### Asymmetric Catalysis

## **Brønsted Acid Catalyzed Enantioselective Semipinacol Rearrangement for the Synthesis of Chiral Spiroethers**\*\*

Qing-Wei Zhang, Chun-An Fan, Hai-Jun Zhang, Yong-Qiang Tu,\* Yu-Ming Zhao, Peiming Gu, and Zhi-Min Chen

Spiroethers, which feature two fused rings joined by a single chiral oxo quaternary carbon center, are a versatile structural motif found in a variety of biologically significant natural products and pharmaceuticals.<sup>[1]</sup> The effective synthesis of spiroethers,<sup>[2]</sup> and particularly asymmetric syntheses are of great importance in modern synthetic chemistry. To date, however, only a few reports of their chiral synthesis have been described in the literature, wherein their asymmetric construction was achieved mainly through use of chiral resolution procedures<sup>[3]</sup> or chiral substrates.<sup>[4]</sup> Therefore, the catalytic enantioselective synthesis of such spiroethers is particularly appealing.<sup>[5]</sup> Among the reported syntheses of spiroethers, one potential pathway involves the semipinacol rearrangement reaction, which is one of the most fundamental carboncarbon bond formation reactions.<sup>[6]</sup> In connection with our interest in the construction of quaternary carbon stereocenters, we have developed a series of synthetic methodologies that employ the semipinacol rearrangement of allylic alcohols (Scheme 1).<sup>[7]</sup> However, the catalytic asymmetric semipinacol rearrangement reaction for the construction of chiral oxo quaternary stereogenic centers in spiroethers remains challenging and elusive.<sup>[5,8,9]</sup>

During the past few years, chiral Brønsted acids have emerged as versatile enantioselective catalysts,<sup>[10]</sup> and their use in a variety of enantioselective procedures has been widely reported. One such class of chiral Brønsted acid catalysts, BINOL-derived phosphoric acids,<sup>[11]</sup> are promising catalysts for the asymmetric activation of imines or iminium ions,<sup>[12]</sup> for which the hydrogen bonding interaction is one of the

crucial factors in controlling enantioselectivity. Inspired by the successful employment of such chiral BINOL-derived phosphoric acid catalysts, and following our long-standing interest in semipinacol rearrangement reactions, we envi-

```
[*] Q.-W. Zhang, Prof. Dr. C.-A. Fan, H.-J. Zhang, Prof. Dr. Y.-Q. Tu,
Y.-M. Zhao, Dr. P. Gu, Z.-M. Chen
Department of Chemistry
State Key Laboratory of Applied Organic Chemistry
Lanzhou University, Lanzhou 730000 (China)
Fax: (+86) 931-8912582
E-mail: tuyq@lzu.edu.cn
[**] This work was supported by the NSFC (Nos. 20621091, 20672048,
and 20732002) and the "111" program of MOE. We also thank Brof.
```



**Scheme 1.** Semipinacol rearrangement in the construction of quaternary carbon stereocenters. Phth = phthalimido.

sioned that the synthesis of chiral spiroether motif **3** might be achievable by exploring a chiral phosphoric acid catalyzed semipinacol rearrangement of 2-oxo allylic alcohols **1** (Scheme 2). We postulated that the asymmetric 1,2-migration of the carbon atom might be initiated, in the presence of hydrogen bonding, by acidic proton transfer to the enol ether moiety in **A** before proceeding enantioselectively via chiral ion pair transition state **B**.<sup>[13]</sup> Herein, we report our preliminary results for this chiral phosphoric acid catalyzed semipinacol rearrangement reaction.

The initial evaluation of the reaction conditions was performed using **1a** and 10 mol% (*R*)-**2b** at room temperature. Among the solvents examined (Table 1, entries 1–7), nonpolar CCl<sub>4</sub> showed the most promising enantioselectiv-



**Scheme 2.** Design of the catalytic enantioselective semipinacol rearrangement reaction in the synthesis of spiroethers with oxo quaternary carbon centers.

ities in the control reaction (Table 1, entries 6 and 7). Surprisingly, the Lewis basic solvent 1,2-dimethoxyethane (DME) inhibited this rearrangement reaction completely (Table 1, entry 5). Importantly, it was found that by varying the chiral phosphoric acid catalyst (2a and 2c-2e, Table 1, entries 8-11), the substituents on the 3,3'-positions of the chiral phosphoric acid (R)-2 played a key role for the enantioselectivity of this reaction, with the bulky di-(2,4,6triisopropylphenyl)-substituted phosphoric acid (R)-2e affording both a high enantioselectivity (94% ee) and excellent yield (96%); (Table 1, entry 11). Moreover, the in situ generation of phosphoric acid (R)-2e was also investigated by employing the corresponding silver phosphate (R)-2f (Table 1, entry 12).<sup>[14]</sup> The desired spiroether 3a was obtained with excellent enantiocontrol (98% ee) and high vield (90%). This procedure, which involves silver-proton exchange between alcohol 1a and silver phosphate (R)-2f



8572

and 20732002) and the "111" program of MOE. We also thank Prof. Henri B. Kagan (Université de Paris-Sud (XI), France) for helpful discussion.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200904565.

Table 1: Optimization of the reaction conditions.<sup>[a]</sup>



Entry	2	Solvent	Yield [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup> 16	
1	2 b	CH <sub>2</sub> Cl <sub>2</sub>	94		
2	2 b	<i>n</i> -Hexane	92	42	
3	2 b	PhH	95	36	
4	2 b	CH₃CN	80	-4	
5	2 b	DME <sup>[f]</sup>	-	_	
6	2 b	CCl₄	95	52	
7 <sup>[d]</sup>	2 b	CCl₄	96	52	
8 <sup>[d,e]</sup>	2 a	CCl <sub>4</sub>	95	32	
<b>9</b> <sup>[d]</sup>	2 c	CCl₄	94	48	
10 <sup>[d]</sup>	2 d	CCl <sub>4</sub>	90	46	
11 <sup>[d]</sup>	2 e	CCl <sub>4</sub>	96	94	
12 <sup>[d]</sup>	2 f	CCL	90	98	

[a] **2a**: R=H, X=H; **2b**: R=Ph, X=H; **2c**: R=2-naphthyl, X=H; **2d**: R=9-anthryl, X=H; **2e**: R=2,4,6-(*i*Pr)<sub>3</sub>C<sub>6</sub>H<sub>2</sub>, X=H; **2f**: R=2,4,6-(*i*Pr)<sub>3</sub>C<sub>6</sub>H<sub>2</sub>, X=Ag. Conditions: Catalyst **2** (0.01 mmol) and solvent (0.5 mL) were added to a Schlenk flask. The mixture was stirred for 10 min at room temperature, and then a solution of substrate (0.1 mmol) in solvent (0.5 mL) was added. The reaction mixture was stirred for 2 h unless otherwise indicated. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] 5 Å molecular sieves (100 mg) were added. [e] Reaction proceeded for 24 h. [f] 1,2-Dimethoxy-ethane.

provides relatively mild, less acidic conditions, thus effectively realizing this semipinacol rearrangement reaction in the presence of 5 Å molecular sieves.<sup>[15]</sup> The absence of 5 Å molecular sieves (apart from Table 1, entries 6 and 7) usually resulted in the observation of varied, irreproducible *ee* values (Table 1, entries 8–12) suggesting that the addition of 5 Å molecular sieves is necessary for the reproducibility of reaction enantioselectivity in these cases. Therefore, the optimal conditions for the asymmetric semipinacol rearrangement reaction were found to be the use of (*R*)-2**e** as the catalyst or the less acidic (*R*)-2**f** as precatalyst.

Further exploration of this novel chiral Brønsted acid catalyzed asymmetric rearrangement was conducted using a series of 2-oxo allylic alcohols 1b-i with dihydropyranyl and dihydrofuranyl moieties (Table 2). For comparison with 1a (Table 2, entry 1), several substituted dihydropyranyl units were used (1b-g; Table 2, entries 3-8). Those bearing geminal dimethyl substitutents at the C4 or C6 position on the dihydropyranyl ring (Table 2, entries 3-6 and 8) showed some retardation of enantiocontrol (77-87% ee). For 1b-e (Table 2, entries 3–6), use of catalyst (R)-2e instead of the less acidic (R)-2f as precatalyst was also effective in this reaction, and comparable enantioselectivities could be obtained. For 1f and 1g (Table 2, entries 7 and 8), however, the more acidic (R)-2e was the only compatible catalyst. If silver phosphate (R)-2 f was used as precatalyst in the reaction of 1f and 1g, the desired rearrangement proceeded very slowly, and did not go to completion, even after 8 days. We also examined two substrates with dihydrofuranyl moieties (1h and 1i; Table 2, entries 9 and 10), which are highly acidTable 2: Asymmetric semipinacol rearrangement.[a]

		он _	10 mol CCl <sub>4</sub> , F	% (R)- <b>2</b>		\$
Entry	Substrate		2	Product	Yield [%] <sup>[b]</sup>	ee [%] <sup>[c,d]</sup>
1 2	ОН	1a 1a	2 e 2 f	3a 3a	96 90	94 98
	R R O OH					
3	R = Me	1 b	2 f	3 b	81	87 <sup>[e]</sup>
4	R = Et	1c	2 f	3 c	94	83 <sup>[e]</sup>
5	R = 🔨 🤇	1 d	2 f	3 d	98	85 <sup>[e]</sup>
6	R =	le	2 f	3 e	91	74
7	O OH	1f	2e	3 f	89	95
8	O, OH	lg	2e	3 g	91	77
9	ОСОН	1h	2 f	3 h	51	89 <sup>[f]</sup>
10	O I I I I O H	1i	2 f	3i	85	90 <sup>[f]</sup>

[a] For experimental details, see the Supporting Information. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] The absolute configuration of **3h** (Table 2, entry 9) is assigned as "*S*" by a comparison of its optical rotation with the literature value, and accordingly the absolute stereochemistry of entries 1–8 and 10 was provisionally established as indicated. [e] The reaction was conducted in  $CCl_4$  (0.4 mL). [f] The reaction proceeded at 0°C.

sensitive.<sup>[3a]</sup> Good enantioselectivities (about 90% *ee*) were achieved at 0°C with the less acidic (*R*)-**2 f** catalyst, whilst only about 50% *ee* could be obtained for the reaction of **1h** using the phosphoric acid catalyst (*R*)-**2e**. It should be noted that the low yield in the reaction of **1h** (51%; Table 2, entry 9) was due to the volatility of the product **3h** and its undesired dimerization.<sup>[3a]</sup> In order to investigate the enantioselectivity of this reaction, the absolute configuration of **3h** is further unambiguously assigned as "*S*" by the comparison of its optical rotation with the literature data.<sup>[3a]</sup>

In summary, we have discovered a novel chiral phosphoric acid, which can also be generated in situ by a silver–proton exchange process. This acid catalyzed an asymmetric ring expansion-type semipinacol rearrangement reaction that affords synthetically relevant chiral spiroethers in up to 98% *ee* and good to high yields under mild conditions. This catalytic asymmetric method provides an efficient route to enantiomerically pure spiroethers containing one chiral oxo quaternary carbon stereogenic center and one carbonyl keto group for further synthetic elaboration. The present method demonstrates the feasibility of the enantioselective 1,2-carbon migration via an oxocarbonium ion under the catalysis with a chiral Brønsted acid. Further research on the substrate scope and the enantioselective mechanism is currently underway.

# Communications

#### **Experimental Section**

Typical procedure for the enantioselective semipinacol rearrangement of **1a**: 5 Å molecule sieves (100 mg), catalyst (*R*)-**2e** or (*R*)-**2f** (0.01 mmol) and CCl<sub>4</sub> (0.5 mL) were added to a Schlenk flask. The mixture was stirred for 10 min at room temperature, and then a solution of substrate (0.1 mmol) in CCl<sub>4</sub> (0.5 mL) was added. The reaction was monitored by TLC until the substrate disappeared completely. The reaction mixture was directly subjected to column chromatography on silica gel and eluted with pentane/Et<sub>2</sub>O (10:1 $\rightarrow$ 5:1) to afford **3a** as colorless oil (14.7 mg, 96% yield). (Note: reactions using silver phosphate (*R*)-**2f** as the catalyst were carried out in the dark.) For further details of the synthesis and characterization, see Supporting Information.

Received: August 16, 2009 Published online: October 8, 2009

**Keywords:** asymmetric catalysis · Brønsted acids · semipinacols · rearrangements · spirocompounds

- a) K. Ishibashi, R. Nakamura, J. Agric. Chem. Soc. Jpn. 1958, 32, 739; b) S. Nozoe, M. Morisaki, K. Tsuda, Y. Iitaka, N. Tokahashi, S. Tamura, K. Ishibashi, M. Shirasaka, J. Am. Chem. Soc. 1965, 87, 4968; c) Y. Hirasawa, H. Morita, M. Shiro, J. Kobayashi, Org. Lett. 2003, 5, 3991; d) S. Aoki, Y. Watanabe, M. Sanagawa, A. Setiawan, N. Kotoku, M. Kobayashi, J. Am. Chem. Soc. 2006, 128, 3148; e) F. A. Macías, J. L. G. Galindo, R. M. Varela, A. Torres, J. M. G. Molinillo, F. R. Fronczek, Org. Lett. 2006, 8, 4513.
- [2] a) L. A. Paquette, D. E. Lawhom, C. A. Teleha, *Heterocycles* 1990, 30, 765; b) L. A. Paquette, J. C. Lanter, J. N. Johnston, J. Org. Chem. 1997, 62, 1702; c) I. E. Markó, A. Mekhalfia, D. J. Bayston, H. Adams, J. Org. Chem. 1992, 57, 2211; d) G. L. Plourde, *Tetrahedron Lett.* 2002, 43, 3597; e) G. Sabitha, K. B. Reddy, M. Bhikshapathi, J. S. Yadav, *Tetrahedron Lett.* 2002, 47, 2807.
- [3] a) L. A. Paquette, D. R. Owen, R. T. Bibart, C. K. Seekamp, A. L. Kahane, J. C. Lanter, M. A. Corral, *J. Org. Chem.* 2001, 66, 2828; b) L. A. Paquette, J. C. Lanter, D. R. Owen, F. Fabris, R. T. Bibart, M. A. Corral, *Heterocycles* 2001, 54, 49; c) M. E. Trân-Huu-Dâu, R. Wartchow, E. Winterfeldt, Y. S. Wong, *Chem. Eur. J.* 2001, 7, 2349.
- [4] a) R. E. Ireland, P. Maienfisch, J. Org. Chem. 1988, 53, 640;
  b) M. D. Lord, J. T. Negri, L. A. Paquette, J. Org. Chem. 1995, 60, 191;
  c) N. Haddad, I. Rukhman, Z. Abramovich, J. Org. Chem. 1997, 62, 7629;
  d) N. Noguchi, M. Nakada, Org. Lett. 2006, 8, 2039;
  e) M. Lejkowski, P. Banerjee, J. Runsink, H. J. Gais, Org. Lett. 2008, 10, 2713.
- [5] For molybdenum catalyzed enantioselective synthesis of spiroethers using olefin metathesis, see: X. Teng, D. R. Cefalo, R. R. Schrock, A. H. Hoveyda, J. Am. Chem. Soc. 2002, 124, 10779.
- [6] For reviews on the semipinacol rearrangement, see: a) B. Rickborn in *Comprehensive Organic Synthesis, Vol. 3* (Ed.: B. M. Trost), Pergamon, Oxford, **1991**, p. 733; b) T. Snape, *J. Chem. Soc. Rev.* **2007**, *36*, 1823.
- [7] a) Y. Q. Tu, L. D. Sun, P. Z. Wang, J. Org. Chem. 1999, 64, 629;
  b) B. M. Wang, Z. L. Song, C. A. Fan, Y. Q. Tu, W. M. Chen, Synlett 2003, 1497; c) X.-D. Hu, C.-A. Fan, F.-M. Zhang, Y. Q. Tu, Angew. Chem. 2004, 116, 1734; Angew. Chem. Int. Ed. 2004, 43, 1702; d) P. Gu, Y.-M. Zhao, Y. Q. Tu, Y. Ma, F. Zhang, Org. Lett. 2006, 8, 5271.
- [8] For the related palladium- and gold-catalyzed asymmetric Wagner-Meerwein rearrangements, see: a) B. M. Trost, T. Yasukata, J. Am. Chem. Soc. 2001, 123, 7162; b) B. M. Trost, J. Xie, J. Am. Chem. Soc. 2006, 128, 6044; c) B. M. Trost, J. Xie, J. Am. Chem. Soc. 2008, 130, 6231; d) F. Kleinbeck, F. D. Toste, J.

*Am. Chem. Soc.* **2009**, *131*, 9178. For the asymmetric α-ketol rearrangement, see: e) H. Brunner, F. Stöhr, *Eur. J. Org. Chem.* **2000**, 2777; f) H. Brunner, H. B. Kagan, G. Kreutzer, *Tetrahedron: Asymmetry* **2001**, *12*, 497; g) H. Brunner, H. B. Kagan, G. Kreutzer, *Tetrahedron: Asymmetry* **2003**, *14*, 2177; h) T. Ooi, A. Saito, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 3220; i) T. Ooi, K. Ohmatsu, K. Maruoka, *J. Am. Chem. Soc.* **2007**, *129*, 2410.

- [9] For the asymmetric synthesis of spiroethers, see Refs [3] and [4].
  [10] For reviews on chiral Brønsted acid catalysis, see: a) P. R. Schreiner, *Chem. Soc. Rev.* 2003, *32*, 289; b) P. M. Pihko, *Angew. Chem.* 2004, *116*, 2110; *Angew. Chem. Int. Ed.* 2004, *43*, 2062; c) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* 2007, *107*, 5713; d) X. Yu, W. Wang, *Chem. Asian J.* 2008, *3*, 516.
- [11] For reviews on chiral phosphoric acids, see: a) S. J. Connon, Angew. Chem. 2006, 118, 4013; Angew. Chem. Int. Ed. 2006, 45, 3909; b) T. Akiyama, Chem. Rev. 2007, 107, 5744; c) G. Adair, S. Mukherjee, B. List, Aldrichimica Acta 2008, 41, 31; d) M. Terada, Chem. Commun. 2008, 4097.
- [12] For selected examples of phosphoric acid catalyzed reactions, see: a) D. Uraguchi, M. Terada, J. Am. Chem. Soc. 2004, 126, 5356; b) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, Angew. Chem. 2004, 116, 1592; Angew. Chem. Int. Ed. 2004, 43, 1566; c) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, Org. Lett. 2005, 7, 3781; d) G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang, J. C. Antilla, J. Am. Chem. Soc. 2005, 127, 15696; e) S. Hoffmann, A. M. Seayad, B. List, Angew. Chem. 2005, 117, 7590; Angew. Chem. Int. Ed. 2005, 44, 7424; f) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, J. Am. Chem. Soc. 2006, 128, 84; g) X.-H. Chen, X.-Y. Xu, H. Liu, L.-F. Cun, L.-Z. Gong, J. Am. Chem. Soc. 2006, 128, 14802; h) Q. Kang, Z.-A. Zhao, S.-L. You, J. Am. Chem. Soc. 2007, 129, 1484; i) Y.-X. Jia, J. Zhong, C.-M. Zhang, Q.-L. Zhou, Angew. Chem. 2007, 119, 5661; Y.-X. Jia, J. Zhong, C.-M. Zhang, Q.-L. Zhou, Angew. Chem. 2007, 119, 5661; Angew. Chem. Int. Ed. 2007, 46, 5565; j) M. Lu, D. Zhu, Y. Lu, X. Zeng, B. Tan, Z. Xu, G. Zhong, J. Am. Chem. Soc. 2009, 131, 4562; k) H. Liu, G. Dagousset, G. Masson, P. Retailleau, J. Zhu, J. Am. Chem. Soc. 2009, 131, 4598.
- [13] For a recent example of a chiral Brønsted acid catalyzed intermolecular addition of an enol ether via oxocarbonium ion, see: M. Terada, H. Tanaka, K. Sorimachi, J. Am. Chem. Soc. 2009, 131, 3430.
- [14] a) G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* 2007, 317, 496; b) G. L. Hamilton, T. Kanai, F. D. Toste, *J. Am. Chem. Soc.* 2008, 130, 14984.
- [15] The proposed pathway on the semipinacol rearrangement of 2-oxo allylic alcohol 1a under the catalysis of silver phosphate (*R*)-2f was depicted as follows, in which the in situ generation of (*R*)-2e was performed by silver-proton exchange between the alcohol and silver phosphate.



asymmetric semipinacol rearrangement

in situ generation of (R)-2e through Ag-H exchange

## 8574 www.angewandte.org

© 2009 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Angew. Chem. Int. Ed. 2009, 48, 8572-8574