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Chiral Brønsted-Acid-Catalyzed Enantioselective Arylation of Ethyl Trifluoroacetoacetate and Ethyl Trifluoropyruvate

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Chiral phosphoric acid was found to be an effective organocatalysts for the direct enantioselective arylation of ethyl 4,4,4-trifluoroacetoacetate (ETFAA). A series of chiral trifluoromethyl-substituted tertiary alcohols were obtained in moderate to high yields with up to 78% *ee*. Several desired products were obtained with excellent optical purities after a single recrystallization. This method was also extended to ethyl trifluoropyruvate, which is complementary to systems catalyzed by Lewis acids and cinchona alkaloids.

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Introduction

The asymmetric synthesis of chiral trifluoromethyl-substituted secondary and tertiary alcohols has become the subject of recent interest[1] due to the occurrence of this moiety found in chiral reagents[2a] and in a number of biologically active compounds including anticancers,[2b] anticonvulsants,[2c] proteinase inhibitors,[2d] anti-HIV agents[2e] as well NK-1 receptor antagonists[2f] (Figure 1). Thus, several approaches for the direct trifluoromethylation of carbonyl compounds with Ruppert–Prakash reagent[3] have been designed toward their asymmetric synthesis.[4] However, only the limited examples have addressed high enantioselectivities (exceeding 90% *ee*). An alternative strategy for the construction of trifluoromethyl-substituted secondary and tertiary alcohols would be the asymmetric addition of carbon nucleophiles to prochiral trifluoromethyl carbonyl compounds.[5] But few methods allow expedient preparation of a wide series of derivatives from readily available starting materials. For example, some elegant methods have been developed for the asymmetric catalytic addition of carbon nucleophiles to trifluoroacetaldehyde and hemiacetal (**A**),[6] trifluoropyruvates (**B**),[7] and simple trifluoromethyl ketones (**C**).[8] However,

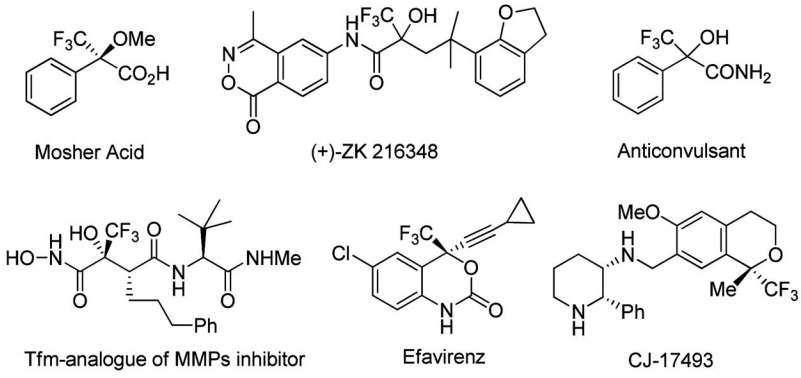

Figure 1. Chiral trifluoromethyl-substituted tertiary alcohols.

to the best of our knowledge, these otherwise extensively studied reactions have not been successfully applied to 4,4,4-trifluoroacetoacetates (**D**) (Figure 2).

For the past few years, enantioselective organocatalysis has become one of the most efficient approaches for the preparation of chiral compounds.[9] In this context, a vari-

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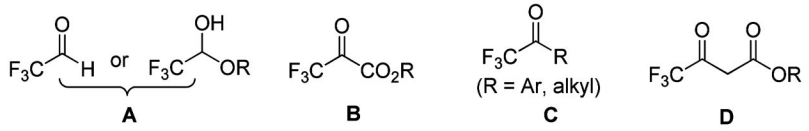


Figure 2. Several prochiral trifluoromethyl carbonyl compounds.

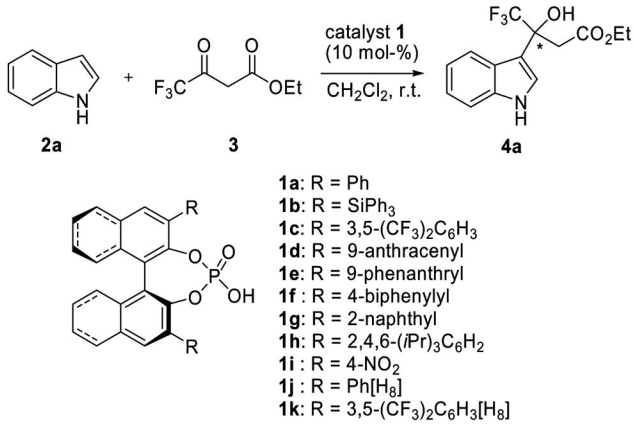
ety of phosphoric acids have been shown to be excellent nonmetal chiral organocatalysts for the asymmetric activation of various substrates, such as imines, enamides, *meso*-aziridines as well as ketones.[10] Recently, we have demonstrated that chiral phosphoric acids can catalyze some arylation reactions of trifluoroacetaldimines (generated in situ) and simple trifluoromethyl ketones with good to excellent enantioselectivities.[11] As a part of our ongoing studies, we would like to report our preliminary results on chiral Brønsted-acid-catalyzed enantioselective direct arylation of ethyl 4,4,4-trifluoroacetoacetate (ETFAA) and ethyl trifluoropyruvate.

Results and Discussion

4,4,4-Trifluoroacetoacetates (TFAA) are commercially available candidates for the construction of chiral trifluoromethyl tertiary alcohols. In contrast to the wide use of the similar structure such as trifluropyruvates,[7] TFAA are less applicable in asymmetric synthesis due to its significantly weaker electrophilic reactivity.[12] In addition, rapid formation of inacitive β-enolate chelate complexes limited the utilization of TFAA in metal-mediated asymmetric transformations.[12c–12d] We hypothesized that chiral Brønsted acids could be suitable organocatalysts for the activation of TFAA. Considering our previous work, we chose to begin an evaluation of BINOL-derived phosphoric acids **1** in the asymmetric arylation of ETFAA **3** with indole **2a** (Table 1). The results of our catalyst screening showed that phosphoric acid **1** with bulky 2,4,6-triisopropylphenyl groups at the 3,3′-positions of the binaphthyl scaffold gave the desired product **4a** in quantitative yield with 64% *ee* (Table 1, Entries 1–11). Moreover, the aldol self-condensation of ETFAA and the diarylation of ETFAA were not observed. Subsequently, this arylation reaction was conducted in different solvents with **1h** as catalyst (Table 1, Entries 12–16). Dichloromethane was found to be the best with respect to catalytic activity and asymmetric induction. When the catalyst loading was decreased to 5 mol-%, the yield of 66% was obtained with the prolonged time (Entry 17). However, no obvious variation in the stereoselectivity was observed by increasing the catalyst loading (Entry 18). Substantial changes of the reaction temperature did not have any significant effects on the enantioselectivity (Entries 19 and 20).

With the optimal conditions in hand, the scope of the organocatalytic arylation of ETFAA **3** was explored with a series of indoles **2**. As indicated in Table 2, the halogenated indoles gave the corresponding products in low to good yields (36–89%) with moderate enantioselectivities(55–64%) (Entries 2–5). It is surprising that no product was observed when 5-methoxycarbonylindole was employed. Apparently, the electron-withdrawing substituent could decrease the nucleophilicity of this substrate (Entry 6). Several alkyl and alkoxyl groups can be readily tolerated on the phenyl rings of indoles (Entries 7–10). Excellent yields (97–99%) and good enantioselectivities (65–78% *ee*) were obtained. However, 2-methylindole provided the desired product with low enantioselectivity (26% *ee*) (Entry 11). In addition, several desired products were obtained with excellent optical purities after single recrystallization from

Table 1. Optimization of arylation reaction conditions.



Entry[a]	Catalyst	Solvents	*t* [h]	% Yield[b]	% *ee*[c]
1	**1a**	CH_2Cl_2	240	60	15
2	**1b**	CH_2Cl_2	240	66	8
3	**1c**	CH_2Cl_2	240	39	2
4	**1d**	CH_2Cl_2	144	40	7
5	**1e**	CH_2Cl_2	144	67	16
6	**1f**	CH_2Cl_2	144	35	18
7	**1g**	CH_2Cl_2	144	58	15
8	**1h**	CH_2Cl_2	96	99	64
9	**1i**	CH_2Cl_2	240	49	3
10	**1j**	CH_2Cl_2	240	86	14
11	**1k**	CH_2Cl_2	240	45	15
12	**1h**	toluene	96	70	56
13	**1h**	Et_2O	96	83	36
14	**1h**	$CHCl_3$	96	87	60
15	**1h**	DCE	96	94	64
16	**1h**	CH_3CN	96	65	47
17[d]	**1h**	CH_2Cl_2	120	66	61
18[e]	**1h**	CH_2Cl_2	96	99	65
19[f]	**1h**	CH_2Cl_2	72	99	60
20[g]	**1h**	CH_2Cl_2	120	54	67

[a] The reaction employed a molar ratio of **2**/**3** = 1:1.2 (equiv.), with a concentration of **2** being 0.56 M. [b] Isolated yield. [c] Enantiometric excess was determined by chiral HPLC analysis. [d] 5 mol-% of catalyst was used. [e] 20 mol-% of catalyst was used. [f] The reaction was performed at 40 °C. [g] The reaction was performed at 0 °C.

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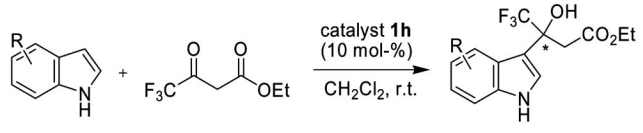
EtOAc/hexane (Entries 2, 8 and 10). As far as we know this is the first example of catalytic asymmetric transformation of the promising prochiral ETFAA for the construction of chiral trifluoromethyl-substituted tertiary alcohols.

Table 2. Scope of the enantioseletive Brønsted acid catalyzed arylation of ETFAA **3** with various indoles **2**.



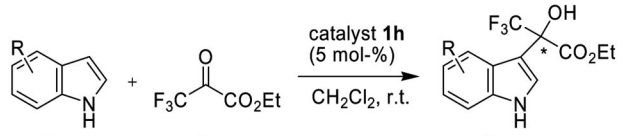
2 **3** **4**

Entry[a]	R	4	*t* [h]	% Yield [b]	% *ee*[c]
1	H	**4a**	96	99	64
2	5-F	**4b**	120	89	64 (95)[d]
3	5-Cl	**4c**	120	66	61
4	5-Br	**4d**	120	36	61
5	6-Cl	**4e**	120	56	55
6	5-MeO_2C	**4f**	168	no reaction	–
7	5-Me	**4g**	96	99	65
8	5-MeO	**4h**	96	97	77 (99.9)[d]
9	7-Me	**4i**	76	99	74
10	7-Et	**4j**	76	99	78 (99.5)[d]
11	2-Me	**4k**	96	98	26

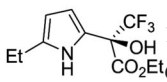
[a] The reaction employed a molar ratio of **2/3** = 1:1.2 (equiv.), the concentration of **2** was 0.56 M. [b] Isolated yield. [c] Enantiometric excess was determined by chiral HPLC analysis. [d] The results in parentheses were obtained after single recrystallization.

This asymmetric protocol was further extended to prochiral ethyl trifluoropyruvate. It is well known that trifluoropyruvate can be used for the enantioselective hydroalkylation of indoles catalyzed by chiral Lewis acids and cinchona alkaloids, however, there is no example available on the use of chiral Brønsted acid to fulfil such asymmetric transformation. Table 3 illustrates the results of chiral Brønsted-acid-catalyzed arylation of ethyl trifluoropyruvate **5** with indoles **2**. The desired products were obtained in almost quantitative yields. However, all cases provided low to moderate *ee* values (20–62%) (Entries 1–10). It should be noted that even lowering of the temperature did not improve the promotion of enantioselectivity.[13] Our attempts to improve the optical purity of products by recrystallization were unsuccessful. For example, both enantiomers of the trifluoromethyl tertiary alcohol **6a** were characterized together by X-ray crystallography (Figure 3).[14] It is noteworthy that the reaction did work well with 2-ethylpyrrole under the current reaction conditions to afford the regioselective product (reaction in 5-position of 2-ethylpyrrole) in 99% yield with 31% *ee* (Entry 11).

Table 3. Asymmetric arylation of ethyl trifluoropyruvate **5** with chiral Brønsted acid catalyst **1h**.



2 **5** **6**

Entry[a]	R	6	*t* [h]	% Yield[b]	% *ee*[c]
1	H	**6a**	10	99	34
2	5-F	**6b**	10	99	26
3	5-Cl	**6c**	10	99	30
4	5-Br	**6d**	12	96	30
5	6-Cl	**6e**	10	98	29
6	5-MeO_2C	**6f**	12	91	48
7	5-Me	**6g**	10	99	20
8	5-MeO	**6h**	10	99	33
9	7-Me	**6i**	6	99	36
10	7-Et	**6j**	6	99	62
11[d]		 **6k**	12	99	31

[a] The reaction employed a molar ratio of **2/5** = 1:1.2 (equiv.), with a concentration of **2** being 0.56 M. [b] Isolated yield. [c] Enantiometric excess was determined by chiral HPLC analysis. [d] The reaction was performed at 0 °C.

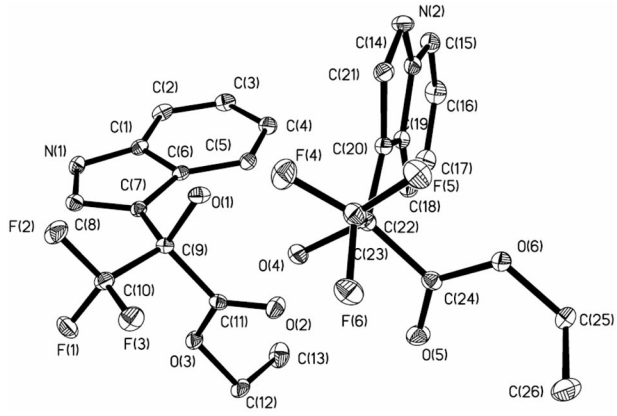


Figure 3. X-ray structure of both enantiomers **6a**.

Conclusions

We have developed an asymmetric arylation reaction of ethyl 4,4,4-trifluoroacetoacetate with indoles by using chiral phosphoric acids as efficient organocatalysts. In most cases, chiral trifluoromethylated tertiary alcohols were obtained in moderate to high yields with good enantioselectivities (55–78% *ee*). Several desired products were obtained with excellent optical purities (95–99.9% *ee*) after a single recrystallization. Furthermore, by extending this protocol to ethyl trifluoropyruvate, the direct arylation reactions proceeded well to afford the desired prodcuts in quantitative yields with 20–62% *ee*. Further efforts in our laboratory will be mainly directed toward improving the selectivity and synthetic application.

Experimental Section

General Procedure for the Catalytic Asymmetric Friedel–Crafts Reactions of Indoles 2 with Ethyl 4,4,4-Trifluoroacetoacetate (ETFAA) 3 or Ethyl Trifluoropyruvate 5: To a flame-dried reaction tube was added indole (0.17 mmol), ethyl 4,4,4-trifluoroacetoacetate

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(ETFAA) (0.21 mmol), a chiral phosphoric acid (0.017 mmol, 10 mol-%), and solvent (CH_2Cl_2, 0.3 mL) at room temperature. After the reaction was completed (monitored by TLC), the crude product was purified directly by flash column chromatography with ethyl acetate/petroleum ether (1:10 to 1:5) to afford the desired products **4a**–**4k** and **6a**–**6k**. The enantiomeric excess was determined by chiral HPLC on chiralcel AD-H or OD-H columns.

Supporting Information (see also the footnote on the first page of this article): Procedures for enantioselective arylation of 4,4,4-trifluoroacetoacetate and trifluoropyruvate; NMR spectra and HPLC behavior of the products.

Acknowledgments

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[13] The **1h**-catalyzed Friedel–Crafts reaction of indole **2** with ethyl trifluoropyruvate **5** was tested at –20 °C; 25% *ee* was observed.

[14] CCDC-720744 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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