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CONVENIENT SYNTHESIS OF OPTICALLY PURE 8-METHOXY-2-METHYL-1,2,3,4-TETRAHYDROQUINOLINE AND 2-METHYL-1,2,3,4-TETRAHYDROQUINOLINE

Jie Tang,^a Guo-Fang Jiang,^{a,*} and Yong-Gui Zhou^{b,*}

^aCollege of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, China. ^bState Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China. E-mail: ygzhou@dicp.ac.cn

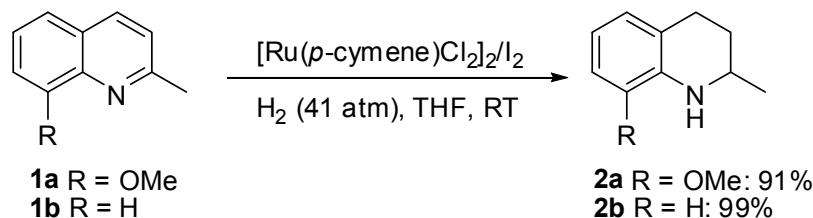
Abstract – A convenient method was developed to synthesize optically pure 8-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (**2a**) and 2-methyl-1,2,3,4-tetrahydroquinoline (**2b**) by combining the methods of catalytic hydrogenation and classical resolution. The catalytic system ($[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2/\text{I}_2$) showed high efficiency in preparing racemic **2a** and **2b**, which were successfully resolved using commercial tartaric acid derivatives, and both enantiomers were obtained in moderate yield with >99% *ee*.

Tetrahydroquinolines are important intermediates for organic synthesis and versatile building blocks for natural products, bioactive compounds, and drugs.¹ Many researchers were devoted to developing efficient approaches for the synthesis of chiral tetrahydroquinolines. Recently, the methods based on asymmetric hydrogenation² were reported continually to synthesize chiral tetrahydroquinolines since Zhou³ and coworkers reported the first asymmetric hydrogenation of quinolines with high enantioselectivities in 2003. Although asymmetric hydrogenation was accepted as the best choice to produce chiral tetrahydroquinoline derivatives, its practicality also faces some challenges due to harsh reaction conditions and expensive ligands. While some traditional methods such as chemical resolutions are still irreplaceable for their convenience and economy.

8-Methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (**2a**) and 2-methyl-1,2,3,4-tetrahydroquinoline (**2b**) are important intermediates in synthesis of natural products⁴ and chiral phosphoramidite ligands.⁵ There were

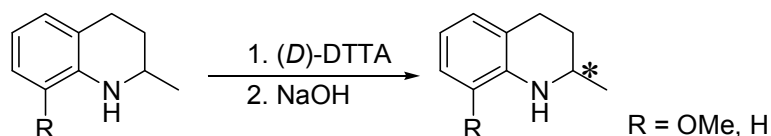
some successful reports on kinetic resolution of **2b** using (*S*)-naproxen acyl chloride⁶ or *N*-tosyl-(*S*)-prolyl chloride.⁷ However, uncommon reagents, troublesome workup and hard separate process are the limitations. Considering the tetrahydroquinolines are basic, chemical resolution should be an alternative for preparing them with chiral acid derivatives. However, few reports on chemical resolution of tetrahydroquinoline **2a** and **2b** appeared with chiral acid derivatives except the analogue 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline.⁸ Herein, we report an efficient and convenient way to optically active tetrahydroquinoline **2a** and **2b** through a classical resolution process. Racemates **2a** and **2b** were prepared by an efficient catalytic hydrogenation. The resolution performed successfully using commercial tartaric acid derivatives as resolving agent. Both enantiomers could be obtained conveniently.

The racemic **2a** and **2b** were conveniently prepared from the commercially available 8-methoxy-2-methylquinoline (**1a**) and 2-methylquinoline (**1b**) according to the method developed by us in 2007 (Scheme 1),⁹ [Ru(*p*-cymene)Cl₂]₂/I₂ was used as catalyst and the hydrogenation reaction proceeded smoothly. To our pleasure, the high yield (**2a**, 91%, **2b**, 99%) kept when the reaction was enlarged; the hydrogenation of 2-methylquinolines was carried out at room temperature with full conversion at S/C of 1000/1. It was also noteworthy that the hydrogenation process can be run in air and undistilled solvent.



Scheme 1. Synthesis of racemic tetrahydroquinolines **2a** and **2b**

The preliminary experiments showed that crystalline diastereoisomeric salts of **2a** could form with di-*p*-toluoyl-tartaric acid (DTTA) in ethyl acetate (Table 1, entry 1, 22% ee). So, the effect of solvent were investigated with (*D*)-DTTA as the resolving agent. Common solvents, ethyl acetate, ethanol, methanol and acetone were examined. (*D*)-DTTA (1.eq.) dissolved in 5 mL solvent was dropped into the bottle of racemate (**2a**, 3 mmol, **2b**, 4 mmol) with stirring at 50 °C, then, cooled to room temperature. The diastereoisomeric salts were filtrated off and cracked by NaOH aqueous solution, enantiomeric excess was analyzed by HPLC. Results were shown in **Table 1**. Nice yields were achieved in ethyl acetate for both **2a** and **2b**, but the enantioselectivity was not satisfactory. No diastereoisomeric salts deposited in ethanol, and the tests in methanol were also disappointed. Acetone gave the best result, after hydrolysis of diastereoisomeric salts, it was obtained in 100% yield with 60% ee for **2a** and 42% yield with 46% ee for **2b**, respectively.

Table 1. The effect of solvent on chemical resolution of racemic **2a** and **2b** with (*D*)-DTTA^a

Entry	compound	Solvent	Yield (%) ^b	Ee (%) ^c	E (%) ^d
1	2a	ethyl acetate	178	22	39
2	2b	ethyl acetate	54	25	14
3	2a	ethanol	-	-	-
4	2b	ethanol	-	-	-
5	2a	methanol	-	-	-
6	2b	methanol	115	4	5
7	2a	acetone	100	60	60
8	2b	acetone	42	46	19

^a **2a** (3 mmol), **2b** (4 mmol) in different solvent (5 mL) at 50 °C to rt.

^b The yield is related to the half of the racemate.

^c Determined by HPLC.

^d Resolution efficiency (E %) = yield (%) × ee (%) / 100.

Next, the effect of resolving agent was also tested. For the resolution of racemate **2a**, no salt formed with dibenzoyl-*D*-tartaric acid ((*D*)-DBTA) (Table 2, entry 2), (*D*)-DTTA was the best resolving agent (Table 2, entry 3). In order to further optimize resolution condition, the effect of concentration was investigated, and noticeable improvement was obtained at low concentration, for **2a**, concentration of 0.4 mmol/mL gave the better result, yield: 100% vs 84%; ee: 84% vs 60% (entry 1 vs entry 3). The optimized condition for **2a** was as follows: (*D*)-DTTA/Acetone/0.4 mol/mL. Repeating this operation twice with (*D*)-DTTA gave the chiral (+)-**2a** (52% yield, >99% ee). The filtrate after resolution was recovered by using the same workup to afford the scalemic **2a**, optically pure (-)-**2a** (88% yield, >99% ee) could be obtained in the same way by using the (*L*)-DTTA as resolution reagent.

For the resolution of racemate **2b**, no salt crystals appeared when (*D*)-CSA, (*L*)-Malic acid and (*R*)-Mandelic acid were used (Table 2, entries 6-8,). Comparing with (*D*)-DTTA and dibenzoyl-*D*-tartaric acid ((*D*)-DBTA), di-*p*-methoxybenzoyl-*D*-tartaric acid ((*D*)-DMTA) gave the best result (74% yield, 67% ee). The effect of solvent on resolution efficiency was also examined using (*D*)-DMTA, acetone is still the best solvent (Table 2, entries 12-14,). The effect of concentration was investigated; the best result was obtained at concentration of 0.8 mmol/mL. So, the optimized resolution condition of racemate **2b**

was as follows: (*D*)-DMTA/Acetone/0.8 mol/mL. Repeating this operation three times with (*D*)-DMTA gave the chiral (*S*)-(-)-**2b** (28% yield, >99% *ee*.) The filtrate after resolution was recovered by using the same workup to afford the scalemic **2b**, optically pure (*R*)-(+)-**2b** (31% yield, >99% *ee*) can be obtained in the same way by using the (*L*)-DMTA as resolution reagent.

In conclusion, optically pure 8-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline and 2-methyl-1,2,3,4-tetrahydroquinoline were synthesized successfully by catalytic hydrogenation of the corresponding quinolines using [Ru(*p*-cymene)Cl₂]₂/I₂ as catalyst and classical chemical resolution using (*D*)-DTTA and (*D*)-DMTA as resolution reagents, respectively. Both enantiomers could be conveniently obtained in >99% *ee*.

Table 2. Effect of resolving agent and optimization of resolution conditions^a

Entry	Compound	Agent (1 eq.)	Solvent	C ^b (mmol/mL)	Yield (%)	Ee (%) ^c	E (%) ^d
1	2a	(<i>D</i>)-DTTA	acetone	3/5	100	60	60
2	2a	(<i>D</i>)-DBTA	acetone	6/15	-	-	-
3	2a	(<i>D</i>)-DTTA	acetone	6/15	84	84	71
4	2b	(<i>D</i>)-DTTA	acetone	4/5	42	46	19
5	2b	(<i>D</i>)-DBTA	acetone	4/5	166	0	0
6	2b	(<i>D</i>)-CSA	acetone	4/5	-	-	-
7	2b	(<i>L</i>)-Malic acid	acetone	4/5	-	-	-
8	2b	(<i>R</i>)-Mandelic acid	acetone	4/5	-	-	-
9	2b	(<i>D</i>)-DMTA	acetone	4/5	74	67	50
10	2b	(<i>D</i>)-DMTA	acetone	4/6	48	68	33
11 ^e	2b	(<i>D</i>)-DMTA	acetone	4/3	38	50	19
12	2b	(<i>D</i>)-DMTA	ethyl acetate	4/5	108	17	18
13	2b	(<i>D</i>)-DMTA	ethanol	4/5	132	21	28
14	2b	(<i>D</i>)-DMTA	methanol	4/5	114	30	34

^a **2a** (3 mmol), **2b** (4 mmol) in different solvent (5 mL) at 50 °C to rt.

^b C = **2** (mmol)/ Solvent (mL).

^c Determined by HPLC.

^d Resolution efficiency (E %) = yield (%) × *ee* (%) / 100.

^e (*D*)-DMTA was used in 0.5 equiv.

EXPERIMENTAL

General Experimental Procedures

8-Methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (2a): In the air, to the reaction bottle A was added 8-methoxy-2-methylquinoline (12.470 g, 72 mmol) and I₂ (0.300 g), followed by 80 mL THF. The mixture was stirred until the iodine is dissolved. At the same time, to the reaction bottle B was added [Ru(*p*-cymene)Cl₂]₂ (0.050 g, 0.08 mmol) and 20 mL undistilled THF. The mixture was stirred until the solution is homogeneous. Then to the reaction bottle A was added the solution of [Ru(*p*-cymene)Cl₂]₂ of THF in bottle B. Then the resulted reaction mixture was placed in an autoclave, and the autoclave was pressurized to 600 psi hydrogen and stirred at room temperature for 16 h, after carefully releasing the hydrogen, the reaction mixture was concentrated to afford the crude product. Purification was performed by a silica gel column eluted with hexane/EtOAc to give pure product **2a** as light yellow oil (11.601 g, 91% yield). ¹H NMR (400 MHz, CDCl₃): δ 6.63-6.54 (m, 3H), 4.12 (s, 1H), 3.81 (s, 3H), 3.39-3.35 (m, 1H), 2.85-2.80 (m, 1H), 2.76-2.74 (m, 1H), 1.94-1.90 (m, 1H), 1.62-1.58 (m, 1H), 1.23 (d, *J* = 6.4 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 146.1, 134.6, 121.5, 121.2, 115.9, 107.3, 55.3, 46.8, 30.2, 26.5, 22.7.

The chemical resolution of racemic 8-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (2a): Racemic 8-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (**2a**) (16.590 g, 93 mmol) was diluted by 70 mL acetone with heating to 50 °C. (*D*)-DTTA (35.656 g, 93 mmol) was dissolved in 100 mL acetone and the solution was dropped into the bottle of 8-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline, keep stirring 30 minutes. Then the mixture was cooled to room temperature and crystals appeared. The crystals were filtered and the residue was washed with acetone (20 mL) and dried to afford the solid diastereoisomeric salt, workup of the diastereoisomeric salt was as follows: The crystals were suspended in NaOH aqueous solution (0.6 mol/L, 150 mL) and stirred for 30 min. The mixture was extracted with CH₂Cl₂ for three times. Then combined organic phase was dried over Na₂SO₄ and the solvent was removed *in vacuo* to afford the product. Repeating this operation twice gave the chiral (+)-8-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (**2a**) (4.293 g, 52% yield, 99% *ee*), [α]_D²¹ +68.4 (*c* 0.66, CHCl₃). HPLC (IC Column, Hexane/*i*-PrOH = 99.5/0.5, 0.5 mL/min, 30 °C, 254 nm): (+) *t*₁ = 9.4 min, (-) *t*₂ = 9.9 min.

The filtrate after resolution was recovered and cracked by NaOH aqueous solution, the scalemic **2a** was obtained after extraction by CH₂Cl₂. Optically pure (-)-**2a** (88% yield, >99% *ee*) can be obtained by using the (*L*)-DTTA as resolution reagent with the same operation.

2-Methyl-1,2,3,4-tetrahydroquinoline (2b): The synthesis of 2-methyl-1,2,3,4-tetrahydroquinoline (**2b**) (99% yield) was similar to that of **2a** (The reaction was carried out at S/C 1000). (Known compound, see ref 3). ¹H NMR (400 MHz, CDCl₃): δ 6.95-6.93 (m, 2H), 6.61-6.57 (m, 1H), 6.46 (d, *J* = 8.2 Hz, 1H), 3.64 (br, 1H), 3.40-3.36 (m, 1H), 2.83-2.73 (m, 2H), 1.94-1.89 (m, 1H), 1.60-1.56 (m, 1H), 1.21-1.18 (m, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 144.9, 129.4, 126.9, 121.3, 117.1, 114.1, 47.3, 30.3, 26.8, 22.8.

The chemical resolution of 2-methyl-1,2,3,4-tetrahydroquinoline (2b): Racemic 2-methyl-1,2,3,4-tetrahydroquinoline (24.673 g, 168 mmol) was diluted by 40 mL acetone with heating to 50 °C. (*D*)-DMTA (80.867 g, 168 mmol) was dissolved in 150 mL acetone and the solution was dropped into the bottle of 2-methyl-1,2,3,4-tetrahydroquinoline, keep stirring 30 min. Then the mixture was cooled to room temperature and crystals appeared. The crystals were filtered and the residue was washed with acetone (20 mL) and dried to afford the solid diastereoisomeric salt, workup of the diastereoisomeric salt was as follows: The crystals were suspended in NaOH aqueous solution (0.6 mol/L, 280 mL) and stirred for 30 min. The mixture was extracted with dichloromethane for three times. Then combined organic phase was dried over Na₂SO₄ and the solvent was removed *in vacuo* to afford the product. Repeating this operation three times gave (-)-(*S*)-2-methyl-1,2,3,4-tetrahydroquinoline **2b** (3.369 g, 28% yield, 99% *ee*). [α]_D²⁰ -91.7 (*c* 1.23, CHCl₃). HPLC (OJ-H Column, Hexane/*i*-PrOH = 95/5, 1.0 mL/min, 30 °C, 254 nm): (*S*)-(-) *t*₁ = 11.2 min, (*R*)-(+) *t*₂ = 12.3 min.

The filtrate after resolution was recovered and cracked by NaOH aqueous solution, the scalemic **2b** was obtained after extraction by CH₂Cl₂. Optically pure (*R*)-(+)-**2b** (31% yield, >99% *ee*) could be obtained by using the (*L*)-DMTA as resolution reagent with the same operation.

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REFERENCES (AND NOTES)

- (a) I. Jacquemond-Collet, J. M. Bessiere, S. Hannedouche, C. Bertrand, I. Fouraste, and C. Moulis, *Phytochem. Anal.*, 2001, **12**, 312; (b) I. Jacquemond-Collet, S. Hannedouche, N. Fabre, I. Fouraste, and C. Moulis, *Phytochemistry*, 1999, **51**, 1167; (c) P. J. Houghton, T. Z. Woldemariam, Y. Watanabe, and M. Yates, *Planta Med.*, 1999, **65**, 250.
- (a) Y.-G. Zhou, *Acc. Chem. Res.*, 2007, **40**, 1357; (b) D.-W. Wang, D.-S. Wang, Q.-A. Chen, and Y.-G. Zhou, *Chem. Eur. J.*, 2010, **16**, 1133; (c) D.-S. Wang, J. Zhou, D.-W. Wang, Y.-L. Guo, and Y.-G. Zhou, *Tetrahedron Lett.*, 2010, **51**, 525; (d) D.-W. Wang, X.-B. Wang, S.-M. Lu, C.-B. Yu, and Y.-G. Zhou, *J. Org. Chem.*, 2009, **74**, 2780; (e) Z.-J. Wang, H.-F. Zhou, T.-L. Wang, Y.-M. He, and Q.-H. Fan, *Green Chem.*, 2009, **11**, 767; (f) C. Wang, C. Li, X. Wu, A. Pettman, and J. Xiao, *Angew. Chem. Int. Ed.*, 2009, **48**, 6524; (g) H. Zhou, Z. Li, Z. Wang, T. Wang, L. Xu, Y. He, Q.-H. Fan, J. Pan, L. Gu, and A. S. C. Chan, *Angew. Chem. Int. Ed.*, 2008, **47**, 8464; (h) S.-M. Lu, Y.-Q. Wang, X.-W. Han, and Y.-G. Zhou, *Angew. Chem. Int. Ed.*, 2006, **45**, 2260.
- W.-B. Wang, S.-M. Lu, P.-Y. Yang, X.-W. Han, and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2003, **125**,

10536.

4. (a) H. C. Smith, C. K. Cavanaugh, J. L. Friz, C. S. Thompson, J. A. Saggars, E. L. Michelotti, J. Garciab, and C. M. Tice, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1943; (b) K. Ding, J. Chen, M. Ji, X. Wu, J. Varady, C.-Y. Yang, Y. Lu, J. R. Deschamps, B. Levant, and S. Wang, *J. Med. Chem.*, 2005, **48**, 3171; (c) G. Subramaniam, Y.-M. Choo, O. Hiraku, K. Komiyama, and T.-S. Kam, *Tetrahedron*, 2008, **64**, 1397.
5. W.-B. Liu, H. He, L.-X. Dai, and S.-L. You, *Synthesis*, 2009, **12**, 2076.
6. V. P. Krasnov, G. L. Levit, I. N. Andreeva, A. N. Grishakov, V. N. Charushin and O. N. Chupakhin, *Mendeleev Commun.*, 2002, **12**, 27.
7. V. P. Krasnov, G. L. Levit, I. M. Bukrina, I. N. Andreeva, L. S. Sadretdinova, M. A. Korolyova, M. I. Kodess, V. N. Charushin, and O. N. Chupakhin, *Tetrahedron: Asymmetry*, 2003, **14**, 1985.
8. J. Balint, G. Egri, V. Kiss, A. Gajary, Z. Juvancz, and E. Fogassy, *Tetrahedron: Asymmetry*, 2001, **12**, 3435.
9. S.-M. Lu, X.-W. Han, and Y.-G. Zhou, *J. Organomet. Chem.*, 2007, **692**, 3065.