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Tetrahedron Letters 49 (2008) 1476–1479
Tetrahedron Letters

Organocatalytic enantioselective Friedel–Crafts alkylation of simple phenols with trifluoropyruvate

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Received 11 October 2007; revised 20 December 2007; accepted 25 December 2007
Available online 8 January 2008

Abstract

Enantioselective Friedel–Crafts alkylation of simple phenols (**4a**–**j**) with 3,3,3-trifluoropyruvate (**3**) was accomplished by using chiral cinchona alkaloid catalyst **2h** (10 mol %). High yields and enantioselectivities (71–94% ee) of the Friedel–Crafts alkylation products were obtained.

Keywords: Organocatalysis; Enantioselective Friedel–Crafts alkylation; Phenol; Trifluoropyruvate

Friedel–Crafts alkylation of aromatic and heteroaromatic compounds with carbonyls is one of the most important carbon–carbon bond forming reactions.[1] There have been tremendous progress in recent years with reactions now proceeding in an enantioselective manner, which can provide optically active aromatic compounds possessing biological and pharmaceutical activities. Both electron-rich aromatic and heteroaromatic compounds as well as less active aromatic compounds, for example, anisole derivatives have been shown to be good C-nucleophiles catalyzed by chiral Lewis acids.[2] In 1990 Erker reported the first example of the asymmetric Friedel–Crafts alkylation of 1-naphthol with pyruvate catalyzed by chiral zirconium complex.[3] However, since then, enantioselective Friedel–Crafts reactions of directly using phenols as C-nucleophiles have been less studied. It could be attributed to the relatively low reactivities of simple phenol compounds as C-nucleophiles and strong interaction of unprotected hydroxyl group with metallic catalysts as well as the difficulty in controlling stereochemistry of transition states.

Recently, organocatalysis for asymmetric synthesis has attracted considerable attention in terms of its unique properties.[4] Limited studies on organocatalytic enantioselective Friedel–Crafts alkylations were also reported. Among them, bifunctional cinchona alkaloid derivatives have been demonstrated to be efficient catalyst for the enantioselective Friedel–Crafts alkylation of indoles[5] and 2-naphthol.[6] However, to the best of our knowledge, the catalytic enantioselective Friedel–Crafts alkylation of phenol compounds, especially simple phenols is still a challenge and has not been reported up to now. We speculated that the use of organocatalysts would provide an opportunity to solve the problem encountered in the enantioselective Friedel–Crafts alkylation of phenols. To continue our interest in catalytic enantioselective Friedel–Crafts alkylation for generating optically active CF_3-containing compounds for biological application,[7] herein we would like to report an organocatalyzed enantioselective Friedel–Crafts alkylation of simple phenols with trifluoropyruvate under mild conditions.

Recently, we reported a highly enantioselective Friedel–Crafts alkylation of aromatic ether, for example, anisole, with trifluoropyruvate catalyzed by chiral (4*R*,5*S*)-BOX-DiPh-Cu(OTf)$_2$ (**1**) to give the product in 90% yield with

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0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.12.129

up to 93% ee.[8] However, when the chiral catalyst **1** was employed in the reaction of phenol **4a** with ethyl 3,3,3-trifluoropyruvate **3** at −25 °C for 48 h, only trace amount of product **5a** was detected by TLC (Fig. 1, Scheme 1). As a result, we focused on the enantioselective Friedel–Crafts alkylation catalyzed by organocatalyst. Thus, natural cinchona alkaloids such as cinchonidine (**2a**), quinine (**2b**), and quinidine (**2c**) served as bifunctional chiral organocatalyst in the Friedel–Crafts alkylation of 2,6-dimethylphenol **4b** with **3** in dichloromethane (DCM) under the given conditions, respectively (Table 1). By using the standard conditions (10 mol % catalyst loading), product **5b**, ethyl 3,3,3-trifluoro-2-hydroxy-2-(4-hydoxy-3,5-dimethylphenyl) propanoate, was obtained in good yields (65–96%). Although it was shown by Torok et al.[5a] that **2a** and **2b** (or **2c**) are efficient catalysts for the highly enantioselective reaction of indoles with **3**, only modest enantioselectivities were obtained in the reaction of phenol compound **4b** with **3** (36–44% ee) (Table 1, entries 1 and 2). To improve the enantioselectivity, a series of cinchona alkaloid derivatives (**2d–i**) were prepared (Fig. 1), and employed as catalysts in the reaction of **4b** with **3**. If both 6′-OH and 9-OH were blocked by methyl and benzyl groups, respectively, lower ability of catalyst (**2d**) and poor enantioselectivity of product **5b** were observed (entry 4).

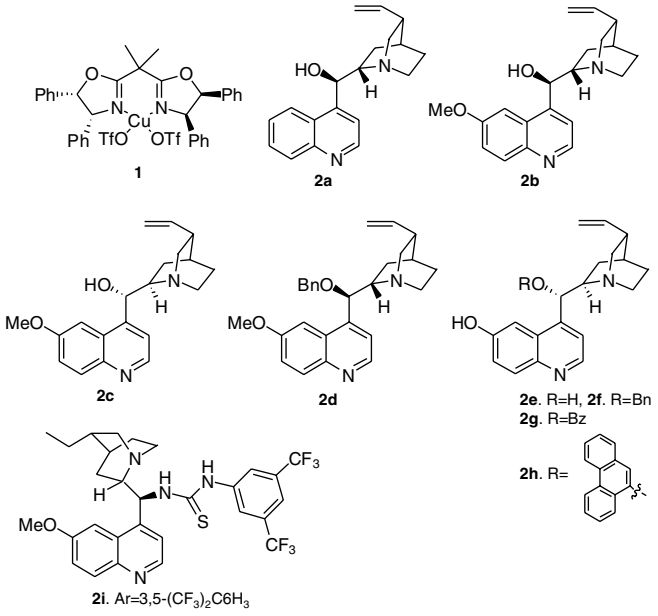
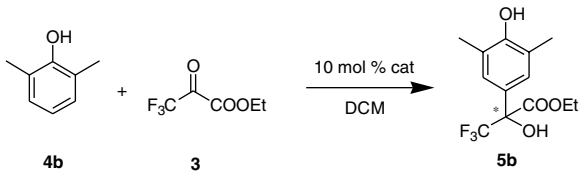


Fig. 1. Chiral catalysts **1** and **2a–i**.

Scheme 1.

Table 1
Screening catalyst by reaction of **3** with **4b**



Entry	Cat[a]	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**2a**	25	23	96	44
2	**2b**	25	23	85	36
3	**2c**	25	24	81	−30
4	**2d**	25	24	65	15
5	**2e**	−10	24	85	−4
6	**2f**	−10	16	95	72
7	**2g**	−10	24	85	58
8	**2h**	−10	16	88	92
9	**2i**	−10	48	30	−11

[a] Catalyst loading: 10 mol %.
[b] Isolated yield.
[c] Determined by chiral HPLC.

Furthermore, for unprotected 6′-OH and 9-OH, catalyst **2e** afforded very low enantioselectivity (entry 5). The poor enantioselectivity could be due to the fact that both hydroxyl groups could participate in forming hydrogen bonding with substrates and resulted in the loss of selectivity. When 6′-OH was free and 9-OH was blocked (**2f–h**), the ee values of **5b** increased significantly. To our delight, with a bulky phenanthrene (PHN) group in 9-OR (**2h**) the enantioselectivity of **5b** reached 92% ee (entry 8).[9] An attempt to increase the enantioselectivity by introducing a thiourea group at 9-position (**2i**) was not successful (entry 9).

When the catalyst loading was reduced from 10 mol % to 5 mol %, 2 mol % and 1 mol %, respectively, the yields decreased noticeably and the ee lowered slightly (Table 2, entries 1–3). The reaction temperature also affected the enantioselectivities. At 0 °C, the reaction between **4b** and **3** gave the product **5b** with 84% ee, while the enantioselectivity was increased to 92% at −10 °C and 94% at −40 °C, with a prolonged reaction time (entries 4–6).

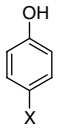
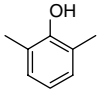
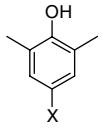
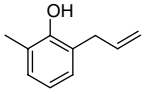
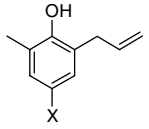
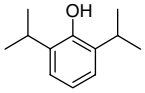
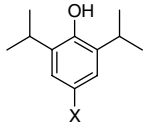
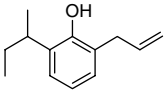
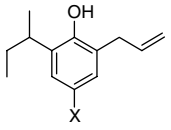
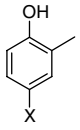
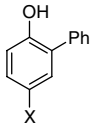
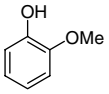
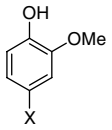
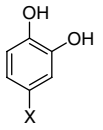
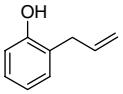
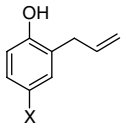
Subsequently, various phenols (**4a–j**) were reacted with **3** in the presence of chiral organocatalyst **2h** (10 mol %) in DCM under given reaction conditions (Scheme 1, Table 3).[10] Moderate to high yields (58–96%) and high enantio-

Table 2
Effects of temperature and catalyst loading on the reaction of **4b** and **3**

Entry	Cat[a] (mol %)	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	5	−10	24	86	88
2	2	−10	24	76	85
3	1	−10	48	21	83
4	10	0	6	96	84
5	10	−10	16	88	92
6	10	−40	72	78	94

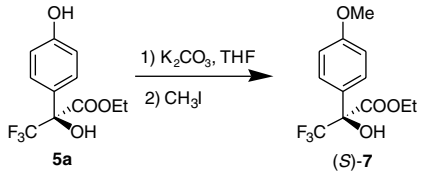
[a] Catalyst: **2h**.
[b] Isolated yield.
[c] Determined by chiral HPLC.

Table 3
Organocatalytic enantioselective Friedel–Crafts alkylation of phenols (**4a**–**j**) with **3**[a]

Entry		Phenol	Temp (°C)	Time (h)		Product[b]	Yield[c] (%)	ee[d] (%)
1	**4a**		−25	72	**5a**		76	86
2	**4b**		−40	72	**5b**		78	94
3	**4c**		−20	24	**5c**		83	88
4	**4d**		−30	72	**5d**		75	86
5	**4e**		−20	24	**5e**		96	81
6	**4f**		−10	60	**5f**		88	86
7	**4g**		−10	68	**5g**		67	75
8	**4h**		−10	60	**5h**		87	71
9	**4i**		−10	48	**5i**		82	78
10	**4j**		−20	24	**5j**		58	91

[a] Catalyst: **2h** (10 mol %) in DCM.
[b] X: $F_3CC(OH)CO_2Et$.
[c] Isolated yield.
[d] Determined by chiral HPLC.

selectivities (71–94% ee) were obtained in each case (Table 3). The ^1H NMR spectra of the products showed that the Friedel–Crafts alkylation of phenols has excellent para regioselectivity, even in the case of 2-methoxyphenol **4h**, the alkylation reaction occurred at the *para*-position of hydroxyl group exclusively, but not at the *para*-position of methoxyl group. On the other hand, the reaction between anisole (**6**) with **3** did not proceed under the same reaction conditions, and the starting materials were recovered completely.



Scheme 2.

To assign the absolute configuration, **5a** was converted to corresponding methylation product **7** under mild conditions (Scheme 2). Compared the rotation sign of **7** ($[\alpha]_D$ +17.1) with the known compound,[8] the absolute configuration of **5a** was assigned as *S*.

In conclusion, an enantioselective Friedel–Crafts alkylation of simple phenols with trifluoropyruvate catalyzed by cinchona alkaloid derivatives was achieved. The method provides a practical synthetic approach to optically active CF_3-containing α-hydoxyl-α-aryl-carboxylate compounds bearing functional phenolic hydroxyl groups.

Acknowledgments

We thank the National Natural Science Foundation of China and The Chinese Academy of Sciences for financial support.

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10. *Typical experimental procedure*: To a solution of **2h** (7.2 mg, 0.015 mmol) in freshly distilled CH_2Cl_2 (0.3 mL) phenol **4a** (14.1 mg, 0.15 mmol) was added at ambient temperature, followed by stirring at −25 °C for 10 min. Ethyl trifluoro- pyruvate **3** (24 μL, 30.6 mg, 0.18 mmol) was injected under Ar atmosphere. The mixture was stirred at the same temperature for 72 h. The mixture was purified by flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 8:1 v/v) to give **5a** as a colorless oil (30.1 mg, 76% yield with 86% ee).