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Asymmetric Catalysis

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

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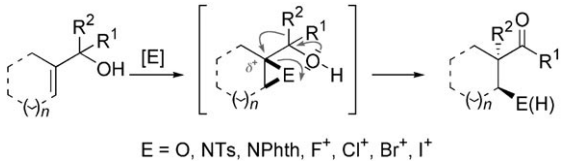
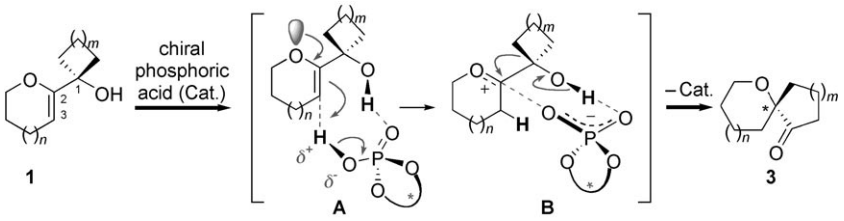
Spiroethers, which feature two fused rings joined by a single chiral oxo quaternary carbon center, are a versatile structural motif found in a variety of biologically significant natural products and pharmaceuticals.[1] The effective synthesis of spiroethers,[2] and particularly asymmetric syntheses 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[3] or chiral substrates.[4] Therefore, the catalytic enantioselective synthesis of such spiroethers is particularly appealing.[5] Among the reported syntheses of spiroethers, one potential pathway involves the semipinacol rearrangement reaction, which is one of the most fundamental carbon–carbon bond formation reactions.[6] 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).[7] However, the catalytic asymmetric semipinacol rearrangement reaction for the construction of chiral oxo quaternary stereogenic centers in spiroethers remains challenging and elusive.[5,8,9]



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

During the past few years, chiral Brønsted acids have emerged as versatile enantioselective catalysts,[10] 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,[11] are promising catalysts for the asymmetric activation of imines or iminium ions,[12] 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 envisioned 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**.[13] Herein, we report our preliminary results for this chiral phosphoric acid catalyzed semipinacol rearrangement reaction.



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

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_4 showed the most promising enantioselectivities 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-(2,4,6-triisopropylphenyl)-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).[14] The desired spiroether **3a** was obtained with excellent enantiocontrol (98% *ee*) and high yield (90%). This procedure, which involves silver–proton exchange between alcohol **1a** and silver phosphate (*R*)-**2f**

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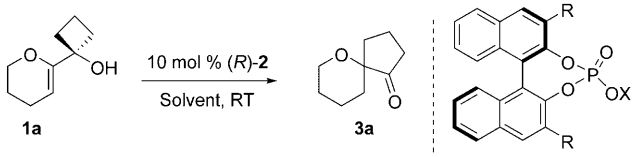
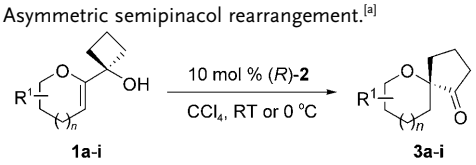
Table 1: Optimization of the reaction conditions.[a]

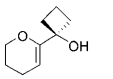
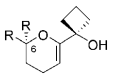
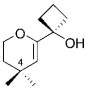
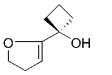
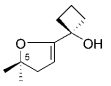


Entry	2	Solvent	Yield [%][b]	*ee* [%][c]
1	**2b**	CH_2Cl_2	94	16
2	**2b**	*n*-Hexane	92	42
3	**2b**	PhH	95	36
4	**2b**	CH_3CN	80	−4
5	**2b**	DME[f]	–	–
6	**2b**	CCl_4	95	52
7[d]	**2b**	CCl_4	96	52
8[d,e]	**2a**	CCl_4	95	32
9[d]	**2c**	CCl_4	94	48
10[d]	**2d**	CCl_4	90	46
11[d]	**2e**	CCl_4	96	94
12[d]	**2f**	CCl_4	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-(iPr)$_3$C$_6$H$_2$, X = H; **2f**: R = 2,4,6-(iPr)$_3$C$_6$H$_2$, 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-Dimethoxyethane.

Table 2: Asymmetric semipinacol rearrangement.[a]



Entry	Substrate		2	Product	Yield [%][b]	*ee* [%][c,d]
1		**1a**	**2e**	**3a**	96	94
2		**1a**	**2f**	**3a**	90	98
3	R = Me	**1b**	**2f**	**3b**	81	87 [e]
4	R = Et	**1c**	**2f**	**3c**	94	83 [e]
5	R = 	**1d**	**2f**	**3d**	98	85 [e]
6	R = 	**1e**	**2f**	**3e**	91	74
7		**1f**	**2e**	**3f**	89	95
8		**1g**	**2e**	**3g**	91	77
9		**1h**	**2f**	**3h**	51	89 [f]
10		**1i**	**2f**	**3i**	85	90 [f]

[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.

provides relatively mild, less acidic conditions, thus effectively realizing this semipinacol rearrangement reaction in the presence of 5 Å molecular sieves.[15] 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*)-**2e** as the catalyst or the less acidic (*R*)-**2f** 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*)-**2f** 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 acid–sensitive.[3a] Good enantioselectivities (about 90% *ee*) were achieved at 0 °C with the less acidic (*R*)-**2f** 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.[3a] 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.[3a]

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.

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_4 (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_4 (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_2O (10:1→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.

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[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.