naphthyl	45	99 (**4j**)	98 (−)
11	F	C_6H_5	45	97 (**4k**)	92 (−)
12[d]	MeO	C_6H_5	45	91 (**4l**)	92 (−)
13[e]	H	(*E*)-styryl	45	61 (**4m**)	96 (−)
14[e]	H	(*E*)-4-fluorostyryl	45	51 (**4n**)	94 (−)
15[e]	H	(*E*)-4-chlorostyryl	45	59 (**4o**)	91 (−)

[a] Reactions were performed with **1** (0.125 mmol) and **2d** (2.4 equiv) in benzene (5.0 mL) with catalyst (*S*)-**3g** (5 mol%) for 12–48 h. The d.r. values of products were determined by ^{1}H NMR spectroscopy. In all cases, d.r. > 20:1. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] Because the *cis* product was unstable, when the reduction was finished, triethylamine was added to promote the epimerization to *trans* product. [e] 7.5 mol% (*S*)-**3g** was used.

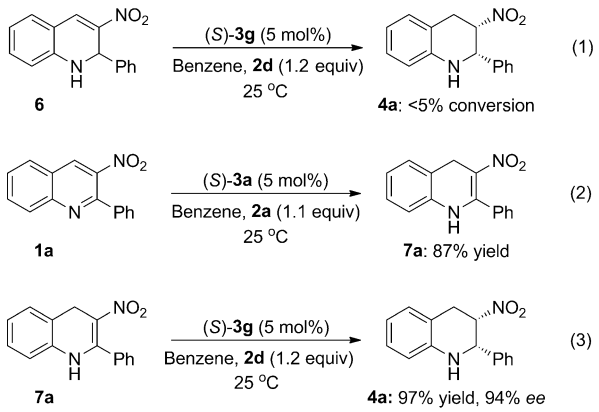
interesting 2-styryl derivatives could also be reduced with moderate yields and excellent enantioselectivities while the conjugated C=C double bond was preserved (Table 2, entries 13–15). Unfortunately, although the 2-alkyl substituted substrate 2-butyl-3-nitro-quinoline could be completely transformed, the partially hydrogenated product 2-butyl-3-nitro-1,4-dihydro-quinoline was obtained in 97% yield.

The absolute configuration of hydrogenation product **4a** was determined to be *cis*-(*S,S*) based on single-crystal X-ray diffraction analysis of its *N*-tosyl derivative **5** by a simple two-step transformation of reduction and protection with *p*-toluenesulfonyl chloride (Scheme 1).[13]



Scheme 1. Determination of the absolute configuration of **4a**.

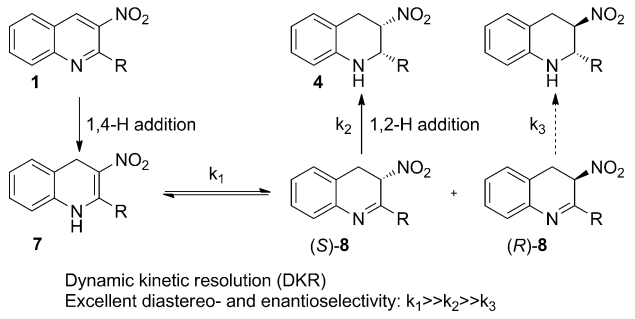
To explore the mechanism, a series of control experiments were conducted (Scheme 2). The transfer hydrogenation of 3-nitro-2-phenyl-1,2-dihydroquinoline (**6**), which was considered as the probable intermediate in case of initial 1,2-H addition, failed to proceed [Eq. (1)]. This finding suggested that the reaction might be initiated by 1,4-H addition. Fortunately, when the amount of **2a** was decreased to 1.1 equiv, the 1,4-H addition intermediate 2-phenyl-3-nitro-1,4-dihydroquinoline (**7a**) was obtained as main product with 87% yield [Eq. (2)]. To confirm the former hypothesis, **7a** was



Scheme 2. Mechanistic investigation of the asymmetric transfer hydrogenation of 3-nitroquinolines **1**.

subjected to the transfer hydrogenation under the optimized reaction conditions [Eq. (3)]. As expected, **4a** was afforded with 97% yield and 94% *ee*, which was consistent with the result of the direct transformation of **1a** (Table 2, entry 1).

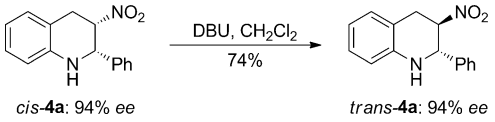
On the basis of the above experimental results, and in consideration of the recent report that the transfer hydrogenation of β-amino nitroolefin was conducted via its imine intermediate,[4k] a stepwise transfer hydrogenation was proposed (Scheme 3). The reaction is initiated by 1,4-H addi-



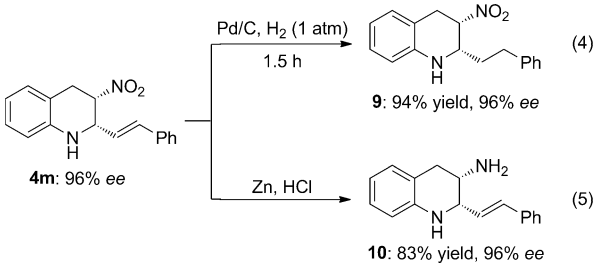
Scheme 3. Proposed transfer hydrogenation mechanism.

tion to provide the partial reductive intermediate **7**, followed by a rapid acid-catalyzed enamine/imine isomerization between **7** and **8**. Then a diastereoselective 1,2-hydrogenation occurs to deliver the desired *cis* product **4**. It is noteworthy that the enantioselectivity is controlled by the isomerization of enamine **7** to imine **8** and the hydrogenation of the C=N bond, which is in fact a dynamic kinetic resolution process.[14] The excellent diastereo- and enantioselectivity achieved in this transfer hydrogenation is attributed to the fact that the rate of the tautomerization is faster than that of the diastereoselective hydrogenation of **8**, and reduction rate of (*S*)-**8** is quicker than that of (*R*)-**8**, that is, $k_1 \gg k_2 \gg k_3$. Notably, similar mechanism have been proposed before by Rueping et al., us, and others in the hydrogenation of quinoline derivatives.[6c,e,11a,c,f,j] However, it is the first time that the key 1,4-H addition intermediate was isolated and used to elucidate the mechanism. In addition, an alternative mechanism that involves the direct reduction of enamine **7** cannot currently be ruled out.

With the chiral *cis* products in hand, we conducted further investigation of their epimerization into the corresponding *trans* products. To our delight, when 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU) was employed, chiral *trans*-**4a** with identical optical purity could be obtained smoothly from *cis*-**4a** in 74% yield (Scheme 4), which is generally difficult to prepare through the direct asymmetric hydrogenation.



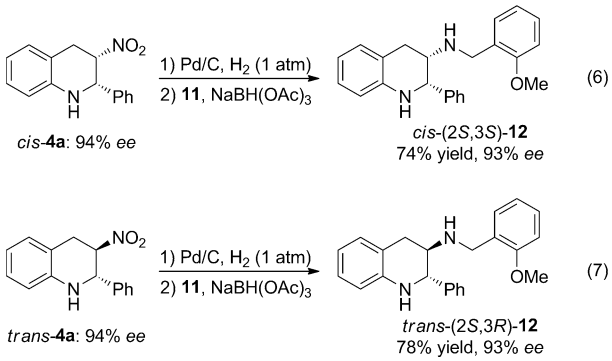
Scheme 4. DBU-mediated epimerization of *cis*-**4a** into *trans*-**4a**.



Scheme 5. Derivatization of transfer hydrogenation product **4m**.

To demonstrate the further utility of the chiral 2-styryl products, as illustrated in Scheme 5, the derivatization of **4m** was conducted. Using Pd/C as catalyst, hydrogenated product (2*S*,3*S*)-2-phenethyl-3-nitro-1,2,3,4-tetrahydroquinoline (**9**) was delivered selectively in 94% yield without loss of optical purity [Eq. (4)]. Furthermore, the product with a reduced nitro group, (2*S*,3*S*)-2-styryl-1,2,3,4-tetrahydroquinolin-3-amine (**10**), was obtained in 83% yield in the presence of Zn and HCl [Eq. (5)].

Finally, we applied this attractive protocol to the synthesis of substance P antagonist **12**[15] (Scheme 6). The synthetic route began with the reduction of *cis*-**4a** with Pd/C under H_2



Scheme 6. Stereoselective synthesis of substance P antagonist **12**.

(1 atm), followed by the reductive amination with 2-methoxybenzaldehyde (**11**) in the presence of $NaBH(OAc)_3$ to furnish the antagonist *cis*-(2*S*,3*S*)-**12** [Eq. (6)]. The enantiomeric excess was maintained with an overall yield of 74%. With the same method, the *trans* analogue (2*S*,3*R*)-**12** was also conveniently synthesized in 78% yield from *trans*-**4a** (eq. 7).

In conclusion, we have developed the first organocatalyzed asymmetric transfer hydrogenation of 3-nitroquinolines with up to 99% *ee*. The new methodology provides a direct and facile access to a series of valuable enantiopure cyclic nitro compounds with two contiguous stereocenters. The key 1,4-H addition intermediate was isolated, and a preliminary mechanistic study indicated that the 1,4-H addition was the initial step in the reaction. Further detailed mechanistic studies of the reaction and investigations on the application of the developed strategy are currently ongoing in our laboratory.

Experimental Section

Typical Procedure for Asymmetric Transfer Hydrogenation of 3-Nitroquinolines

A mixture of 3-nitroquinoline **1** (0.125 mmol), dihydropyridine **2d** (58 mg, 0.30 mmol, 2.4 equiv), and chiral phosphoric acid **3g** (3.6 mg, 0.00625 mmol, 5 mol%) in dry benzene (5.0 mL) was stirred at 25 or 45 °C under nitrogen for 12–48 h. After the reaction was complete (determined by TLC), the crude product was purified directly by silica gel column chromatography (petroleum ether/CH_2Cl_2 1:1) to give the pure product **4**. The enantiomeric excesses were determined by chiral HPLC.

Acknowledgements

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Keywords: asymmetric catalysis · organocatalysis · nitro compounds · transfer hydrogenation

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