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Direct Asymmetric Friedel–Crafts Reaction of Naphthols with Acetals Catalyzed by Chiral Brønsted Acids

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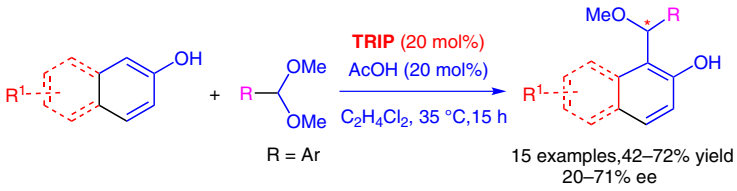

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Abstract The Friedel–Crafts method synthesis of chiral ethers from various acetals and naphthols catalyzed by chiral Brønsted acids with acetic acid as an effective additive is described. We found that the chiral phosphoric acid (*R*)-TRIP could efficiently catalyze the asymmetric Friedel–Crafts reaction of naphthols with acetals affording chiral ethers in good enantioselectivity and yield.

Key words Friedel–Crafts reaction, chiral ethers, acetals, chiral Brønsted acid, asymmetric organocatalysis

Chiral ethers are ubiquitous in natural products and pharmaceutical candidates, show beneficial effects in human health, such as anticancer, antiobesity, antidiabetes effects, antibacterial, antioxidative, and antihypercholesterolemic properties (Figure 1).[2]

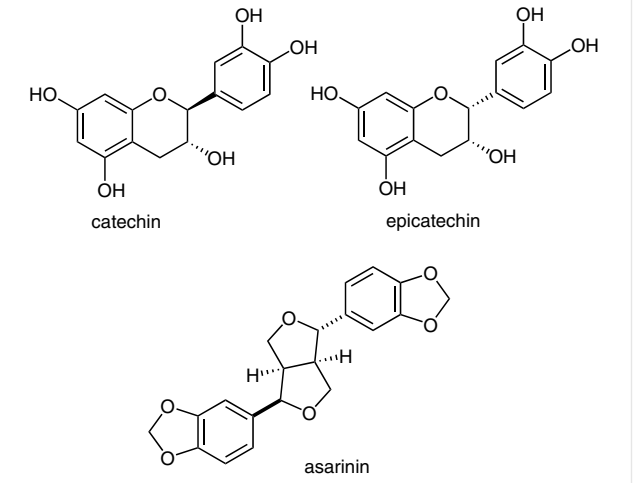
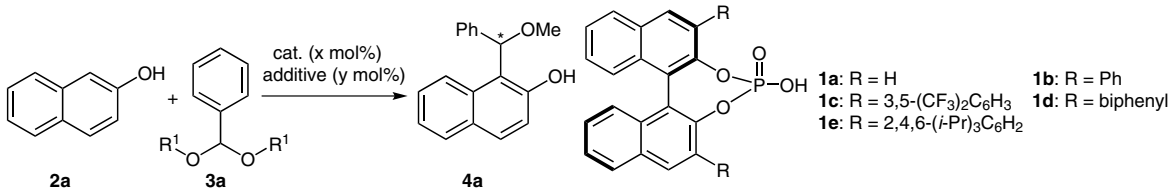


Figure 1 Structures of chiral ethers

Acetals are widely used in carbon–carbon bond-forming reactions with a variety of nucleophiles for the synthesis of ethers. Already used nucleophiles include vinyl ethers and arylboronic esters,[3] alkynes,[4] allyl acetates,[5] indoles[6] and allyltrimethylsilanes.[7] However, the asymmetric substitute of naphthols as nucleophiles to acetals have not been reported so far. We were very interested in developing an effective approach to realize the Friedel–Crafts[8] reaction of phenols and acetals for chiral ethers. Chiral Brønsted acid catalysis has been widespread in asymmetric synthesis over the past decade because of it being easy to handle, generally stable toward oxygen and water, and friendly to environment.[9] Many organic chemists have focused their attention on the development of chiral binaphthol-derived phosphoric acids as the chiral Brønsted acidic catalysts in a variety of organic transformations,[10] such as nucleophilic addition to aldimines,[11] aza Diels–Alder reactions,[12] transfer hydrogenations[13] and as a result have been actively investigated. Therefore, we chose chiral BINOL-based phosphoric acids as catalysts to promote the enantioselective Friedel–Crafts reaction of naphthols with acetals for chiral ethers. Herein, we disclose results on this study.

In initial experiments, various solvents were investigated in the model Friedel–Crafts reaction of β-naphthol and the dimethyl acetal of benzaldehyde by using 20 mol% chiral phosphoric acid **1d** at 50 °C without any additive (Table 1, entries 1–5). The results showed that the enantioselectivities were very low; both toluene and 1,2-dichloroethane achieved the similar enantioselectivity values higher than other solvents. Toluene gave 15% ee and 71% isolated yield (Table 1, entry 1) while 1,2-dichloroethane achieved 13% ee and 75% isolated yield (Table 1, entry 3). For increase of the enantioselectivity, we chose toluene and 1,2-dichloroethane as solvents for further optimization of the other reaction conditions. A series of acidic additives that could also affect the pK_a were introduced to raise the enantioselectivity (Table 1, entries 6–16). The results indicated that only in 1,2-dichloroethane, acetic acid was an optimal acidic additive with increased yield (up to 77%) and enantiose-

Table 1 The Optimization of the Reaction Conditions[a]



2a 3a 4a

Entry	Solvent	Additive[b]	Cat.	R^1	x	y	Temp (°C)	Time (h)	Yield (%)[c]	ee (%)[d]
1	toluene	–	**1d**	Me	20	–	50	27	71	15
2	THF	–	**1d**	Me	20	–	50	25	21	5
3	$C_2H_4Cl_2$	–	**1d**	Me	20	–	50	25	75	13
4	dioxane	–	**1d**	Me	20	–	50	26	56	4
5	DMF	–	**1d**	Me	20	–	50	30	43	5
6	toluene	CF_3COOH	**1d**	Me	20	20	50	22	78	15
7	toluene	Et_3N	**1d**	Me	20	20	50	25	65	11
8	toluene	AcOH	**1d**	Me	20	20	50	24	79	25
9	$C_2H_4Cl_2$	AcOH	**1d**	Me	20	20	50	10	77	40
10	$C_2H_4Cl_2$	$BrCH_2COOH$	**1d**	Me	20	20	50	10	76	31
11	$C_2H_4Cl_2$	EtCOOH	**1d**	Me	20	20	50	12	58	35
12	$C_2H_4Cl_2$	DNP[e]	**1d**	Me	20	20	50	7	55	15
13	$C_2H_4Cl_2$	PhCOOH	**1d**	Me	20	20	50	11	76	33
14	$C_2H_4Cl_2$	4-$MeOC_6H_4COOH$	**1d**	Me	20	20	50	11	68	35
15	$C_2H_4Cl_2$	4-$O_2NC_6H_4COOH$	**1d**	Me	20	20	50	9	63	31
16	$C_2H_4Cl_2$	$Al(OAc)_3$	**1d**	Me	20	20	50	5	75	15
17	$C_2H_4Cl_2$	AcOH	**1a**	Me	20	20	50	18	76	<1
18	$C_2H_4Cl_2$	AcOH	**1b**	Me	20	20	50	20	72	12
19	$C_2H_4Cl_2$	AcOH	**1c**	Me	20	20	50	18	54	21
20	$C_2H_4Cl_2$	AcOH	**1e**	Me	20	20	50	10	61	61
21	$C_2H_4Cl_2$	AcOH	**1e**	Me	5	20	50	13	55	33
22	$C_2H_4Cl_2$	AcOH	**1e**	Me	10	20	50	11	58	49
23	$C_2H_4Cl_2$	AcOH	**1e**	Me	25	20	50	10	64	58
24	$C_2H_4Cl_2$	AcOH	**1e**	Me	20	30	50	9	60	54
25	$C_2H_4Cl_2$	AcOH	**1e**	Me	20	100	50	7	70	56
26	$C_2H_4Cl_2$	AcOH	**1e**	Me	20	20	35	15	64	68
27	$C_2H_4Cl_2$	AcOH	**1e**	Me	20	20	20	46	46	58
28	$C_2H_4Cl_2$	AcOH	**1e**	Et	20	20	35	28	58	66

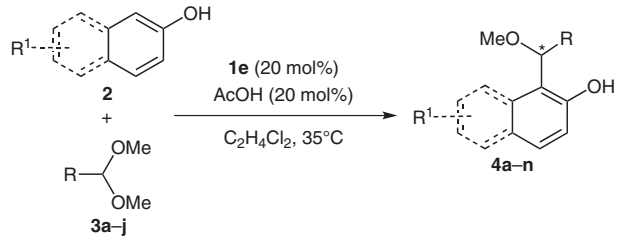
[a] Unless otherwise specified, the reaction was carried out with **2a** (0.4 mmol) and **3a** (0.2 mmol) in the presence of catalysts **1**, additives and solvent (1 mL).
[b] Additive was used in entries 6–27.
[c] Isolated yield.
[d] Determined by HPLC analysis.
[e] DNP = 2,4-dinitrophenol.

lectivity (up to 40%; Table 1, entry 9).[14] Then we found that phosphoric acid **1e** showed the highest enantioselectivity (61%) among the investigated five catalysts (Table 1, entries 17–20). Changing the loading of the catalyst not only increased the enantioselectivity but also shortened the reaction time (Table 1, entries 21–23). Increase of the acetic acid load could accelerate the reaction but did not lead to significant improvement in enantioselectivity. At last the reaction temperature was observed. Decreasing the reaction temperature to 35 °C slightly improved the enantioselectivity (from 61% to 68%). But at the decreased temperature of 20 °C, both the enantioselectivity and the yield of

the transformation were sharply reduced (Table 1, entries 26 and 27). When we used (diethoxymethyl)benzene as the substrate, yield and ee of the reaction decreased slightly (Table 1, entry 28).

With the optimized reaction conditions in hand, the scope of substrates for various acetals with naphthols was explored. As the results in Table 2 show, the reactions proceeded smoothly and the acetals with electron-donating substituents afforded higher levels of enantioselectivities (Table 2, entries 2–5) while acetals with electron-withdrawing groups in the benzene rings slightly lowered the enantioselectivity (Table 2, entries 6–9). *m*-Tolualdehyde dimethyl acetal produced the highest ee value (71%) with good 61% yield (Table 2, entry 3). *m*-Methoxybenzaldehyde dimethyl acetal afforded the highest yield of up to 68% (Table 2, entry 5). Similarly, 2-naphthaldehyde dimethyl acetal achieved a moderate 66% ee (Table 2, entry 10). To extend the scope of the naphthol, 6-bromo-2-naphthol, 1-naphthol and *m*-methoxyphenol were utilized in the reaction. The reaction proceeded with 2-naphthols (Table 2, entries 11–13). However, 1-naphthol completed the reaction very fast but with very low enantioselectivity (Table 2, entry 14). And *m*-methoxyphenol failed to give the chiral ether (Table 2, entry 15). When cinnamic aldehyde was used, the reaction became complicated and the desired product was not found (Table 2, entry 16).

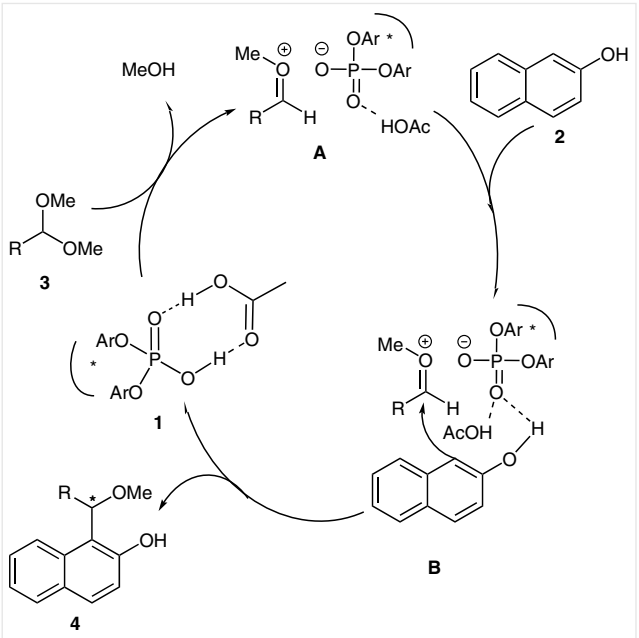
Table 2 Direct Asymmetric Substitute Reactions of Various Acetals with Naphthol



Entry	2	R	Yield (%)[a]	ee (%)[b]
1	2-naphthol (**2a**)	Ph (**3a**)	64	68
2	2-naphthol (**2a**)	*o*-MeC_6H_4 (**3b**)	58	55
3	2-naphthol (**2a**)	*m*-MeC_6H_4 (**3c**)	61	71
4	2-naphthol (**2a**)	*p*-MeC_6H_4 (**3d**)	54	63
5	2-naphthol (**2a**)	*m*-$MeOC_6H_4$ (**3e**)	68	63
6	2-naphthol (**2a**)	*o*-ClC_6H_4 (**3f**)	42	40
7	2-naphthol (**2a**)	*p*-ClC_6H_4 (**3g**)	55	58
8	2-naphthol (**2a**)	*p*-BrC_6H_4 (**3h**)	51	33
9	2-naphthol (**2a**)	*p*-FC_6H_4 (**3i**)	46	50
10	2-naphthol (**2a**)	2-naphthyl (**3j**)	44	66
11	6-bromo-2-naphthol (**2b**)	Ph (**3a**)	57	57
12	6-bromo-2-naphthol (**2b**)	*m*-MeC_6H_4 (**3c**)	58	66
13	6-bromo-2-naphthol (**2b**)	*m*-$MeOC_6H_4$ (**3e**)	54	66
14	1-naphthol (**2c**)	Ph (**3a**)	72	20
15	*m*-methoxyphenol (**2d**)	Ph (**3a**)	–[c]	–[c]
16	2-naphthol (**2a**)	styryl	–[c]	–[c]

[a] Isolated yield.
[b] Determined by chiral HPLC analysis.
[c] Not determined.

Regarding the reaction mechanism, we speculate that the acetal **3** first loses methanol catalyzed by the chiral phosphoric acid **1** to result in the reactive oxocarbonium intermediate **A**,[15] which is coupled with the anionic phosphoric acid **1**. The hydrogen atom of acetic acid forms H-bonding with the basic oxygen atom of the chiral phosphoric acid **1**, thus greatly increasing the catalyst acidity. The subsequent H-bonding interaction of basic oxygen atom of the chiral phosphoric acid **1** with the hydroxyl group of β-naphthol increases the nucleophilicity of β-naphthol. The nucleophilic attack of 2-naphthol to the oxocarbonium intermediate **A** yields the chiral ether **4** and the heterodimeric catalyst **1** is regenerated to catalyze the next cycle Friedel–Crafts reaction (Scheme 1).



Scheme 1 Proposed mechanism of the reaction

In summary, we have reported for the first time an effective asymmetric Friedel–Crafts reaction of the naphthol with acetals under mild reaction conditions in the catalysis of the chiral BINOL-based phosphoric acid in good yields and enantioselectivities.[16] A series of optically active ethers can be easily synthesized with this approach.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561279.

Reference and Notes

(1) L.Q. and P.W. contributed equally.

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(16) **General Catalytic Enantioselective Reaction of the Naphthol with Acetals**: Into a 5-mL dry round bottom flask containing a magnetic stirring bar were added the catalyst (0.04 mmol) and the naphthol (0.4 mmol) under argon. Anhydrous 1,2-dichloroethane (1 mL), acetals (0.2 mmol) and AcOH (0.04 mmol) were added sequentially at r.t. The reaction mixture was stirred at 35 °C until the reaction was complete (checked by TLC). Then the reaction was cooled to 0 °C and a few drops of sat. $NaHCO_3$ were added to quench the reaction. After extraction with CH_2Cl_2 (3 × 2 mL), the combined organic phases were dried with anhyd Na_2SO_4 and concentrated under vacuum to give the crude product. Finally purification by column chromatography afforded the expected chiral ethers.

1-[Methoxy(*o*-tolyl)methyl]naphthalen-2-ol (4b): white crystal; mp 85–87 °C; $[\alpha]_D^{20}$ +23 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.65 (s, 3 H), 3.60 (s, 3 H), 6.35 (s, 1 H), 6.88–6.90 (d, *J* = 6.0 Hz, 1 H), 6.97–7.01 (m, 1 H), 7.18–7.35 (m, 5 H), 7.41–7.43 (m, 1 H), 7.78–7.81 (m, 2 H), 9.23 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3, 58.2, 81.6, 119.4, 121.1, 123.0, 126.3, 126.8, 127.8, 128.8, 128.9, 130.3, 130.8, 154.9. HRMS (ESI, +ve): *m*/*z* [M – H] calcd for $C_{19}H_{17}O_2$: 277.1234; found: 277.1228. ee = 55%, determined by chiral HPLC with an OD-H column (hexane–*i*-PrOH, 99:1); flow rate = 1.0 mL/min; t_R = 7.26 (major), t_R = 8.97 (minor).

2-[Methoxy(phenyl)methyl]naphthalen-1-ol (4n): yellow oil; $[\alpha]_D^{20}$ +3 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.52 (s, 3 H), 5.57 (s, 1 H), 6.96–6.98 (d, *J* = 8.4 Hz, 1 H), 7.28–7.38 (m, 6 H), 7.46–7.47 (m, 2 H), 7.73–7.75 (m, 1 H), 8.29–8.31 (m, 1 H), 9.04 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 57.4, 87.6, 119.2, 122.3, 125.2, 125.4, 126.2, 126.4, 127.2, 127.4, 128.3, 128.6, 134.0, 140.0, 150.9. ee = 20%, determined by chiral HPLC with an OD-H column (hexane–*i*-PrOH, 99:1); flow rate: 1.0 mL/min; t_R = 8.70 (major), t_R = 12.30 (minor).