Transfer Hydrogenation of Isoquinolinium Salts Catalyzed by a Rhodium Complex

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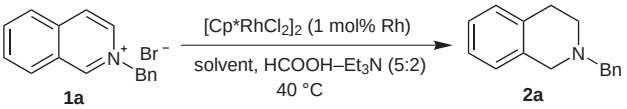
Abstract: Regio- and chemoselective transfer hydrogenation of isoquinolinium salts catalyzed by $[Cp^*RhCl_2]_2$ using HCOOH–Et_3N (5:2) as a hydrogen source was realized. A variety of *N*-methyl- and *N*-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloids were obtained in high yields by the present catalyst system.

Key words: transfer hydrogenation, rhodium(III) complex, isoquinoline, isoquinolinium salt, tetrahydroisoquinoline

The synthesis of 1,2,3,4-tetrahydroisoquinolines is of great interest due to their importance as structural units in naturally occurring alkaloids and biologically active compounds.[1] Direct hydrogenation of heteroaromatics provides an attractive and convenient approach to heterocycloalkanes. The catalytic hydrogenation using molecular hydrogen, which has been demonstrated to be highly efficient in the reduction of a variety of heteroaromatics,[2] was proved to be ineffective in the direct reduction of isoquinolines and activating agents should be added in order to obtain reasonable yields.[2d] Murahashi utilized water gas shift conditions to hydrogenate nitrogen heteroaromatics in the presence of rhodium carbonyl cluster, but only moderate conversions were observed for isoquinolines.[3] In 2004, Yamaguchi and co-workers reported that a Cp*Ir complex, which was highly effective for the transfer hydrogenation[4] of quinolines, was found to be totally inactive in the case of isoquinolines.[5] More recently, a bipyridine–rhodium(III) complex was also found to have moderate activity in the transfer hydrogenation of quinolines and pyridines.[6] However, the transfer hydrogenation of isoquinolines was only achieved by activating the azaaromatic ring under heterogeneous conditions.[7,8] During the course of our study on the homogeneous transfer hydrogenations of a variety of unsaturated compounds,[9] such as activated olefins,[9a] ketones[9b–d] and imines,[9e,9f] we found that the reactivity of imines could be greatly enhanced by the formation of iminium salts.[10] Herein, we report our initial results for a rhodium(III)-complex-catalyzed transfer hydrogenation of isoquinolinium salts[2b–d] under mild conditions with high reactivity.

Table 1 Influence of Solvent and Catalyst on Transfer Hydrogenation of **1a**[a]



1a **2a**

Entry	Solvent	Time (h)	Yield (%)[b]
1	CH_2Cl_2	4	96
2	MeCN	4	93
3	DMF	4	94
4	EtOH	4	90
5	H_2O	13	95
6[c]	CH_2Cl_2	4	69

[a] Reaction condition: 0.5 mmol **1a**, $[Cp^*RhCl_2]_2$ (1 mol% Rh), 1.5 mL solvent and 0.125 mL HCOOH–Et_3N (5:2) at 40 °C.
[b] Isolated yield.
[c] $[RuCl_2(cymene)]_2$ used as catalyst and 1,2-dihydroisoquinoline as minor product.

First, the isoquinolinium salt **1a** obtained by benzylation of isoquinoline with benzyl bromide was selected as standard substrate. The effects of solvents in the Cp*Rh-catalyzed transfer hydrogenation of **1a** are summarized in Table 1. Thus, the transfer hydrogenation of **1a** was best effected with a 5:2 formic acid–triethylamine azeotropic mixture in CH_2Cl_2 at 40 °C leading to the corresponding *N*-benzyl-1,2,3,4-isoquinoline (**2a**) in 96% yield after 4 hours (entry 1). The reaction also went smoothly in solvents like MeCN, DMF and EtOH (entries 2–4). Water could also be used as solvent, but relatively low reactivity was observed and the yield of the product was 95% after 13 hours (entry 5). It was noticeable that the present reaction was highly regio- and chemoselective and **2a** was isolated as the only product. While $[RuCl_2(cymene)]_2$ was used as catalyst, *N*-benzyl-1,2-dihydroisoquinoline was detected as minor product (entry 6).

The effectiveness of the present catalytic system was demonstrated by the synthesis of various naturally[1d,11] and unnaturally occurring *N*-methyl- and *N*-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloids with high yields under the optimal conditions, and the results were summarized in Table 2.[12] *N*-Benzyl isoquinolinium salts bearing methyl group at 1- or 3-position were reduced smoothly to give

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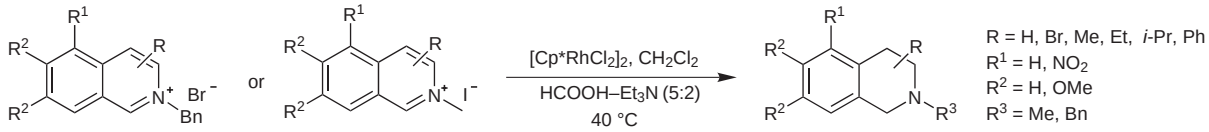
Table 2 Cp*Rh-Catalyzed Transfer Hydrogenation of Substituted Isoquinolinium Salts[a]



1a–l **2a–l**

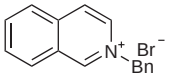
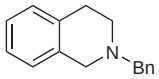
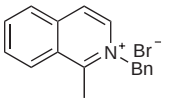
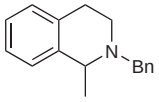
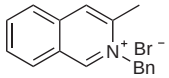
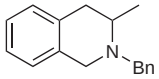
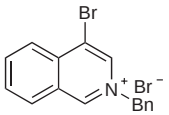
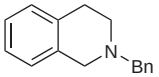
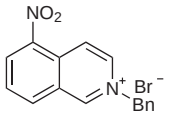
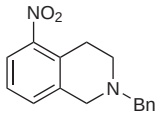
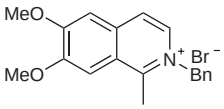
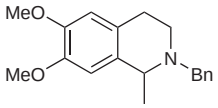
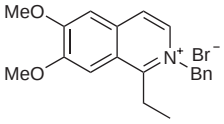
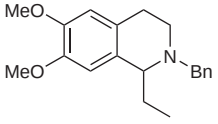
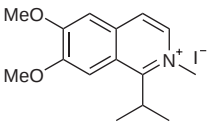
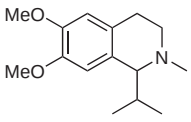
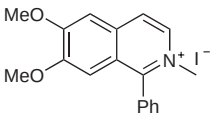
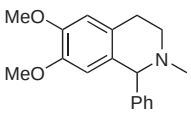
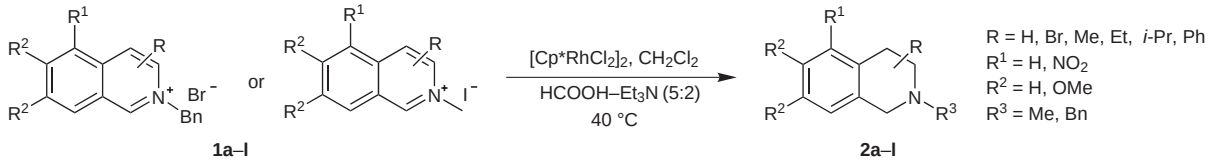
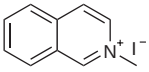
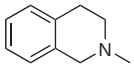
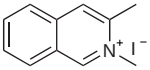
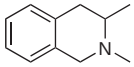
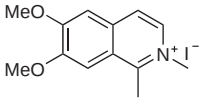
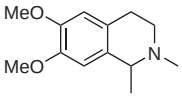
Entry	Substrate	Time (h)	Product	Yield (%)[b]
1	 **1a**	4	 **2a**	96
2	 **1b**	8	 **2b**	94
3	 **1c**	8	 **2c**	90
4[c]	 **1d**	8	 **2a**	75
5	 **1e**	12	 **2e**	70
6	 **1f**	8	 **2f**	90
7	 **1g**	8	 **2g**	93
8	 **1h**	24	 **2h**	75
9	 **1i**	24	 **2i**	86

Table 2 Cp*Rh-Catalyzed Transfer Hydrogenation of Substituted Isoquinolinium Salts[a] (continued)



1a–l **2a–l**

Entry	Substrate	Time (h)	Product	Yield (%)[b]
10	 **1j**	24	 **2j**	80
11	 **1k**	24	 **2k**	94
12	 **1l**	24	 **2l**	89

[a] Reaction conditions: 0.5 mmol **1**, $[Cp^*RhCl_2]_2$ (1 mol% Rh), 1.5 mL CH_2Cl_2 and 0.125 mL HCOOH–Et_3N (5:2) at 40 °C.
[b] Isolated yield.
[c] At 80 °C, 1.5 mL DMF was used as solvent.

1,2,3,4-tetrahydroisoquinolines in excellent yields after eight hours (entries 2 and 3). Reactions of isoquinolinium salts with electron-withdrawing substituent also proceeded successfully in good yields (entries 4 and 5). For the transfer hydrogenation of 4-bromoisoquinolinium salt **1d**, an elevated temperature (80 °C) was required with DMF as solvent (entry 4). Like the palladium-catalyzed transfer hydrogenation,[8b] a debromination product **2a** was obtained instead of the corresponding *N*-benzyl-5-bromo-1,2,3,4-tetrahydroisoquinoline. No product was isolated when the reaction was carried out under the standard conditions. The nitro group remained unaffected in the transfer hydrogenation of **1e** and the desired product **2e** was obtained in 70% yield after 12 hours (entry 5). In the case of *N*-benzyl-6,7-disubstituted isoquinolinium salts (**1f** and **1g**), the reduced products (**2f** and **2g**) were obtained in excellent yields (90% and 93%, respectively; entries 6 and 7). *N*-Benzyl isoquinolinium salts of 1-isopropyl- and 1-phenyl-6,7-dimethoxyisoquinolines cannot be obtained by the benzylation due to the bulky group at the 1-position of the isoquinolines. Thus, *N*-methyl isoquinolinium salts **1h** and **1i** were prepared by methylation with iodomethane. Compound **1h** was reduced to *N*-methyl-1-isopropyl-1,2,3,4-tetrahydroisoquinoline (**2h**) in 75% yield with relatively low reactivity (entry 8). *N*-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**2i**) was also obtained in good yield (86%) after 24 hours (entry 9). Transfer hydrogenations of *N*-methyl isoquinolinium salts **1j** and **1k** also resulted in 80% and 94% yields, respectively, after 24 hours (entries 10 and 11). The usefulness of the method was demonstrated via the synthesis of the naturally occurring alkaloid, carnegine **2l**,[1d] which can be readily obtained by reduction of the *N*-methyl salt **1l** in a single step with 89% yield (entry 12).

In summary, a variety of *N*-methyl- and *N*-benzyl-1,2,3,4-tetrahydroisoquinolines, some of which are naturally occurring products,[1d,11] was prepared in high yield via the Cp*Rh-complex-catalyzed regio- and chemoselective transfer hydrogenation of isoquinolinium salts under mild conditions using HCOOH–Et_3N (5:2) as the hydrogen donor. Further studies aimed at asymmetric catalytic transfer hydrogenation of the isoquinolinium salts are currently underway in our laboratory.

Acknowledgment

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(7) (a) No product was observed when isoquinoline was refluxed in MeCN catalyzed by $[Cp^*RhCl_2]_2$ with 5:2 formic acid–Et_3N azeotropic mixture. (b) Watanabe, Y.; Ohta, T.; Tsuji, T.; Hiyoshi, T.; Tsuji, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2440.
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(12) **General Procedure.**
To a solution of **1** (0.5 mmol) and $[Cp^*RhCl_2]_2$ (0.0025 mmol) in CH_2Cl_2 (1.5 mL) under an atmosphere of argon was added a 5:2 formic acid–Et_3N azeotropic mixture (0.125 mL). The resulting mixture was stirred at 40 °C for a certain period of time, made basic by addition of aq Na_2CO_3, and then extracted with CH_2Cl_2. Purification on silicon gel afforded the desired products **2**, which were characterized by ^1H NMR, ^{13}C NMR and IR spectroscopy, and HRMS. The data of unknown compounds was shown as the following:
Compound **2a**: colorless oil. IR: 3061, 3024, 2916, 2799, 1602, 1495, 1464, 1453, 739 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.80 (t, *J* = 5.9 Hz, 2 H), 2.96 (t, *J* = 5.8 Hz, 2 H), 3.70 (s, 2 H), 3.74 (br s, 2 H), 7.04 (br s, 1 H), 7.12–7.17 (m, 3 H), 7.31–7.47 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.1, 50.6, 56.1, 62.7, 125.5, 126.0, 126.5, 127.0, 128.2, 128.6, 129.0, 134.3, 134.8, 138.3 ppm. HRMS (ESI): *m/z* calcd for $C_{16}H_{17}N$ [M + H]: 224.1434; found: 224.1443.
Compound **2b**: colorless oil. IR: 3061, 3024, 2968, 2925, 2804, 1603, 1582, 1493, 1452, 1365, 757 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (d, *J* = 6.7 Hz, 3 H), 2.74–2.83 (m, 2 H), 2.91–3.06 (m, 1 H), 3.13–3.16 (m, 1 H), 3.78 (d, *J* = 13.6 Hz, 1 H), 3.90 (d, *J* = 13.6 Hz, 1 H), 3.97 (q, *J* = 6.7 Hz, 1 H), 7.13–7.22 (m, 4 H), 7.33–7.49 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7, 27.4, 43.8, 56.2, 58.2, 125.6, 125.8, 126.8, 127.4, 128.2, 128.7, 128.8, 134.3, 139.5, 140.4 ppm. HRMS (ESI): *m/z* calcd for $C_{17}H_{19}N$ [M + H]: 238.1590; found: 238.1593.
Compound **2c**: colorless oil. IR: 3058, 3024, 2991, 2930, 2867, 2830, 2803, 1607, 1513, 1492, 1462, 1353, 741 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 6.4 Hz, 3 H), 2.66 (dd, *J* = 5.8, 16.2 Hz, 1 H), 3.03–3.20 (m, 2 H), 3.62 (d, *J* = 13.2 Hz, 1 H), 3.66 (d, *J* = 15.7 Hz, 1 H), 3.75 (d, *J* = 15.8 Hz, 1 H), 3.87 (d, *J* = 13.2 Hz, 1 H), 6.90–7.00 (m, 1 H), 7.12–7.15 (m, 3 H), 7.29–7.44 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1, 35.5, 51.5, 52.1, 57.2, 125.5, 126.0, 126.4, 126.9, 128.2, 128.8, 128.9, 134.0, 134.4, 139.4 ppm. HRMS (ESI): *m/z* calcd for $C_{17}H_{19}N$ [M + H]: 238.1590; found: 238.1579.
Compound **2e**: yellow oil. IR: 2921, 2832, 1610, 1575, 1524, 1452, 1465, 821, 800, 771, 733, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.76 (t, *J* = 5.9 Hz, 2 H), 3.18 (t, *J* = 5.9 Hz, 2 H), 3.69 (s, 2 H), 3.70 (s, 2 H), 7.24–7.26 (m, 2 H), 7.29–7.41 (m, 5 H), 7.80–7.83 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.2, 49.9, 56.0, 62.5, 122.8, 126.1, 127.4, 128.4, 129.0, 130.3, 131.7, 137.6, 138.0 ppm. HRMS (ESI): *m/z* calcd for $C_{16}H_{17}N_2O_2$ [M + H]: 269.1285; found: 269.1281.
Compound **2g**: light yellow oil. IR: 3058, 3024, 2991, 2929, 2867, 2830, 1607, 1513, 1492, 1462, 730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.3 Hz, 3 H), 1.73–1.79 (m, 2 H), 2.46–2.54 (m, 1 H), 2.73–2.84 (m, 2 H), 3.13–3.18 (m, 1 H), 3.46 (t, *J* = 6.2 Hz, 1 H), 3.69 (d, *J* = 13.5 Hz, 1 H), 3.80 (d, *J* = 13.5 Hz, 1 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 6.54 (s, 1 H), 6.59 (s, 1 H), 7.24–7.41 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.9, 24.2, 29.0, 43.6, 55.7, 55.9, 57.8, 61.9, 110.6, 111.2, 126.5, 126.7, 128.1, 128.8, 130.6, 140.0, 147.1 ppm. HRMS (ESI): *m/z* calcd for $C_{20}H_{25}NO_2$ [M + H]: 312.1958; found: 312.1968.
Compound **2h**: light yellow oil. IR: 2950, 2904, 2867, 2831, 1608, 1513, 1463, 1375, 1358, 770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 (d, *J* = 6.8 Hz, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H), 1.85–1.92 (m, 1 H), 2.42 (s, 3 H), 2.57–2.69 (m, 3 H), 3.09–3.17 (m, 2 H), 3.82 (s, 3 H), 3.83 (s, 3 H), 6.53 (s, 1 H), 6.56 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.0, 20.1, 25.4, 34.3, 44.1, 48.2, 55.7, 55.8, 69.4, 111.0, 111.8, 127.4, 128.7, 146.3, 147.0 ppm. HRMS (ESI): *m/z* calcd for $C_{15}H_{24}NO_2$ [M + H]: 250.1802; found: 250.1805.
Compound **2i**: white solid; mp: 80–81 °C. IR: 3022, 2946, 2907, 2832, 1607, 1513, 1488, 1463, 1451, 1364, 741, 716 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 3 H), 2.57–2.65 (m, 1 H), 2.71–2.78 (m, 1 H), 3.06–3.22 (m, 2 H), 3.56 (s, 3 H), 3.85 (s, 3 H), 4.18 (s, 1 H), 6.09 (s, 1 H), 6.60 (s, 1 H), 7.22–7.34 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.9, 44.2, 52.2, 55.7, 71.0, 110.6, 111.4, 126.5, 127.3, 128.2, 129.5, 130.3, 143.8, 147.0, 147.3 ppm. HRMS (ESI): *m/z* calcd for $C_{18}H_{22}NO_2$ [M + H]: 284.1645; found: 284.1639.
Compound **2k**: light yellow oil. IR: 3024, 2964, 2918, 2838, 1588, 1494, 1454, 1443, 1370, 735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 6.1 Hz, 3 H), 2.42 (s, 3 H), 2.61–2.72 (m, 2 H), 2.80–2.88 (m, 1 H), 3.57 (d, *J* = 15.4 Hz, 1 H), 3.83 (d, *J* = 15.4 Hz, 1 H), 7.00–7.15 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.9, 36.7, 41.4, 54.8, 57.2, 125.5, 126.0, 128.4, 134.0, 134.4 ppm. HRMS (ESI): *m/z* calcd for $C_{11}H_{15}N$ [M + H]: 162.1277; found: 162.1282.