NJC

LETTER

View Article Online
View Journal

Cite this: DOI: 10.1039/c6nj02249a

Received (in Montpellier, France)
19th July 2016,
Accepted 21st September 2016

DOI: 10.1039/c6nj02249a

www.rsc.org/njc

Enantioselective transfer hydrogenation, a key step for the synthesis of 3-aminotetrahydroquinolines†

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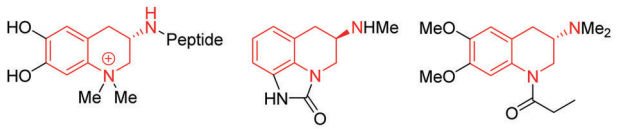
An enantioselective transfer hydrogenation has been successfully achieved to furnish 3-aminotetrahydroquinolines. The reaction was conducted in the presence of Hantzsch dihydropyridine and a catalytic amount of chiral phosphoric acid under mild conditions.

1,2,3,4-Tetrahydroquinoline (THQ) scaffolds are found in many biologically active molecules including natural and unnatural products. In addition, they are widely used as building blocks for organic synthesis. Among the synthetic pathways to access enantioenriched THQs, the reduction of their parent quinoline derivatives represents one of the most common and powerful strategies.[1]

Since the first report on chiral phosphoric acid-catalyzed asymmetric transfer hydrogenation (ATH) of C=N bonds,[2] efforts have been made to significantly extend the scope of this reaction.[3] Although a broad range of quinolines were successfully reduced in this way,[4] only recently were heterosubstituted derivatives studied affording 3-nitro and 3-amino THQs with excellent enantio- and diastereoselectivities.[5]

As part of our ongoing interest in the synthesis of relevant therapeutic agents,[6] we were interested in the formation of enantiopure 2-unsubstituted-3-aminotetrahydroquinolines. These privileged structures are in particular identified in Anachelin H, an antimicrobial siderophore isolated from the cyanobacterium *Anabaena cylindrica*,[7] but also in Sumanirole, a highly selective agonist for the dopamine D2 receptor and a potential anti-Parkinson agent[8] or in the 1-[(*S*)-3-(dimethylamino)-3,4-dihydro-6,7-dimethoxyquinolin-1(2*H*)-yl]propanone (*S*)-903, recently identified as a potentially attractive positive inotropic agent (Fig. 1).[9]

Among the strategies developed to access these molecules or their precursors, most are based on the use of the chiral pool[10]



Anachelin H Sumanirole (*S*)-903

Fig. 1 Biologically relevant 3-aminotetrahydroquinolines.

and few examples are related to asymmetric catalysis[11] including organocatalysis.[12]

Following our research in the field of organocatalysis,[13] we decided to reduce enantioselectively in this fashion the model substrate **1a**. For this purpose, we first investigated the conditions previously described by Zhou and coworkers for the synthesis of 3-amino-2-substituted-tetrahydroquinolines.[5] Unfortunately, although the product was obtained with a good (88%) yield, a 40% enantiomeric excess (ee) was observed.

This disappointing result prompted us to investigate a more appropriate reductive system for the transfer hydrogenation of such unsubstituted 3-aminoquinolines.

Hence, our initial investigations were focused on finding both the best nitrogen-substituted quinoline and organocatalyst. For this study, three quinolines **1a–c** possessing a tosylamide, a carbamate or an acetamide group, respectively, in position 3 were considered (Fig. 2). To promote the asymmetric transfer hydrogenation transformation, we restricted our attention to the phosphoric acid derivatives of (*S*)-BINOL **3a–e** and (*S*)-VAPOL **3f**.

The reactions on quinoline derivative **1** were performed in toluene for 24 h in the presence of Hantzsch dihydropyridine **4** and 5 mol% of catalyst **3**. When the reduction was carried out on *N*-tosylquinoline **1a**, despite lower reactivity, the highest enantioselectivity was achieved with MacMillan phosphoric acid **3e** (44% yield and 90% ee, Table 1, entry 5).

Although the yield was improved to 90% by increasing the temperature to 70 °C, the ee decreased to 83% ee (Table 1, entry 6). Finally, the best conditions in terms of reactivity and enantioselectivity were found when the reaction was conducted at 50 °C

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† Electronic supplementary information (ESI) available. CCDC 1484089. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6nj02249a

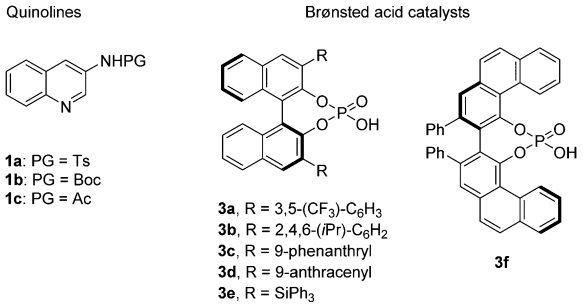
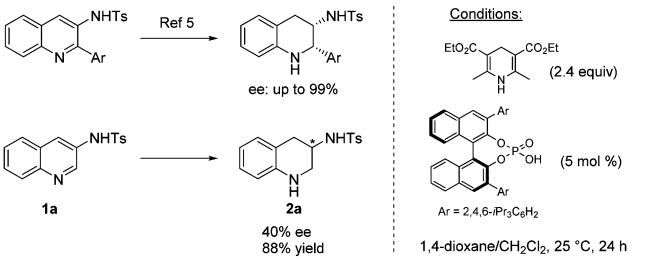
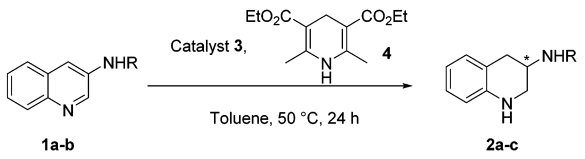


Fig. 2 Quinolines and catalysts evaluated for the optimization.



Scheme 1 Zhou's conditions applied to the transfer hydrogenation of 3-tosylaminoquinoline **1a**.

Table 1 Identification of the best 3-aminoquinoline derivative **1** and catalyst **3** for the transfer hydrogenation[a]



Entry	Reagent	Catalyst	Product	Yield[b] (%)	ee[c] (%)
1	**1a**	**3a**	**2a**	82	9
2	**1a**	**3b**	**2a**	80	39
3	**1a**	**3c**	**2a**	82	17
4	**1a**	**3d**	**2a**	74	36
5	**1a**	**3e**	**2a**	44	90
6[d]	**1a**	**3e**	**2a**	83	83
7[e]	**1a**	**3e**	**2a**	78	88
8	**1a**	**3f**	**2a**	81	0
9	**1b**	**3f**	**2b**	75	22
10	**1b**	**3a**	**2b**	96	25
11	**1b**	**3b**	**2b**	98	2
12	**1b**	**3c**	**2b**	98	27
13	**1b**	**3d**	**2b**	98	49
14[f]	**1b**	**3d**	**2b**	79	73
15	**1b**	**3e**	**2b**	40	73
16[d]	**1b**	**3e**	**2b**	96	61
17	**1c**	**3d**	**2c**	82	48
18	**1c**	**3e**	**2c**	Trace	Nd[g]
19[d]	**1c**	**3e**	**2c**	30	78

[a] Reaction conditions: **1** (1 equiv.), **4** (2.4 equiv.), **3** (5 mol%), toluene, 50 °C, 24 h. [b] Isolated yields. [c] Determined by chiral stationary phase HPLC. [d] Reaction performed at 70 °C. [e] Reaction performed for 48 h. [f] Reaction performed at 20 °C. [g] Not determined.

for 48 h (78% yield and 88% ee, Table 1, entry 7). Interestingly, when the reaction was performed on **1a** with catalyst **3b**, the enantioselectivity of product **2a** was comparable to the one observed in our preliminary trial (Table 1, entry 2, *vs.* Scheme 1). Thus it appears, afterwards, that the disappointing ee of **2a** under Zhou's conditions was mainly due to an inappropriate catalyst.

To improve these conditions, we next performed the reaction on *N*-carbamate quinoline **1b**. As observed with **1a**, the 3,3′-triphenylsilyl-substituted catalyst **3e** appeared to be more selective but less reactive than the 9-anthracenyl derivative **3d** (40% yield and 73% ee *vs.* 98% yield and 49% ee, Table 1, entries 15 *vs.* 13). With catalyst **3d**, the enantioselectivity was improved to 73% by decreasing the temperature to 20 °C, but only 79% yield was achieved (entry 14). Besides this, in the case where catalyst **3e** was used, increasing the temperature to 70 °C improved the reactivity of the transformation but was detrimental to the selectivity (96% yield, 61% ee, entry 16).

Furthermore, it is worth noting that *N*-acetyl quinoline **1c** in the presence of the best catalysts **3d** and **3e** did not furnish the transfer hydrogenation product in good yields and/or selectivities (entries 17–19).

Following this survey, we decided to continue the optimizations with quinoline **1a** in combination with the triphenylsilyl BINOL derivative **3e**. Our attention then turned to the solvent effect on the transfer hydrogenation (Table 2). The results revealed that the nature of the solvent had much less impact on the enantioselectivity than on the reactivity. Among the solvents screened in this scope, benzene exhibited the highest activity with a good enantioselectivity (96% yield and 90% ee, Table 2, entry 2). Decreasing the temperature or the catalyst loading resulted in a lower efficiency for the reaction (Table 2, entries 8–10). Chlorinated solvents maintained the yields to a satisfying level but resulted in a slightly lower selectivity (Table 2, entries 3 and 4). The use of ethereal solvents such as THF or methyl-*tert*-butyl ether has a dramatic impact on the yield even though the tetrahydroadduct was obtained with 91% and 89% ee respectively (Table 2, entries 5 and 6).

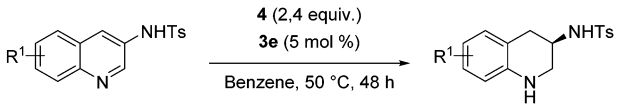
From this preliminary study, it was therefore decided to extend the scope of asymmetric transfer hydrogenation to diversely substituted *N*-tosylquinolines, in the presence of 5 mol% of catalyst **3e**, in benzene at 50 °C for 48 h.

Table 2 Screening of solvents and catalyst loading for the transfer hydrogenation of **1a**[a]

Entry	Solvent	Yield[b] (%)	ee[c] (%)
1	Toluene	78	88
2	Benzene	96	90
3	$CHCl_3$	87	86
4	CH_2Cl_2	95	87
5	THF	38	91
6	MTBE	20	89
7	CH_3CN	35	70
8[d]	Benzene	38	91
9[e]	Benzene	84	85
10[f]	Benzene	89	43

[a] Reaction conditions: **1a** (1 equiv.), **4** (2.4 equiv.), **3e** (5 mol%), solvent, 50 °C, 48 h. [b] Isolated yields. [c] Determined by chiral stationary phase HPLC. [d] Reaction performed at 30 °C. [e] Reaction performed using 2 mol% of the catalyst. [f] Reaction performed using 1 mol% of the catalyst. THF: tetrahydrofuran, MTBE: methyl-*tert*-butyl ether.

Table 3 Scope of the transfer hydrogenation[a]



Entry	Reagent	R	Product	Yield[b] (%)	ee[c] (%)
1	**1a**	H	**2a**	96	90
2	**1d**	6-Cl	**2d**	98	85
3	**1e**	6-Br	**2e**	88	60
4	**1f**	7-Br	**2f**	87	87
5	**1g**	7-CF_3	**2g**	69	75
6	**1h**	5-NO_2	**2h**	43	56
7	**1i**	6,7-OCH_2O	**2i**	0	—
8	**1j**	7-OMe	**2j**	90	84
9	**1k**	6-OMe	**2k**	30	87
10	**1l**	7-Ph	**2l**	0	—
11	**1m**	6-Ph	**2m**	75	85

[a] Reaction conditions: **1** (1 equiv.), **4** (2.4 equiv.), **3e** (5 mol%), benzene, 50 °C, 48 h. [b] Isolated yields. [c] Determined by chiral stationary phase HPLC.

Among the quinolines evaluated, none of them furnished the corresponding product with a better ee than **2a**. The first experiments proved that the presence of electron withdrawing groups in position 6 or 7 was compatible with the transfer hydrogenation reaction (Table 3, entries 2–5). However, a nitro substituent in position 5 resulted in a lower yield and reactivity (Table 3, entry 6). The enantioselectivity dropped down when a chloride in position 6 was replaced by a bromo substituent (Table 3, entries 2 *vs.* 3). Our first trial with electron donating group derivatives was performed on the 6,7-methylenedioxy quinoline **1i** and unfortunately did not furnish any traces of compound **2i** (Table 3, entry 7). Therefore we decided to evaluate separately the 6 and the 7-methoxy quinoline derivatives. Although the selectivity was comparable, these experiments clearly demonstrated that the presence of a methoxy group in position 6 was detrimental to the reactivity (Table 3, entries 8 *vs.* 9). Besides this, surprisingly no conversion was observed when the transfer hydrogenation was attempted on the 7-phenyl-3-aminoquinoline **1l**. Therefore the reaction was attempted on the 6-phenyl substituted substrate **1m**. The adduct was obtained with a satisfying yield and 85% ee. Such a difference in reactivity between substitution on position 6 and position 7 with an electron donating group or an aryl group is intriguing and still remains to be clarified.

The absolute configuration of adduct **2a** was unambiguously determined to be (*R*) by X-ray diffraction analysis (Fig. 3) and those of other products were assigned by analogy.

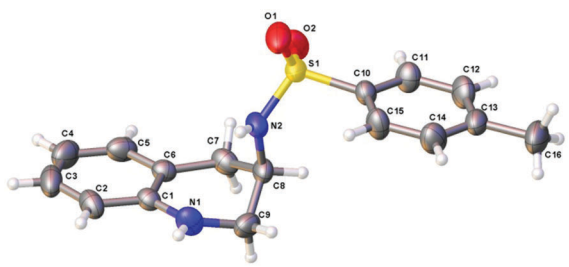


Fig. 3 X-ray crystal structure of (R)-**2a**.

Scheme 2 Synthesis of Sumanirole from **2a**.

In conclusion, we have achieved an effective and enantioselective transfer hydrogenation of 3-tosylaminoquinolines. The tetrahydroadducts accessible in this way could therefore be considered for the synthesis of biologically interesting scaffolds. In particular, product **2a**, following a five-step synthetic pathway developed in the literature, could lead to (*R*)-Sumanirole (Scheme 2).[13b]

Experimental

In a typical procedure, the 3-aminoquinolines (1 mmol, 1 equiv.), 4-toluenesulfonyl chloride (1 mmol, 1 equiv.) and DMAP (0.15 mmol, 0.15 equiv.) were suspended in pyridine (10 mL $mmol^{-1}$) in a Schlenk tube under a nitrogen atmosphere. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. After completion, the mixture was diluted in water (30 mL), extracted with DCM (5 × 10 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography to give the desired product **2**.

Description of product **2a**: a white solid with 96% yield. R_f: 0.47 (petroleum ether/ethyl acetate: 1/1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 7.9 Hz, 2H), 7.02–6.97 (m, 1H), 6.81 (d, J = 7.5 Hz, 1H), 6.64 (td, J = 7.4, 1.1 Hz, 1H), 6.50 (dd, J = 8.0, 0.9 Hz, 1H), 4.99 (d, J = 8.7 Hz, 1H), 3.90–3.81 (m, 1H), 3.30–3.25 (m, 1H), 3.11–3.05 (m, 1H), 2.93–2.87 (m, 1H), 2.60–2.53 (m, 1H), 2.44 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 143.5, 143.3, 138.4, 130.5, 129.9, 127.6, 127.1, 118.4, 117.6, 114.5, 46.4, 46.2, 33.6, 29.8, 21.7. $[\alpha]_D^{20}$ −15.2 (c 0.3; $CHCl_3$). HPLC conditions: Chiracel® OJ-H (Hex/EtOH = 70/30, 0.9 mL min^{-1}), major enantiomer: t_R = 72.67 min, minor enantiomer: t_R = 64.10 min, 90% ee. HRMS m/z (ESI) calcd for $C_{16}H_{19}O_2N_2S$ $[M + H]^+$ 303.1162, found 303.1146.

Acknowledgements

We are grateful to the ''Conseil Régional Nord-Pas de Calais'' (program PRIM, grant for AA) and the ''Comité Nord de la Ligue contre le Cancer'' for financial support. The Chevreul Institute (FR no. 2638), Ministère de l'Enseignement Supérieur et de la Recherche, Région Nord-Pas de Calais and FEDER are acknowledged for funding of X-ray diffractometers.

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