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Desymmetrization of Cyclohexadienones via Brønsted Acid-Catalyzed Enantioselective Oxo-Michael Reaction

Qing Gu, Zi-Qiang Rong, Chao Zheng, and Shu-Li You*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

Received January 10, 2010; E-mail: slyou@mail.sioc.ac.cn

The oxo-Michael addition reaction is one of the most important methods for forming C−O bonds.[1] In particular, intramolecular this reaction provides a straightforward route to oxoheterocycles, which are frequently encountered in biologically active natural products and pharmaceuticals.[2] However, the oxo-Michael reaction suffers from drawbacks such as low reactivity and reversibility, which impede the development of its corresponding asymmetric version.[1] To date, only a few examples of highly enantioselective oxo-Michael reactions, utilizing chiral secondary amines,[3] thioureas,[4] cinchona catalysts,[5] or Lewis acids,[6] have been described.

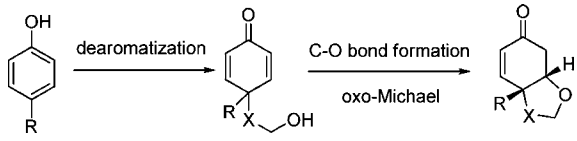
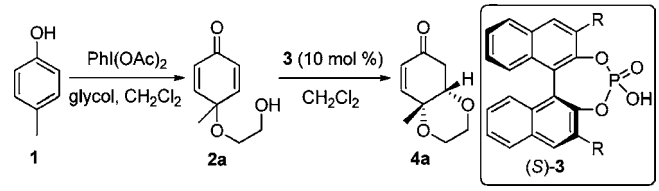


Figure 1. Dearomatization/desymmetrization oxo-Michael reaction.

Desymmetrization reaction is one of the most common and powerful methods for enantioselective synthesis of chiral molecules.[7] When coupled with a dearomatization process, it provides a facile construction of optically active cyclic and polycyclic compounds from readily available starting materials. Recently, this strategy was successfully demonstrated in asymmetric desymmetrization of cyclohexadienone using intramolecular Heck,[8] Stetter,[9] and Michael reactions,[10] providing efficient carbon−carbon bond-formation methods. Intrigued by these elegant works, we envisaged that the desymmetrization and dearomatization strategy might be suitable for the synthesis of enantioenriched oxygen-containing polycyclic compounds by enantioselective oxo-Michael reaction (Figure 1). We recently found that chiral phosphoric acids[11] can catalyze the enantioselective oxo-Michael reaction, providing highly enantioenriched 1,4-dioxane and tetrahydrofuran derivatives. By this method, the natural products cleroindicin C, D, and F were synthesized in a highly concise fashion. In this paper, we report our study on this subject.

We began our studies by examining different chiral Brønsted acids in the oxo-Michael reaction. Cyclohexadienone **2a**, which is readily prepared from *p*-cresol, was chosen as the model substrate. As summarized in Table 1, with 10 mol % readily available chiral phosphoric acid (**3a**−**g**) in CH_2Cl_2 at room temperature, the reactions all proceeded smoothly to give the desired product **4a** with 4−76% ee (Table 1). Chiral phosphoric acid **3g** bearing 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$ groups proved to be an efficient catalyst, affording product **4a** with 76% ee (entry 7). Lowering the temperature to 0 °C did not improve the enantioselectivity of the reaction (70% ee; entry 8). To our delight, an increase in ee was obtained by adding 4 Å molecular sieves (93% ee; entry 9). Chiral phosphoric acid **3h** bearing 2,6-(^{i}Pr)$_2$-4-^{t}BuC$_6$H$_2$ groups further improved the enantioselectivity to 94% ee (entry 10). Varying the solvents disclosed that CH_2Cl_2 was the optimal one (for details, see the Supporting Information).

Table 1. Screening of Chiral Phosphoric Acid Catalysts



entry[a]	3, R	time (h)	conv. (%)[b]	ee (%)[c]
1	**3a**, phenyl	0.6	>99	4
2	**3b**, $SiPh_3$	2	>99	−19
3	**3c**, 1-naphthyl	0.5	>99	11
4	**3d**, 2-naphthyl	0.5	>99	10
5	**3e**, 9-anthryl	0.6	>99	5
6	**3f**, 9-phenanthryl	1	>99	16
7	**3g**, 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$	3	>99	76
8[d]	**3g**, 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$	10	>99	70
9[e]	**3g**, 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$	3	>99	93
10[e]	**3h**, 2,6-(^{i}Pr)$_2$-4-^{t}BuC$_6$H$_2$	3	>99	94

[a] Reaction conditions: **3** (10 mol %) and **2a** (0.05 mol/L) in CH_2Cl_2 at room temperature. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC analysis (Chiralpak OB-H). [d] At 0 °C. [e] With 4 Å molecular sieves (activated) as an additive.

Under the above optimized reaction conditions, different substrates were examined to test the generality of the current reaction. The results are summarized in Table 2. The enantioselective intramolecular oxo-Michael reaction was found to be general with a wide range of substrates. The alkyl group at the 4-position of the cyclohexadienone has great influence on the enantioselectivity and reactivity (entries 1−3). Both the enantioselectivity and reactivity decreased when a more sterically hindered group was introduced (Me, 94% ee; Et, 78% ee; ^{i}Pr, 61% ee). Notably, neat substrates **2a**−**c** underwent the cyclization slowly, and carrying out the reaction immediately after the purification of these substrates was important for obtaining the best enantioselectivity. Delightfully, different aromatic groups at the 4-position were all well-tolerated. The intramolecular cyclization of cyclohexadienone derivatives **2d**−**l**, containing either electron-donating or electron-withdrawing groups on the phenyl ring, all led to their desired products in 81−93% yield and 88−95% ee (entries 4−12). Notably, many of the products are crystalline compounds, and optically pure products (>99% ee) could be obtained after one simple recrystallization (entries 1, 4−8, 10, and 11). To determine the absolute configuration of the products, crystals of enantiopure **4g** were obtained, and single-crystal X-ray analysis revealed the configuration to be (4a*S*, 8a*S*) (see the Supporting Information).

The intramolecular oxo-Michael adduct can be readily transformed. As shown in Scheme 1, hydrogenation of enantiopure **4d** afforded ketone **5** in 85% yield, and selective reduction of the ketone moiety in **4d** led to cyclohexene **6** in 58% yield over three steps. In both cases, the products were obtained without loss of optical purity.

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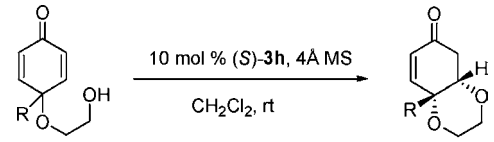
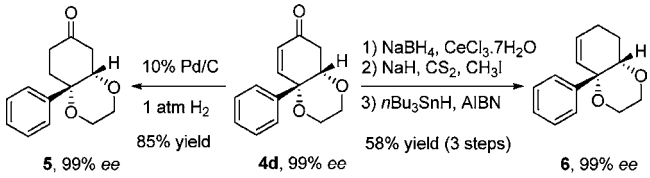
Table 2. Enantioselective Intramolecular Oxo-Michael Reaction



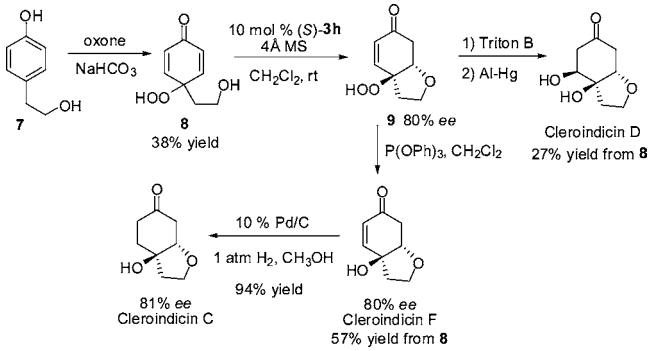
entry[a]	2, R	time (h)	4, yield (%)[b,d]	ee (%)[c,d]
1	**2a**, [Me	3	**4a**, [91 [62]	94 [99]
2	**2b**, [Et	5	**4b**, [91	78
3	**2c**, [^{i}Pr	24	**4c**, [71	61
4	**2d**, [Ph	10	**4d**, [92 [68]	91 [99]
5	**2e**, [4-FC_6H_4	8	**4e**, [91 [78]	90 [99]
6	**2f**, [4-ClC_6H_4	8	**4f**, [90 [68]	91 [99]
7	**2g**, [4-BrC_6H_4	10	**4g**, [84 [64]	90 [99]
8	**2h**, [4-MeC_6H_4	10	**4h**, [91 [72]	92 [99]
9	**2i**, [3-MeC_6H_4	10	**4i**, [91 [75]	91 [96]
10	**2j**, [2-MeC_6H_4	20	**4j**, [92 [57]	95 [99]
11	**2k**, [3,5-$Me_2C_6H_3$	8	**4k**, [81 [60]	90 [99]
12	**2l**, [3,5-$(CF_3)_2C_6H_3$	10	**4l**, [93	88

[a] Reaction conditions: **3h** (10 mol %) in CH_2Cl_2 at room temperature. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] Values after one recrystallization are given in brackets.

Scheme 1. Derivatization of the Oxo-Michael Adduct

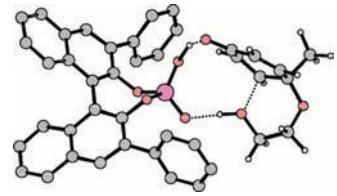


Scheme 2. Asymmetric Synthesis of Cleroindicins



As a further demonstration of the utility of the dearomatization/desymmetrization process, we developed concise and efficient total syntheses of cleroindicins C, D, and F, natural products isolated from *Clerodendum indicum*, a plant used in China to treat malaria and rheumatism.[12] Despite extensive synthetic efforts on their total synthesis, there have been only limited reports on their enantioselective synthesis.[13] As shown in Scheme 2, cyclohexadienone **8** was readily prepared through oxidative dearomatization of commercially available 4-(2-hydroxyethyl)phenol (**7**) mediated by oxone.[13e] With 10 mol % (*S*)-**3h**, cyclohexadienone **8** underwent the intramolecular oxo-Michael reaction smoothly with 80% ee, affording cleroindicin D in 27% yield (three steps) after successive epoxidation and reduction by aluminum amalgam. In addition, intramolecular oxo-Michael addition of **8** and reduction by $P(OPh)_3$ furnished cleroindicin F in 57% yield and 80% ee. Further hydrogenation of cleroindicin F afforded cleroindicin C in 94% yield (81% ee). The physical data for all these synthetic compounds matched those previously reported.[13d]

The catalytic working model shown below was proposed for desymmetrization process. The chiral phosphoric acid acts as a bifunctional catalyst in which the acidic proton and the P═O moiety of the catalyst form hydrogen bonds with the carbonyl group and the hydroxyl group, respectively.



In summary, we have developed chiral phosphoric acid-catalyzed desymmetrization of cyclohexadienones via oxo-Michael reaction, affording enantioenriched 1,4-dioxane derivatives in excellent yield. With this newly established methodology, enantioselective synthesis of cleroindicins could be realized in a highly efficient and concise manner.

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Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Review: Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2008**, *37*, 1218.
(2) Reviews: (a) Tang, Y.; Oppenheimer, J.; Song, Z.-L.; You, L.-F.; Zhang, X.-J.; Hsung, R. P. *Tetrahedron* **2006**, *62*, 10785. (b) Shi, Y.-L.; Shi, M. *Org. Biomol. Chem.* **2007**, *5*, 1499.
(3) (a) Govender, T.; Hojabri, L.; Matloubi, M. F.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2006**, *17*, 1763. (b) Kano, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron* **2007**, *63*, 8658. (c) Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem.—Eur. J.* **2007**, *13*, 574. (d) Bertelsen, S.; Dinér, P.; Johansen, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 1536. (e) Li, H.; Wang, J.; E-Nunu, T.; Zu, L.-S.; Jiang, W.; Wei, S.-H.; Wang, W. *Chem. Commun.* **2007**, 507. (f) Zu, L.-S.; Zhang, S.-L.; Xie, H.-X.; Wang, W. *Org. Lett.* **2009**, *11*, 1627. (g) Reyes, E.; Talavera, G.; Vicario, J. L.; Badía, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 5701. (h) Kotame, P.; Hong, B.-C.; Liao, J.-H. *Tetrahedron Lett.* **2009**, *50*, 704.
(4) Biddle, M. M.; Lin, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3830.
(5) (a) Sekino, E.; Kumamoto, T.; Tanaka, T.; Ikeda, T.; Ishikawa, T. *J. Org. Chem.* **2004**, *69*, 2760. (b) Dittmer, C.; Raabe, G.; Hintermann, L. *Eur. J. Org. Chem.* **2007**, 5886. (c) Saito, N.; Ryoda, A.; Nakanishi, W.; Kumamoto, T.; Ishikawa, T. *Eur. J. Org. Chem.* **2008**, 2759. (d) Merschaert, A.; Delbeke, P.; Daloze, D.; Dive, G. *Tetrahedron Lett.* **2004**, *45*, 4697.
(6) Wang, L.-J.; Liu, X.-H.; Dong, Z.-H.; Fu, X.; Feng, X.-M. *Angew. Chem., Int. Ed.* **2008**, *47*, 8670.
(7) Reviews: (a) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313. (b) Studer, A.; Schleth, F. *Synlett* **2005**, 3033. Recent examples: (c) Mori, K.; Katoh, T.; Suzuki, T.; Noji, T.; Yamanaka, M.; Akiyama, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 9652. (d) Sunasee, R.; Clive, D. L. J. *Chem. Commun.* **2010**, 701.
(8) Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 184.
(9) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552.
(10) (a) Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028. (b) Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 404.
(11) Reviews: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Yu, X.; Wang, W. *Chem.—Asian J.* **2008**, *3*, 516. (c) Terada, M. *Chem. Commun.* **2008**, 4097. (d) Adair, G.; Mukherjee, S.; List, B. *Aldrichimica Acta* **2008**, *41*, 31.
(12) (a) Tian, J.; Zhao, Q.-S.; Zhang, H.-J.; Lin, Z.-W.; Sun, H.-D. *J. Nat. Prod.* **1997**, *60*, 766. (b) Cheng, H.-H.; Wang, H.-K.; Ito, J.; Bastow, K. F.; Tachibana, Y.; Nakanishi, Y.; Xu, Z.; Luo, T.-Y.; Lee, K.-H. *J. Nat. Prod.* **2001**, *64*, 915.
(13) (a) Honzumi, M.; Kamikubo, T.; Ogasawara, K. *Synlett* **1998**, 1001. (b) Canto, M.; deMarch, P.; Figueredo, M.; Font, J.; Rodriguez, S.; Alarez-Larena, A.; Piniella, J. F. *Tetrahedron: Asymmetry* **2002**, *13*, 455. (c) You, Z.; Hoveyda, A. H.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 547. (d) Wenderski, T. A.; Huang, S.-L.; Pettus, T. R. R. *J. Org. Chem.* **2009**, *74*, 4104. (e) Barradas, S.; Carreño, M. C.; González-López, M.; Latorre, A.; Urbano, A. *Org. Lett.* **2007**, *9*, 5019.

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