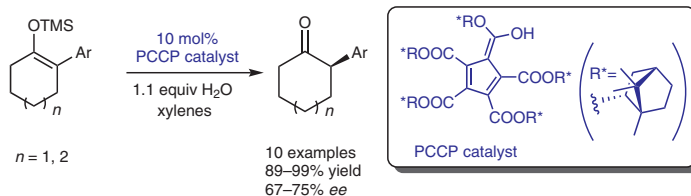


Enantioselective Protonation of Silyl Enol Ethers Catalyzed by a Chiral Pentacarboxycyclopentadiene-Based Brønsted Acid

Jun Li
Shaoyu An
Chao Yuan
Pingfan Li*

Department of Organic Chemistry, Faculty of Science,
Beijing University of Chemical Technology, Beijing
100029, P. R. of China
lipf@mail.buct.edu.cn



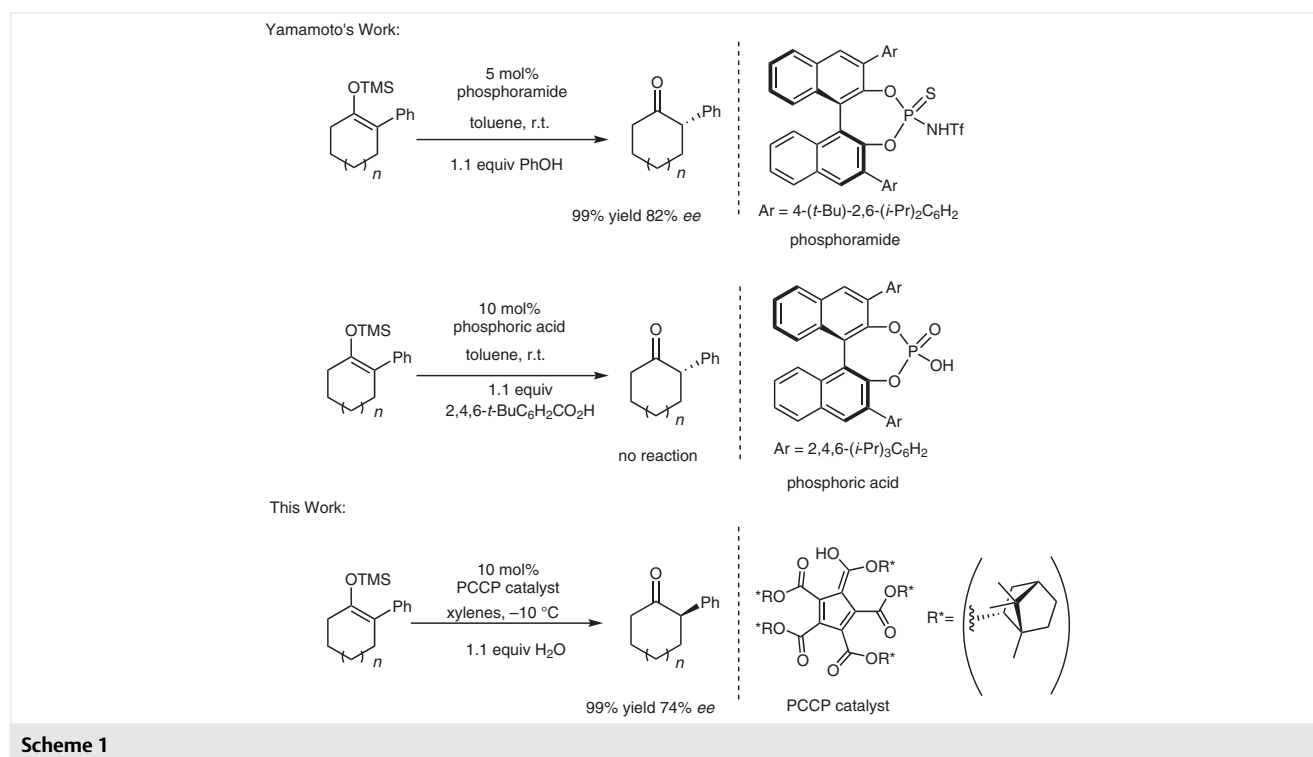
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Abstract The enantioselective protonation of silyl enol ethers was realized in the presence of a pentacarboxycyclopenta-1,3-diene-based chiral Brønsted acid catalyst with water as an achiral proton source to give the corresponding α-aryl ketones in good yields and up to 75% ee.

Key words protonation, Brønsted acids, asymmetric catalysis, organo-catalysis, carbonyl compounds, silyl enol ethers

The asymmetric protonation of prochiral enolate compounds is a simple and straightforward way to prepare optically active α-substituted carbonyl compounds.^{1–3} One

such approach involves the asymmetric protonation of lithium enolates.¹ Another strategy is based on the protonation of silyl enol ethers with an excess of an achiral source of protons in the presence of a chiral Lewis acid or Brønsted acid catalyst.^{2,3} Compared with the first method, the prochiral intermediate silyl enol ethers in the second method are more stable and can be isolated; consequently, this has attracted much study in this field. In 1994, Yamamoto and co-workers reported the first protonation reaction of a silyl enol ether by a Lewis acid-activated Brønsted acid (LBA) by using tin tetrachloride and a chiral binaphthol as the proton source to achieve a series of asymmetric protonation reactions.^{2a} In 1996, they modified the structure of the chiral binaphthol and they successfully achieved an



asymmetric protonation of silyl enol ethers with an excess of an achiral source of protons in the presence of a catalytic amount of an LBA.^{2b} A series of LBA-catalyzed reactions have since been reported.²

Compared with LBA catalysts, chiral phosphoric acids, the most commonly used Brønsted acids, are usually less acidic^{3a,4} and do not, therefore, readily catalyze the protonation of silyl enol ethers. In 2008, Cheon and Yamamoto reported the first Brønsted acid-catalyzed asymmetric protonation reaction of silyl enol ethers. They showed that chiral phosphoric acids are unable to catalyze such reactions and they identified *N*-[2,6-bis(4-*tert*-butyl-2,6-diisopropylphenyl)-4-sulfidodinaphtho[1,2-*f*:2',1'-*d*][1,3,2]dioxaphosphepin-4-yl]-1,1,1-trifluoromethanesulfonamide as a good catalyst and obtained the product in 82% ee.^{3a} (Scheme 1)

In 2016, Lambert and co-workers⁵ reported a novel chiral catalyst based on pentacarboxycyclopenta-1,3-diene (PCCP) that could be easily prepared from readily available pentamethyl cyclopenta-1,3-dienepentacarboxylate and chiral (–)-menthol in one transesterification step. The Lambert catalyst is more acidic and less expensive than most chiral phosphoric acids, and a number of catalytic enantioselective reactions using this catalyst have been reported, including a Mannich reaction, a Diels–Alder reaction of salicylaldehyde acetals with vinyl ethers, and a desymmetri-

zation of epoxides.^{5–8} Here, we report an asymmetric protonation reaction of silyl enol ethers by using a PCCP-based catalyst derived from chiral (–)-borneol, with water as a proton source.

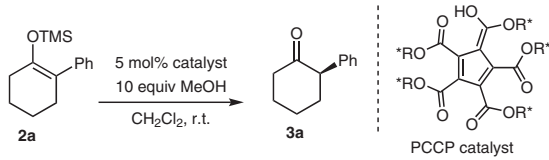
First, five optically active PCCP-type catalysts **1a–e** (Table 1), based on Lambert's work, were prepared from natural chiral alcohols. Next, we examined the protonation reaction of silyl enol ether **2a** with ten equivalents of methanol as a proton source with a 5 mol% loading of the PCCP catalysts **1a–e** in dichloromethane at room temperature for 12 hours as a model reaction. When 5 mol% PCCP catalyst **1b** derived from (–)-borneol was used (Table 1, entry 2), (2*R*)-2-phenylcyclohexanone (**3a**) was obtained in 88% isolated yield and 28% ee. The other catalysts all gave **3a** with less than 10% ee. We therefore focused on screening the reaction conditions for catalyst **1b**.

To further enhance the stereoselectivity of the reaction, we then screened a number of reaction conditions, including the proton source, solvent, temperature, and catalyst loading (Table 2). When phenols were used as proton sources, we found either the yield or the enantioselectivity was low, indicating that phenols were unsuitable for use in the reaction (Table 2, entries 1–3). When 10 equivalents of an alcohol were used as the proton source at room temperature, the protonation product **3a** was obtained with low enantioselectivity (entries 4–9). The enantioselectivity was greatly improved by reducing the number of equivalents of the proton source and lowering the reaction temperature (entries 9–11). We also found that steric hindrance of the achiral proton affected the enantiomeric excess of the product. The effects of propan-2-ol and ethanol as proton sources were worse than that of MeOH (entries 8 versus entries 4 and 5). The best result (67% ee) was obtained when H₂O was used as the proton source (entries 12–21).

With the optimized proton source in hand, we screened a number of solvents and the loading of the catalyst for this reaction (Table 2, entries 14 and 16–20). The best result (74% ee) was obtained when xylenes were used as the solvent at –20 or –10 °C with a 10 mol% loading of **1b** (entries 19 and 20). (For more solvent optimization, see the Supporting Information.) Next, we attempted enhance the selectivity by lowering the reaction temperature; however, the enantioselectivity decreased to 62% ee at –40 °C and to 68% ee at –30 °C (entries 15 and 21), suggesting that the energy gap for the transition states for the stereodetermining step might be different at different temperatures.

Finally, we explored the substrate scope by using 10 mol% of catalyst **1b** and 1.1 equivalents of water in xylenes at –10 °C (Table 3).⁹ Several 2-aryl-substituted cyclic ketones substituted in the *ortho* and *meta* positions were obtained with similar ee values, and ketones bearing electron-donating or electron-withdrawing *para*-substituents were tolerated (Table 3, entries 1–7). A substrate with a seven-membered ring and naphthyl-substituted substrates gave comparable results (entries 8–10).

Table 1 Optimization of the PCCP Catalyst

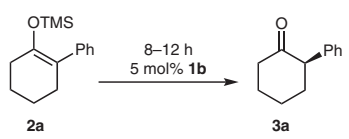
				
Entry	Catalyst ^a	R [*]	Yield ^b (%)	ee (%)
1	1a		59	9
2	1b		88	28
3	1c		97	5
4	1d		NR ^c	–
5	1e		47	8

^a Catalysts **1a–e** were derived from chiral (–)-menthol, (–)-borneol, (–)-8-phenylmenthol, (–)-isopinocampheol, and (+)-norborneol, respectively.

^b Isolated yield for 0.2 mmol scale reaction.

^c No reaction.

Table 2 Optimization of the Reaction Conditions

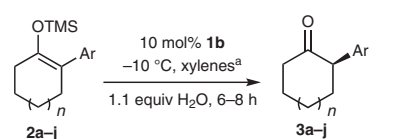


Entry	Achiral Brønsted acid (equiv)	Solvent	Temp (°C)	Time (h)	Yield ^a (%)	ee (%)
1	2,6-Dimethylphenol (2)	CH ₂ Cl ₂	25	24	trace	–
2	2,6-Diphenylphenol (2)	CH ₂ Cl ₂	25	24	trace	–
3	PhOH (2)	CH ₂ Cl ₂	25	24	51	0 ^b
4	EtOH (10)	CH ₂ Cl ₂	25	12	74	16
5	<i>i</i> -PrOH (10)	CH ₂ Cl ₂	25	12	37	7
6	<i>t</i> -BuOH (10)	CH ₂ Cl ₂	25	12	trace	–
7	F ₃ CCH ₂ OH (10)	CH ₂ Cl ₂	25	12	34	0 ^b
8	MeOH (10)	CH ₂ Cl ₂	25	12	88	28
9	MeOH (10)	toluene	25	12	74	34
10	MeOH (1.1)	toluene	25	12	29	39
11	MeOH (1.1)	toluene	–20	8	91	62
12	H ₂ O (1.1)	toluene	25	12	43	60
13	H ₂ O (1.1)	toluene	0	8	94	66
14	H ₂ O (1.1)	toluene	–20	8	94	67
15	H ₂ O (1.1)	toluene	–40	10	77	62
16	H ₂ O (1.1)	PhCl	–20	8	91	69
17 ^c	H ₂ O (1.1)	PhCl	–20	12	86	66
18 ^d	H ₂ O (1.1)	PhCl	–20	8	94	71
19 ^d	H ₂ O (1.1)	xylenes ^e	–20	8	94	74
20 ^d	H ₂ O (1.1)	xylenes	–10	8	99	74
21 ^f	H ₂ O (1.1)	xylenes	–30	12	99	68

^a Isolated yield from 0.2 mmol scale reaction.^b Racemic product.^c 2.5 mol% catalyst loading.^d 10 mol% catalyst loading.^e Commercial mixture of xylenes and ethylbenzene.^f 15 mol% catalyst loading.

In summary, we have found that the chiral PCCP catalyst **1b**, prepared from (–)-borneol, could be successfully used in the asymmetric protonation of silyl enol ethers with water as the proton source. This reaction gave up to 99% yield and 75% ee, whereas Yamamoto et al. achieved up to 90% ee for this reaction by using a chiral *N*-triflylthiophosphoramidate as a catalyst;^{3a} conventional chiral phosphoric acids were found to have no catalytic activity. We have therefore demonstrated the advantages of a chiral pentacarboxycyclopenta-1,3-diene-based Brønsted acid as a cheap and readily accessible alternative to chiral *N*-triflylthiophosphoramidate-type strong acids.

Table 3 Substrate Scope



Entry	<i>n</i>	Ar	Yield ^b (%)	ee (%)
1	1	Ph	99	74
2	1	2-MeC ₆ H ₄	99	69
3	1	3-MeC ₆ H ₄	95	74
4 ^c	1	4-MeC ₆ H ₄	89	73
5 ^c	1	4-MeOC ₆ H ₄	98	75
6	1	4-ClC ₆ H ₄	93	67
7	1	4-FC ₆ H ₄	95	75
8	1	2-naphthyl	96	68
9 ^c	1	1-naphthyl	89	69
10	2	Ph	92	70

^a Commercial mixture of xylenes and ethylbenzene.^b Isolated yield from a 0.2 mmol scale reaction.^c 15 mol% catalyst loading.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1611849>.

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- (9) **(2R)-2-Phenylcyclohexanone (3a); Typical Procedure**
 PCCP catalyst **1b** (19.3 mg, 0.02 mmol, 10 mol%) was weighed into a cryogenic vial. The vial was cooled to $-10\text{ }^{\circ}\text{C}$, and H_2O (4 μL , 1.1 equiv) and anhyd xylenes (2 mL) were added. After 15

min at $-10\text{ }^{\circ}\text{C}$, silyl enol ether **2a** (49 mg, 0.2 mmol, 1.0 equiv) was added dropwise to the stirred mixture. After 8 h, the reaction was quenched by the addition of sat. aq NaHCO_3 (3 mL) and the mixture was extracted with CH_2Cl_2 (25 mL). The organic layer was washed with brine (5 mL), dried (NaSO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography [silica gel, hexanes–EtOAc (100:1 to 10:1)] to give a white solid; yield: 35 mg (99%, 74% ee); $[\alpha]_{\text{D}}^{25} +50.7$ ($c = 0.4$, CHCl_3).

HPLC: Chiralpak Lux 5u cellulose-1 [hexanes–*i*-ProH (99:1), flow rate = 1.0 mL/min; $\lambda = 215\text{ nm}$], t_{R} (minor, S) = 14.8 min; t_{R} (major, R) = 16.2 min. $^1\text{H NMR}$ (400 MHz, CDCl_3): $\delta = 7.33$ (t, $J = 7.4\text{ Hz}$, 2 H), 7.25 (t, $J = 7.4\text{ Hz}$, 1 H), 7.14 (d, $J = 7.4\text{ Hz}$, 2 H), 3.60 (dd, $J = 12.1, 5.4\text{ Hz}$, 1 H), 2.63–2.36 (m, 2 H), 2.26–2.30 (m, 1 H), 2.21–2.09 (m, 1 H), 2.09–1.90 (m, 2 H), 1.90–1.71 (m, 2 H).