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Chiral Brønsted acid-catalyzed regio- and enantioselective arylation of α,β-unsaturated trifluoromethyl ketones

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ABSTRACT

The interesting examples of chiral phosphoric acid-catalyzed regio- and enantioselective arylation of α,β-unsaturated trifluoromethyl ketones were reported. The reaction proceeded well and the desired products were obtained in good yields (up to 99%) with moderate to good enantioselectivities (up to 88% ee). Several desired products were obtained with excellent optical purities after a single recrystallization. Subsequent reduction of enantiopure products with $NaBH_4$ afforded two diastereomers of chiral trifluoromethyl-substituted secondary alcohols with high enantioselectivities (98% ee).

As the most electronegative element, fluorine atom has great influence on the properties and the reactivity of the molecules.[1] Among fluorinated compounds, trifluoromethyl-substituted molecules have gained growing interest during the past decades.[2,3] Compared with non-fluorinated analogues, the introduction of a trifluoromethyl group with strong electron-withdrawing ability can lead to significant changes in physical, chemical, and biological properties of the molecules. Therefore, the development of asymmetric approaches for the synthesis of trifluoromethyl-containing compounds has been such an important object for organic chemists.[4]

Indole represents an attractive structural motif in a variety of natural bioactive products and therapeutic agents.[5,6] In recent years, particular attention has been paid to the enantioselective reactions of indoles with various electrophilic substrates to prepare chiral indole-derivatives. For example, many reports involved chiral metal-complex or small organic molecule-catalyzed asymmetric Michael additions of indoles to α,β-unsaturated carbonyl compounds.[6–18] However, to the best of our knowledge, these otherwise extensively studied reactions have not been successfully applied to α,β-unsaturated trifluoromethyl ketones.[19] BINOL-derived phosphoric acids have been shown to be excellent nonmetal chiral organocatalysts for vast asymmetric transformations.[20–23] Recently, we have demonstrated that chiral phosphoric acids can catalyze several arylation reactions of trifluoroacetaldimines, trifluoromethyl ketones, ethyl 4,4,4-trifluoroacetoacetate, and ethyl trifluoropyruvate with electron-rich arenes with good to excellent enantioselectivities.[24–27] Herein, we would like to report our work about organocatalyzed regio- and enantioselective arylation of α,β-unsaturated trifluoromethyl ketones with indoles.

Based on our previous work, the asymmetric arylation of 1,1,1-trifluoro-4-phenyl-3-buten-2-one **3a** with indole **2a** was chosen as the model reaction for screening the BINOL-derived phosphoric acid catalysts **1** (Fig. 1). Interestingly, 3-alkylated product **4a** of indole was obtained (Table 1, entries 1–14). Other adducts, such as 1,1,1-trifluoro-4-(1*H*-indol-2-yl)-4-phenylbutan-2-one, 1,1,1-trifluoro-2-(1*H*-indol-3-yl)-4-phenylbutan-2-ol, and 1,1,1-trifluoro-2-(1*H*-indol-2-yl)-4-phenylbutan-2-ol, were not observed in the reaction. The best result was obtained using phosphoric acid **1f** with 9-anthracenyl groups at the 3,3′-positions of the binaphthyl scaffold, which gave the desired product **4a** in 97% yield and 48% ee (Table 1, entry 6). Subsequently, the effect of solvents and reaction temperature was examined in the model reaction using **1f** as catalyst (Table 1, entries 16–22). The reaction proceeded with high conversion and moderate enantioselectivities in chlorinated alkanes (Table 1, entries 6, 20 and 21), while higher enantioselectivity was observed in CH_3CN but with a low yield (Table 1, entry 19). Finally, the mixture of $ClCH_2CH_2Cl/CH_3CN$ (1:1) was proved to be a superior co-solvent in which the desired product **4a** was obtained in 96% yield with 53% ee (Table 1, entry 22). When the reaction temperature was lowered to −20 °C, the enantioselectivity could be improved to 72% with the prolonged reaction time (Table 1, entry 24).

With the optimal conditions (10 mol % **1f** as the catalyst, at −20 °C in $ClCH_2CH_2Cl/CH_3CN$ 1:1) in hand, the scope of the organocatalytic enantioselective arylation of α,β-unsaturated trifluoromethyl ketones **3** was explored with indoles **2** (Table 2).[28] In most

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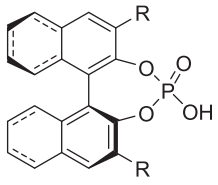
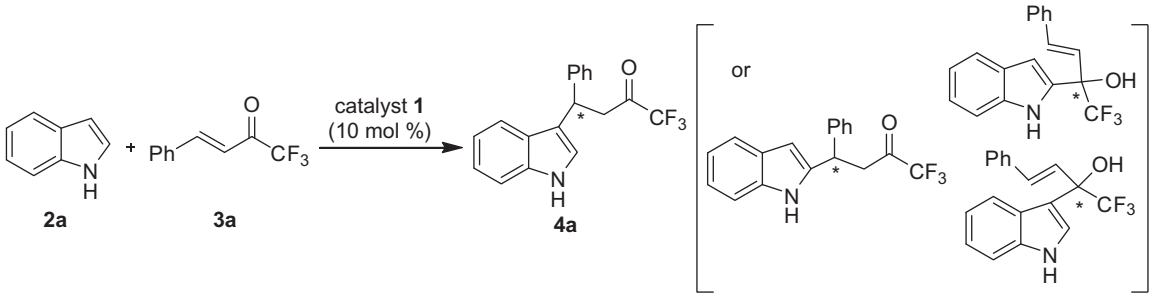


1a: R = H
1b: R = Ph
1c: R = $SiPh_3$
1d: R = 3,5-$(CF_3)_2C_6H_3$
1e: R = 4-$NO_2C_6H_4$
1f: R =9-Anthracenyl
1g: R = 9-Phenanthryl
1h: R = 4-Biphenyl
1i: R = 2-Naphthyl
1j: R = 2,4,6-$(i\text{-}Pr)_3C_6H_2$
1k: R = 4-Ad-2,6-$(i\text{-}Pr)_2C_6H_2$
1l: R = 1-Naphthyl
1m: R = Ph[H_8]
1n: R = 3,5-$(CF_3)_2C_6H_3$[H_8]

Figure 1.

Table 1
Optimization of reaction conditions



Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield[a] (%)	ee[b] (%)
1	**1a**	CH_2Cl_2	25	36	52	5
2	**1b**	CH_2Cl_2	25	36	84	31
3	**1c**	CH_2Cl_2	25	36	30	7
4	**1d**	CH_2Cl_2	25	24	66	9
5	**1e**	CH_2Cl_2	25	24	70	8
6	**1f**	CH_2Cl_2	25	24	97	48
7	**1g**	CH_2Cl_2	25	36	84	17
8	**1h**	CH_2Cl_2	25	24	70	25
9	**1i**	CH_2Cl_2	25	18	95	12
10	**1j**	CH_2Cl_2	25	24	50	8
11	**1k**	CH_2Cl_2	25	24	84	23
12	**1l**	CH_2Cl_2	25	36	72	27
13	**1m**	CH_2Cl_2	25	71	58	23
14	**1n**	CH_2Cl_2	25	36	91	3
15	**1f**	Toluene	25	24	87	24
16	**1f**	Et_2O	25	24	85	17
17	**1f**	THF	25	168	38	37
18	**1f**	1,4-Dioxane	25	72	17	24
19	**1f**	CH_3CN	25	72	22	60
20	**1f**	$CHCl_3$	25	24	90	38
21	**1f**	$ClCH_2CH_2Cl$	25	18	97	51
22	**1f**	$ClCH_2CH_2Cl/CH_3CN$	25	24	96	53
23	**1f**	$ClCH_2CH_2Cl/CH_3CN$	0	72	71	49
24	**1f**	$ClCH_2CH_2Cl/CH_3CN$	-20	120	85	72

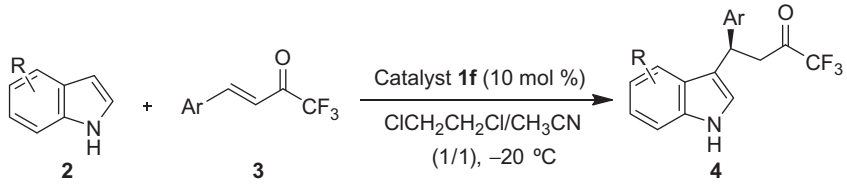
[a] Isolated yield.
[b] The ee was determined by chiral HPLC analysis.

cases, α,β-unsaturated trifluoromethyl ketones bearing either electron-withdrawing groups or electron-donating groups gave the corresponding products in good yields (80–99%) with good enantioselectivities (56–88%) (Table 2, entries 1–9). However, when 1,1,1-trifluoro-4-biphenyl-3-buten-2-one was employed as a substrate, the desired product was obtained in a low yield. Probably, the poor solubility in the mixed solvents decreased the reactivity of this substrate (Table 2, entry 10). Next, several indoles were probed (Table 2, entries 11–14). The reactions took place in good yields (83–93%) with moderate to good enantioselectivities (42–88% ee). 2-Methylindole provided the desired product with low enantioselectivity (18% ee) (Table 2, entry 14). It was noteworthy that several desired products could be obtained with excellent optical purities after single recrystallization from CH_2Cl_2/hexane (Table 2, entries 1, 4, and 8).

These adducts are useful synthetic intermediates and can be readily transformed into trifluoromethyl-substituted secondary alcohols. For example, direct reduction of enantioriched **4a** in the presence of $NaBH_4$ gave trifluoromethylated syn- and anti-alcohols (1:1 dr), which were easily isolated through silica gel column chromatography in 68% overall yield with excellent enantiomeric purities (98% ee) (Scheme 1).[29]

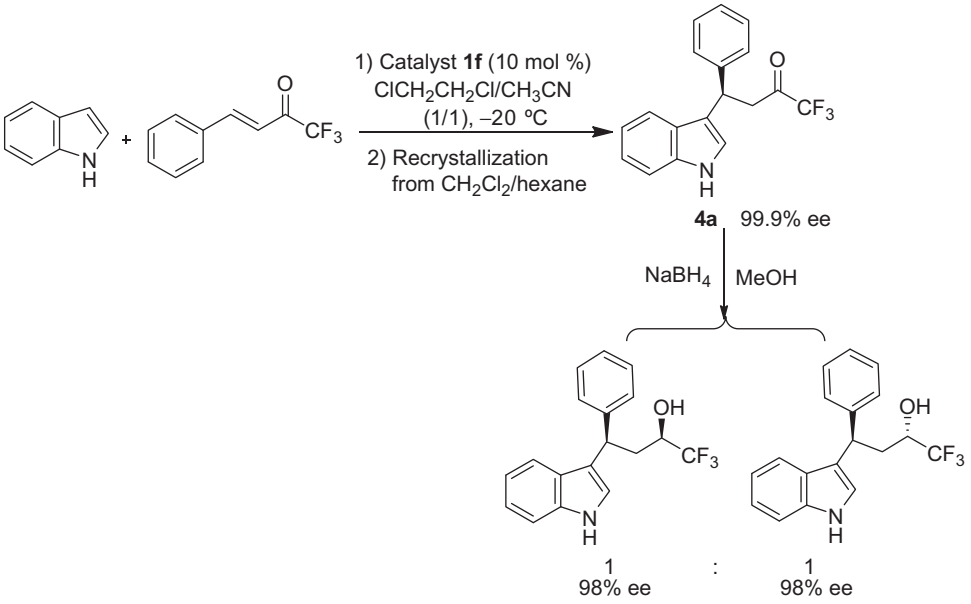
In summary, we have developed an asymmetric arylation reaction of α,β-unsaturated trifluoromethyl ketones with indoles by using chiral phosphoric acids as efficient organocatalysts. In most cases, the transformations proceeded well in good yields (up to 99%) with moderate to good enantioselectivities (up to 88% ee). Several desired products were obtained with excellent optical purities (98–99.9% ee) after a single recrystallization. Moreover, the arylated products could be transformed into two diastereomers

Table 2
Scope of chiral Brønsted acid-catalyzed arylation of α,β-unsaturated trifluoromethyl ketones



Entry	2	Ar	Time (h)	Yield[a] (%)	ee[b] (%)
1	Indole	C_6H_5	120	85	72 (99.9)[c]
2	Indole	*p*-MeC_6H_4	72	87	63
3	Indole	*o*-MeC_6H_4	72	97	56
4	Indole	*p*-$MeOC_6H_4$	72	92	60 (98)[c]
5	Indole	3,5-$Me_2C_6H_3$	96	99	66
6	Indole	1-Naphthyl	72	89	79
7	Indole	2-Naphthyl	72	80	73
8	Indole	4-BrC_6H_4	72	86	76 (98)[c]
9	Indole	3,5-$(CF_3)_2C_6H_3$	80	99	88
10	Indole	4-Biphenyl	120	25	63
11	5-Me-indole	3,5-$(CF_3)_2C_6H_3$	72	85	62
12	7-Me-indole	3,5-$(CF_3)_2C_6H_3$	72	93	88
13	5-Cl-indole	3,5-$(CF_3)_2C_6H_3$	72	85	42
14	2-Me-indole	3,5-$(CF_3)_2C_6H_3$	72	83	18

[a] Isolated yield.
[b] The ee was determined by chiral HPLC analysis. The absolute configuration was assigned according to Ref. 19.
[c] The results in parentheses were obtained after a single recrystallization.



Scheme 1.

of chiral trifluoromethyl-substituted secondary alcohols with high enantioselectivities (98% ee). Further efforts in our laboratory will be mainly directed toward improving the selectivity and synthetic application.

Acknowledgments

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28. *General procedure for catalytic asymmetric arylation of α,β-unsaturated trifluoromethyl ketones with indole*: To a Schlenk tube were added indole **2a** (0.15 mmol), unsaturated trifluoromethyl ketone **3a** (0.18 mmol), chiral phosphoric acid (0.015 mmol), and solvent ($ClCH_2CH_2Cl/CH_3CN$ = 1:1, 0.4 mL). After the solution was stirred for 120 h, the crude product was purified directly by flash column chromatography with ethyl acetate/petroleum ether (1:20 to 1:7) to afford the desired product **4a**. 85% yield, mp: 93–98 °C; $[\alpha]_D^{20}$ −6.3° (*c* 1.0, $CHCl_3$) [lit.[19] $[\alpha]_D^{rt}$ +7.96 (*c* 1.02, $CHCl_3$, >99% ee)]; 72% ee, [Daicel Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, 0.8 mL/min, 254 nm, T_R (minor) = 19.06 min, T_R (major) = 28.26 min]; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 3.47–3.52 (dd, *J* = 18.0 Hz, 1H, CH_2), 3.60 (dd, *J* = 18.0 Hz, 1H, CH_2), 4.96 (t, *J* = 7.0 Hz, 1H, CH), 6.96 (m, 1H), 7.06–7.09 (t, *J* = 7.0 Hz, 1H), 7.18–7.26 (m, 2H), 7.29–7.36 (m, 5H), 7.46–7.46 (d, *J* = 8 Hz, 1H), 8.04 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 37.1, 43.2, 77.3, 111.5, 118.1, 119.4, 119.9, 121.4, 122.7, 126.5, 127.1, 127.8, 128.9, 136.8, 142.8, 190; IR (KBr) ν (cm^{-1}) 3400, 2923, 2357, 1762, 1618, 1459, 1128, 1042, 812, 735, 696, 586, 418; MS (ESI) *m*/*z* 316.11 $[M-H]^-$.
29. *General procedure for the reduction of arylated product*: A mixture of $NaBH_4$ (0.3 mmol) and optically pure **4a** (0.1 mmol, >99.9% ee) in methanol (3 mL) was stirred 24 h under air (monitored by TLC). The diastereoisomers were purified directly by flash column chromatography with ethyl acetate/petroleum ether (1:20 to 1:10) to afford the desired product (anti/syn = 1:1). Total yield: 68%. Diastereomer-1: 98% ee [Daicel Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, 0.8 mL/min, 254 nm; T_R (minor) = 18.078 min, T_R (major) = 33.526 min]. $[\alpha]_D^{20}$ +21.2 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.30 (s, 1H, OH), 2.28–2.32 (m, 1H, CH_2), 2.55–2.61 (m, 1H, CH_2), 4.00 (dd, *J* = 7.5 Hz, 1H, CH), 4.60 (dd, *J* = 11.5, 1H, CH), 7.07–7.10 (m, 2H), 7.19–7.22 (m, 2H), 7.28–7.36 (m, 5H), 7.55–7.56 (d, *J* = 7.5 Hz, 1H), 8.08 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 35.5, 38.3, 63.6, 77.2, 111.3, 119.7, 121.0, 122.5, 127.0, 128.3, 129.0, 136.7, 142.9. IR (KBr) ν (cm^{-1}) 3421, 3062, 2366, 1618, 1454, 1378, 1157, 1009, 778, 522, 492. MS (ESI) *m*/*z* 318.29 $[M-H]^-$. Diastereomer-2: 98% ee. [Daicel Chiralcel OD-H, Hexane/*i*-PrOH = 90:10, 0.8 mL/min, 254 nm, T_R (minor) = 23.033 min, T_R (major) = 49.138 min]. $[\alpha]_D^{20}$ +20.3 (*c* 1.0, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.65 (s, 1H, OH), 2.37–2.42 (m, 1H, CH_2), 2.45–2.49 (m, 1H, CH_2), 3.78 (dd, *J* = 7.5 Hz, 1H, CH), 4.56 (dd, *J* = 11.5, 1H, CH), 7.01–7.07 (m, 2H), 7.17–7.26 (m, 2H), 7.31–7.37 (m, 5H), 7.46–7.48 (d, *J* = 8.0 Hz, 1H), 7.98 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 36.3, 38.1, 69.3, 77.5, 111.5, 117.6, 119.5, 119.9, 121.6, 122.6, 126.6, 127.1, 128.8, 136.7, 144.7. IR (KBr) ν (cm^{-1}) 3425, 3060, 2365, 1600, 1454, 1370, 1150, 1010, 778, 522, 495. MS (ESI) *m*/*z* 318.26 $[M-H]^-$.