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Highly Enantioselective Synthesis of Polysubstituted Tetrahydroquinolines *via* Organocatalytic Michael/Aza-Henry Tandem Reactions

Zhen-Xin Jia, Yong-Chun Luo, and Peng-Fei Xu*

State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P. R. China

xupf@lzu.edu.cn

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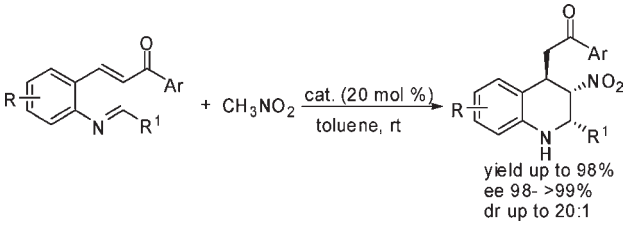
ABSTRACT



Highly enantioselective chiral bifunctional thiourea catalyzed asymmetric tandem reactions for synthesis of substituted tetrahydroquinolines are described. Substituted tetrahydroquinolines were given in good yields (up to 98%), high enantioselectivities (up to >99% ee), and diastereoselectivities (up to 20:1 dr).

The tetrahydroquinoline subunit is present in various natural products, and many tetrahydroquinoline derivatives have shown a wide range of biological activities as antibiotics and antitumor agents.[1] In accordance with their importance, the development of efficient and sustainable procedures toward the synthesis of tetrahydroquinoline derivatives is an important goal of synthetic organic chemists. General synthetic methods include the Povarov reaction, an inverse electron-demand aza Diels–Alder reaction,[2] and various reductions of quinolines.[3] These approaches often facilitate the synthesis of diastereoisomerically pure tetrahydroquinolines, but there are few reports on enantiomerically pure targets.[4] Therefore, the development of new strategies for the synthesis of these enantiomerically enriched heterocyclic frameworks still remains an active field of research.

In the rapidly evolving field of organocatalysis,[5] chiral bifunctional thioureas have become one of the most

(1) (a) Johnson, J. V.; Rauckman, S.; Baccanari, P. D.; Roth, B. *J. Med. Chem.* **1989**, *32*, 1942. (b) Omura, S.; Nakagawa, A. *Tetrahedron Lett.* **1981**, *22*, 2199. (c) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715. (d) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *48*, 15031. (e) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 605. (f) Kouznetsov, V.; Palma, A.; Ewert, C.; Varlamov, A. *J. Heterocycl. Chem.* **1998**, *35*, 761. (g) De Kimpe, N.; Keppens, M. *Tetrahedron* **1996**, *52*, 3705. (h) Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595. (i) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031. (j) Xia, Y.; Yang, Z.-Y.; Xia, P.; Bastow, K. F.; Tachibana, Y.; Kuo, S.- C.; Hamel, E.; Hackl, T.; Lee, K.-H. *J. Med. Chem.* **1998**, *41*, 1155. (k) Paris, D.; Cottin, M.; Demonchaux, P.; Augert, G.; Dupassieux, P.; Lenoir, P.; Peck, M. J.; Jasserand, D. *J. Med. Chem.* **1995**, *38*, 669.

(2) For instance, see: (a) Jia, X.; Han, B.; Zhang, W.; Jin, X.; Yang, L.; Liu, Z.-L. *Synthesis* **2006**, *17*, 2831. (b) Keck, D.; Vanderheiden, S.; Braese, S. *Eur. J. Org. Chem.* **2006**, 4916. (c) Savitha, G.; Perumal, P. T. *Tetrahedron Lett.* **2006**, *47*, 3589. (d) Han, B.; Jia, X.-D.; Jin, X.-L.; Zhou, Y.-L.; Yang, L.; Liu, Z.-L.; Yu, W. *Tetrahedron Lett.* **2006**, *47*, 3545. (e) Gao, K.; Li, Y.; Sun, H.; Fan, R.; Wu, J. *Synth. Commun.* **2007**, *37*, 4425. (f) Sridharan, V.; Perumal, P. T.; Avendano, C.; Menendez, J. C. *Org. Biomol. Chem.* **2007**, *5*, 1351. (g) Ramesh, E.; Raghunathan, R. *Tetrahedron Lett.* **2008**, *49*, 2583.

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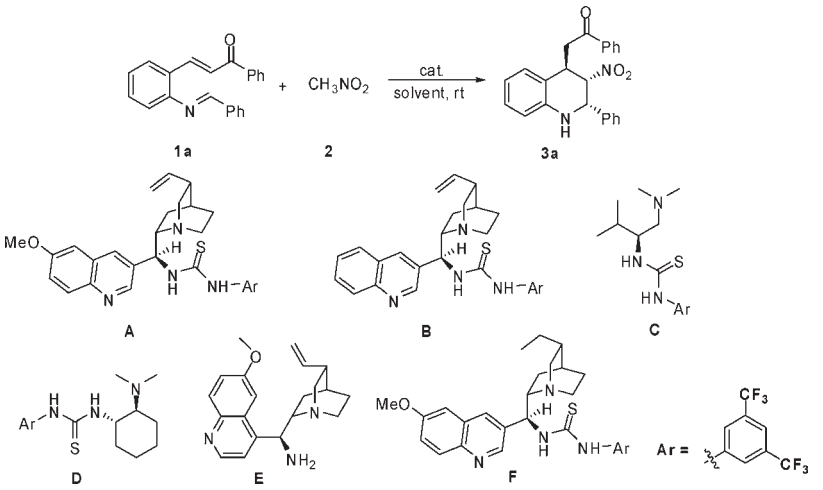
Table 1. Screenings of the Reaction Conditions[a]



entry	cat.	CH_3NO_2 (equiv)	solvent	time[b] (d)	yield (%)[c]	dr[d]	ee (%)[e]
1	**A**	20	toluene	3	33	nd	98
2	**A**	20	toluene	7	78	5:1	98
3	**B**	20	toluene	7	73	4:1	94
4	**C**	20	toluene	7	<20	nd	nd
5	**D**	20	toluene	7	<20	nd	nd
6	**E**	20	toluene	7	nr	nd	nd
7	**F**	20	toluene	6	95	6:1	98
8	**F**	20	$CHCl_3$	6	77	11:1	94
9	**F**	20	CH_2Cl_2	6	82	10:1	95
10	**F**	20	xylene	6	95	8:1	97
11	**F**	20	THF	6	<30	nd	nd
12	**F**	20	CH_3CN	6	44	nd	nd
13	**F**	–	CH_3NO_2	6	86	4:1	90
14	**F**	5	toluene	6	77	6:1	98
15	**F**	10	toluene	6	91	6:1	98

[a] Unless otherwise specified, all reactions were carried out with **1a** (0.1 mmol), **2** (2.0 mmol, 20.0 equiv), and organocatalyst (20 mol %) in the indicated solvent (1.0 mL) at room temperature. [b] Reaction time was determined by TLC. [c] Isolated yield after flash chromatography. [d] Determined by ^{1}H NMR analysis of the crude products. [e] Determined by chiral-phase HPLC analysis (AD column).

powerful and versatile catalysts for a variety of transformations. One of the most important reactions catalyzed by this class of catalysts is the enantioselective Michael reaction, an important carbon−carbon bond forming reaction for the construction of optically active organic compounds.[6] With the development of organic chemistry, tandem reactions now serve as a powerful tool for the rapid and efficient assembly of complex structures.[7] We

(3) For instance, see: (a) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 6801. (b) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536. (c) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (d) Guo, Q.-S.; Du, D.-M.; Xu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 759.

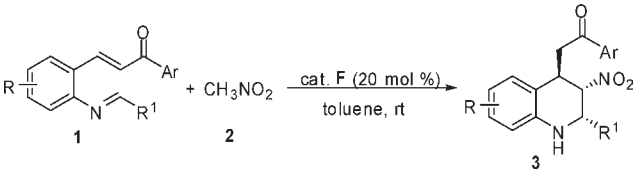
(4) (a) Sundararajan, G.; Prabagaran, N.; Varghese, B. *Org. Lett.* **2001**, *3*, 1973. (b) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070. (c) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2009**, *131*, 4598. (d) Davies, S. G.; Mujtaba, N.; Roberts, P. M.; Smith, A. D.; Thomson, J. E. *Org. Lett.* **2009**, *11*, 1959. (e) Bergonzini, G.; Gramigna, L.; Mazzanti, A.; Fochi, M.; Bernardi, L.; Ricci, A. *Chem. Commun.* **2010**, *46*, 327. (f) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986. (g) Xie, M.-S.; Chen, X.-H.; Zhu, Y.; Gao, B.; Lin, L.-L.; Liu, X.-H.; Feng, X.-M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3799.

(5) For reviews on organocatalytic reactions, see: (a) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (b) Enders, D.; Grondal, C.; Hüttl, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (d) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726.

(6) For organocatalyst-mediated cross Michael reactions, see: (a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (b) Enders, D.; Wang, C.; Liebich, J. X. *Chem.—Eur. J.* **2009**, *15*, 11058. (c) Yu, Z.-P; Liu, X.-H.; Zhou, L.; Lin, L.-L.; Feng, X.-M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5195. (d) Rueping, M.; Kuenkel, A.; Tato, F.; Bats, J. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 3699. (e) Furukawa, T.; Shibata, N.; Mizuta, S.; Nakamura, S.; Toru, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 8051. (f) Zhang, X.-S.; Zhang, S.-L.; Wang, W. *Angew. Chem., Int. Ed.* **2010**, *49*, 1481. (g) Li, H.; Zu, L.; Xie, H.-X.; Wang, J; Jiang, W.; Wang, W. *Org. Lett.* **2007**, *9*, 1833. (h) McGarraugh, P. G.; Brenner, S. E. *Org. Lett.* **2009**, *11*, 5654. (i) Liu, Y.-k.; Ma, C.; Jiang, K.; Liu, T.-Y.; Chen, Y.-C. *Org. Lett.* **2009**, *11*, 2848. (j) Zhou, W.-M.; Liu, H.; Du, D.-M. *Org. Lett.* **2008**, *10*, 2817. (k) Mosse, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559.

(7) For recent reviews of tandem reactions, see: (a) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (c) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143. (d) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967. (e) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551. (f) Zhong, C.; Shi, X.-D. *Eur. J. Org. Chem.* **2010**, 2999.

Table 2. Organocatalytic Reaction for the Synthesis of Tetrahydroquinolines[a]



entry	R^1	Ar	R	product	time[b] (d)	yield (%)[c]	dr[d]	ee (%)[e]
1	Ph	Ph	H	**3a**	6	95	6:1	98
2	3-$CH_3C_6H_4$	Ph	H	**3b**	6	94	8:1	98
3	3-ClC_6H_4	Ph	H	**3c**	6	98	4:1	>99
4	4-BrC_6H_4	Ph	H	**3d**	6	94	3:1	98
5	2-ClC_6H_4	Ph	H	**3e**	6	96	14:1	99
6	2-BrC_6H_4	Ph	H	**3f**	6	96	20:1	>99
7	Ph	4-$CH_3C_6H_4$	H	**3g**	7	98	7:1	98
8	2-ClC_6H_4	4-$CH_3C_6H_4$	H	**3h**	7	95	14:1	98
9	2-BrC_6H_4	4-$CH_3C_6H_4$	H	**3i**	7	95	20:1	98
10	3-ClC_6H_4	4-$CH_3C_6H_4$	H	**3j**	7	97	7:1	99
11	4-BrC_6H_4	4-$CH_3C_6H_4$	H	**3k**	7	95	7:1	98
12	Ph	4-ClC_6H_4	H	**3l**	4	97	3:1	99
13	3-$CH_3C_6H_4$	4-ClC_6H_4	H	**3m**	4	98	3:1	99
14	2-ClC_6H_4	4-ClC_6H_4	H	**3n**	4	96	12:1	99
15	Ph	4-BrC_6H_4	H	**3o**	4	98	5:1	99
16	3-$CH_3C_6H_4$	4-BrC_6H_4	H	**3p**	4	97	6:1	98
17	3-ClC_6H_4	4-BrC_6H_4	H	**3q**	4	98	3:1	99
18	2-ClC_6H_4	4-BrC_6H_4	H	**3r**	4	97	20:1	99
19	3-$CH_3C_6H_4$	3-BrC_6H_4	H	**3s**	4	98	3:1	98
20	Ph	Ph	5-Cl	**3t**	6	94	8:1	98
21	COOEt	Ph	H	**3u**	6	<20	n.d.	n.d.[f]

[a] Unless otherwise specified, all reactions were carried out with **1** (0.1 mmol), **2** (2.0 mmol, 20.0 equiv), and organocatalyst (20 mol %) in the indicated solvent (1.0 mL) at room temperature. [b] Reaction time was determined by TLC. [c] Isolated yield after flash chromatography. [d] Determined by ^{1}H NMR analysis of the crude products. [e] Determined by chiral-phase HPLC analysis (AD column). [f] Not determined.

wish to report herein the tandem Michael addition and aza-Henry reaction in the asymmetric synthesis of 2,3,4-trisubstituted tetrahydroquinolines with high yields and stereoselectivities from chalcones **1** and nitromethane.[8]

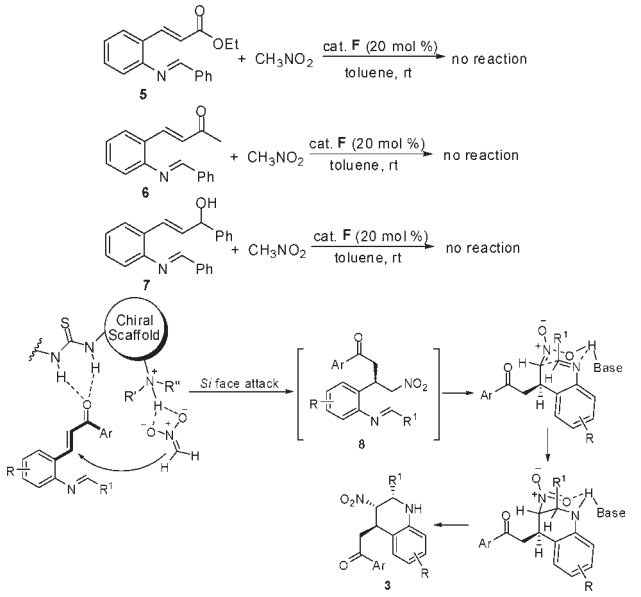
Our initial study began with the reaction of (*E*)-3-(2-((*E*)-benzylideneamino)phenyl)-1-phenyl prop-2-en-1-one **1a** and nitromethane **2**. First, several catalysts were screened for this reaction, and the results are shown in Table 1. Using catalyst **A**, we were delighted to obtain cyclized product **3a** with excellent enantioselectivity (98% ee), but the reaction rate was slow (entries 1 and 2). When catalyst **B** was used, the result was basically the same as that for catalyst **A** (entry 3). For catalyst **C** or **D**, only a small amount of desired product was given and the reaction rate was still slow (entries 4 and 5). No reaction was observed using catalyst **E** (entry 6). Eventually, we found that catalyst **F** was the best one for this tandem process (95% yield, 98% ee).

Second, the solvent effect on the reaction was investigated (entries 7 to 13). A variety of polar solvents and nonpolar solvents were tested. Toluene proved to be the best choice for the solvent. Meanwhile, the amount of nitromethane **2** had a significant effect on the reaction (entries 14 and 15). For example, when nitromethane (5 equiv) was used, the reaction yield was only 77% after 7 days. Ultimately, the use of 20 equiv of nitromethane allowed full conversion of the starting material within a shorter time and provided a slightly higher yield and high enantioselectivity.

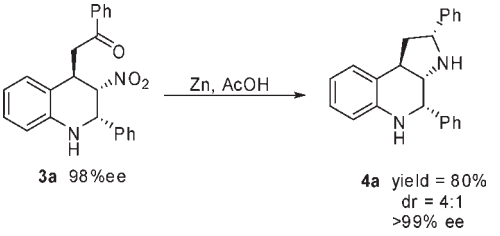
Under the optimized reaction conditions, the generality of the reaction was explored (Table 2). The reactions proceeded efficiently with various α,β-unsaturated ketones in combination with substituted imines. All the reactions afforded the corresponding tetrahydroquinolines in high yields and excellent enantioselectivities. For Ar groups, the reaction went faster with electron-deficient substituents than with electron-rich substituents (entries 12 to 19 vs entries 7 to 11). The substitution pattern of Ar^1 was observed to have a significant effect on the diastereoselectivity. *Ortho*-substituted R^1 groups gave the highest dr values (entries 5 and 6, 8 and 9, 14, 18). Aliphatic imines were also reacted with nitromethane, but the yield was low (< 20%, entry 21). In addition to nitromethane, nitroethane as the nucleophile also reacted with substrates **1a**, but no reaction occurred.

(8) For organocatalyst-mediated cross aza-Henry reactions, see: (a) Eugenia, M. L.; Merino, P.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2009**, 2401. (b) Jiang, X.-X.; Zhang, Y.-F.; Wu, L.-P.; Zhang, G.; Liu, X.; Zhang, H.-L.; Wang, R. *Adv. Synth. Catal.* **2009**, *351*, 2096. (c) Takada, K.; Nagasawa, K. *Adv. Synth. Catal.* **2009**, *351*, 345. (d) Wang, X.; Chen, Y.-F.; Niu, L.-F.; Xu, P.-F. *Org. Lett.* **2009**, *11*, 3310.

Scheme 1. Experiments of Study Mechanism and Postulated Transition-State Model



Scheme 2. Synthetic Transformation of Product **3a**



A series of control experiments were conducted to gain insight into the mechanism of the transformation. Benzylidene imine **5**, enone imine **6**, and enol imine **7** reacted with nitromethane separately, but they did not react. Thus, the results suggested that this transformation occurred first Michael reaction, then aza-Henry reaction was occurred. In the process of the reaction, we did not detect any formation of intermediates through the TLC. The Michael addition reaction is the rate-determining step in this tandem reaction. When the intermediate of the Michael reaction was generated, the intramolecular aza-Henry reaction occurred immediately (Scheme 1).

The absolute and relative configurations were unambiguously confirmed through X-ray crystal structure analysis of the compound **3i**.[9] By single crystal X-ray analysis, the absolute (2*S*,3*S*,4*R*)-configuration was observed. A simplistic meachanistic rationale to account for the observed stereoselectivity of this process may be proposed. Initially, bifunctional catalysts containing hydrogen bond donors and a tertiary amine moiety activated α,*β*-unsaturated ketones and nitromethane, and nitromethane attacked α,*β*-unsaturated ketones from the *Si* face, thereby forming intermediate **8**. Then, an aza-Henry reaction proceeded via a six-membered cyclic transition state in the presence of base, and the intramolecular nucleophilic addition underwent the stable chair form transition state. Finally, the absolute (2*S*,3*S*,4*R*)-configuration was obtained in accordance with X-ray crystal structure analysis (Scheme 1).

Tetrahydroquinolines **3** are useful synthetic intermediates because of the potential biological activities exhibited by their ring-fused derivatives.[10] So we decided to perform a transformation with this multifunctional cycloadduct as outlined in Scheme 1. The reduction of **3a** with Zn/AcOH followed by reductive amination afforded tricyclic compound **4a** in good yield (80%), good diastereoselectivity (4:1), and high enantioselectivity (>99% ee) (Scheme 2). The configuration of the product **4a** was determined by an NOE experiment.

In conclusion, we have developed a novel synthetic method for polysubstituted tetrahydroquinoline derivatives *via* organocatalytic asymmetric tandem Michael addition and the aza-Henry reaction, in which easily prepared chalcone **1** and nitroalkane were employed as the starting materials. The reaction yields were high (94%-98%), and highly diastereo- and enantioenriched tetrahydroquinoline derivatives with a substantial substitution diversity were smoothly delivered (up to >99% ee, dr up to 20:1). Moreover, through a simple transformation, a compound with a tricyclic core was successfully synthesized. The synthetic applications of this tandem reaction are currently under investigation.

Acknowledgment. We are grateful for the National Basic Research Program of China (Nos. 2009CB626604, 2010CB833203), the NSFC (20972058, 21032005), and the "111" program from MOE of P. R. China.

Supporting Information Available. Detailed experimental procedure, characterization data, NMR spectra for new compounds, HRMS data for products **3**, HPLC analysis. The information is available free of charge via the Internet at http://pubs.acs.org.

(9) CCDC 787334 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(10) (a) Staehle, W.; Bruge, D.; Schiemann, K.; Finsinger, D.; Buchstaller, H.-P.; Zenke, F.; Amendt, C. DE 102005027169, 2006. (b) Prossnitz, E. R.; Tkatchenko, S. E.; Revankar, C. M.; Sklar, L. A.; Arterburn, J. B.; Cimino, D. F.; Oprea, T. I.; Bologa, C.-G.; Edwards, B. S.; Kiselyov, A.; Young, S. M. WO 2007019180, 2007.