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Chiral Brønsted Acid-Mediated Enantioselective Organocatalytic Three-Component Reaction for the Construction of Trifluoromethyl-Containing Molecules

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Dedicated to Prof. Manfred T. Reetz on the occasion of his 65th birthday.

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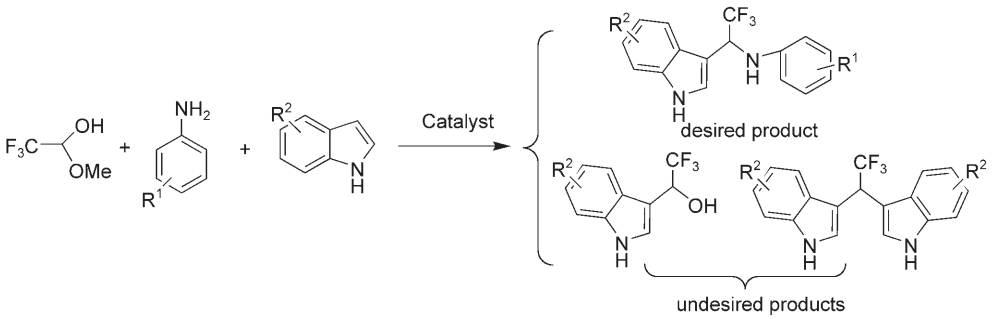
Abstract: In combination with the advantages of organocatalysis, we have developed a highly enantioselective Friedel–Crafts aminoalkylation of indoles with imines generated *in situ* from trifluoroacetaldehyde methyl hemiacetal and aniline. Novel chiral trifluoromethyl-containing compounds were obtained in high yields with excellent enantioselectivities. This methodology was further extended to difluoroacetaldehyde methyl hemiacetal to demonstrate the broad scope of substrates.

Keywords: Brønsted acids; enantioselectivity; Friedel–Crafts reaction; organocatalysis; organofluorine compounds

The incorporation of a CF_3 group with its potent electron-withdrawing ability into organic molecules often leads to significant changes in the physical, chemical, and biological properties of the parent compounds. Thus, over the past decades trifluoromethylated compounds have attracted considerable attention in organic synthesis, medicinal and agrochemical chemistry, and materials sciences.[1] In this context, structures in which the CF_3 group is attached to a stereogenic center are gaining increasing importance. Despite the numerous methodologies available,[2] advances in the synthesis of such compounds are still in great demand. The asymmetric transformation of prochiral trifluoromethylated materials is one of the most important strategies as it provides a powerful route to structurally elaborated molecules.[3] However, previous asymmetric processes of the starting trifluoromethyl-containing chemicals have mostly relied on a stoichiometric amount of chiral auxiliaries. Recently, catalytic asymmetric reactions with chiral metal complexes and small organic molecules have been reported.[4]

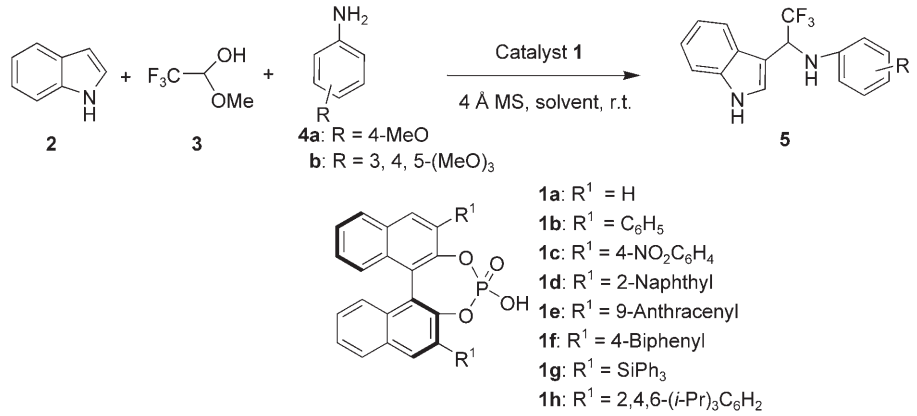
To the best of our knowledge, no enantioselective catalytic three-component reaction for the synthesis of chiral trifluoromethylated compounds has been reported. More recently, chiral phosphoric acids were found to have efficient asymmetric catalytic activities.[5] The applications have been extended to a large range of asymmetric transformations,[6] among which the Friedel–Crafts alkylation of aromatic compounds with imines or enamides has attracted attention over the past several years as a versatile C–C bond-forming process.[7] While these publications are excellent, troublesome imines or enamides have to be prepared beforehand. Herein, we present the first highly enantioselective, organocatalytic Friedel–Crafts aminoalkylation with imines generated *in situ* from trifluoroacetaldehyde hemiacetal and aniline for the synthesis of chiral trifluoromethyl-containing compounds.[8,9]

As trifluoroacetaldehyde hemiacetal itself is an active electrophilic reagent, the reaction conditions must be chosen carefully in accordance with the following terms: 1) the direct reaction of trifluoroacetaldehyde hemiacetal with an indole is likely; therefore, the reaction of the imine or N,O-acetal generated *in situ* from trifluoroacetaldehyde hemiacetal and amine with indole must be faster than the direct reaction. 2) Undesired racemization and bisindole alkylation events must be rigorously avoided (Scheme 1). Taking these considerations into account, we initiated screening experiments using chiral phosphoric acids **1** as organocatalysts. The results are shown in Table 1.[10] The simplest catalyst **1a** was able to catalyze this one-pot reaction smoothly to give the desired product in 90% yield, but with almost no enantioselectivity (entry 1). Accordingly, a series of phosphoric acids with varying



Scheme 1. Three-component reaction for the synthesis of trifluoromethyl-containing compounds.

Table 1. Screening of catalysts and reaction conditions for the three-component reaction.



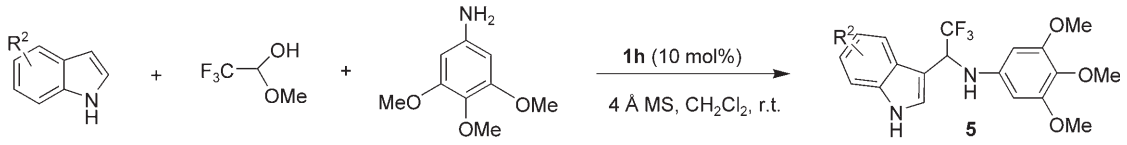
Entry	Catalyst (mol%)	$ArNH_2$ (**4**)	Solvent	Yield [%][a]	*ee* [%][b]
1	**1a** (10)	**4a**	toluene	90	−3
2	**1b** (10)	**4a**	toluene	72	25
3	**1c** (10)	**4a**	toluene	62	17
4	**1d** (10)	**4a**	toluene	93	39
5	**1e** (10)	**4a**	toluene	93	29
6	**1f** (10)	**4a**	toluene	80	39
7	**1g** (10)	**4a**	toluene	66	5
8	**1h** (10)	**4a**	toluene	97	47
9	**1h** (10)	**4a**	$ClCH_2CH_2Cl$	97	64
10	**1h** (10)	**4b**	toluene	99	92
11	**1h** (10)	**4b**	CH_2Cl_2	99	94
12	**1h** (10)	**4b**	$ClCH_2CH_2Cl$	99	92
13	**1h** (10)	**4b**	$CHCl_3$	83	90
14	**1h** (10)	**4b**	CCl_4	85	91
15	**1h** (10)	**4b**	Et_2O	85	95
16[c]	**1h** (10)	**4b**	CH_3CN	42	96
17	**1h** (5)	**4b**	CH_2Cl_2	63	93
18[d]	**1h** (10)	**4b**	CH_2Cl_2	92	92

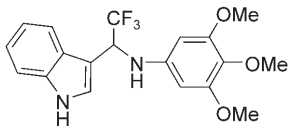
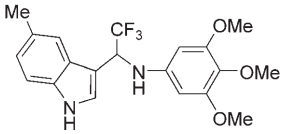
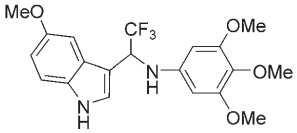
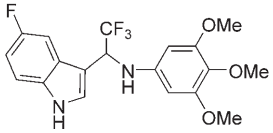
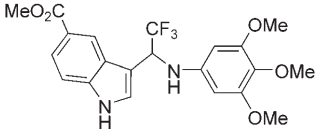
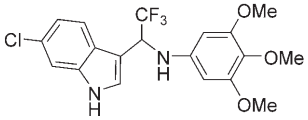
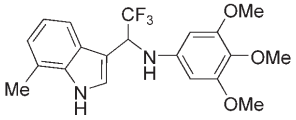
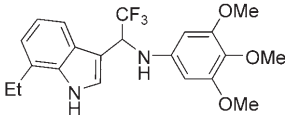
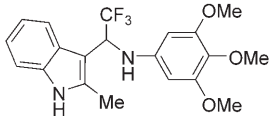
[a] Isolated yield.
[b] Enantiomeric excess was determined by chiral HPLC analysis.
[c] Reaction time: 72 h.
[d] At 0 °C for 48 h.

substituents at the 3,3′-positions of the binaphthyl scaffold was prepared and tested in the model reaction (entries 2–8). The use of catalyst **1h** with bulky 2,4,6-triisopropylphenyl groups at the 3,3′-positions gave both the best selectivity (47% *ee*) and highest chemical yield (97%). The enantioselectivity increased to 64% *ee* when the reaction was carried out in dichloroethane (entry 9). The structure of the

amine component has a considerable effect on the reaction (see Supporting Information). It was encouraging to find that high enantioselectivity and reactivity could be obtained by means of 3,4,5-trimethoxylaniline (entry 10). Following this evaluation of chiral catalysts, a solvent screen was undertaken. The reaction proceeded in toluene, chlorinated alkanes and ether to afford the desired product in good to high yields and with high enantioselectivity (entries 11–15). Acetonitrile gave a slight improvement in the enantiomeric excess, but a low conversion rate was obtained even with a longer reaction time (entry 16). Among the sol-

Table 2. Scope of the enantioselective Brønsted acid catalyzed three-component reaction.



Entry		Product	Time [h]	Yield [%][a]	*ee* [%][b]
1	**5a**		24	99	94 (>99.9)[c]
2	**5b**		72	83	95
3	**5c**		24	99	92
4	**5d**		72	99	94
5	**5e**		72	90	92
6	**5f**		48	95	90
7	**5g**		48	97	96
8	**5h**		48	99	98
9	**5i**		96	80	79

[a] Isolated yield.
[b] Enantiomeric excess was determined by chiral HPLC analysis.
[c] After recrystallization.

vents tested, dichloromethane was found to be the best with respect to catalytic activity and asymmetric induction. When lowering the reaction temperature or decreasing the amount of catalyst, a drop-off in both the reaction rate and *ee* value of the product was observed (entries 17 and 18).

With these optimized conditions in hand, the general scope of indole derivatives was examined in the asymmetric, organocatalytic, three-component reaction in the presence of chiral phosphoric acid **1h**. As highlighted in Table 2, a wide range of functional groups, including alkyl, methoxy, halogen, and ester groups, can be readily tolerated on the indole ring. Excellent enantioselectivities of more than 90% *ee* were obtained, and the enantioenriched products were formed in good yield (entries 1–8). However, by contrast, the substituent at the 2-position of the indole has a little effect on the reactivity and enantioselectivity. For example, the reaction of 2-methylindole needed 96 h to give the desired product in 80% yield with a 79% *ee* value (entry 9). To the best of our knowledge, this is the best enantioselective result reported to date for the Friedel–Crafts reaction of a 2-substituted indole.

It is very interesting that when both *N*-acetylindole and *N*-benzylindole were employed as substrates, respectively, no reaction was observed, thereby demonstrating that the hydrogen on the N atom of the indole is crucial for the activation of the reactant by the phosphoric acid catalyst in this three-component reaction. A weak hydrogen-bonded complex could be formed between the phosphoric acid and the indole.[11] On the other hand, the absolute configuration of the desired adducts was determined to be *R* by X-ray measurements on a single crystal of product **5a**, as well as by comparison with the sign of optical rotation of the deprotected compound reported in the literature (Figure 1).[8b,12] Regarding the mechanism of this one-pot three component reaction, we assume that, in the first step, the reaction of trifluoroacetaldehyde methyl hemiacetal with aniline readily provides the corresponding *N*,*O*-acetal and imine in the presence of phosphoric acid and molecular sieves at room temperature. Moreover, the *N*,*O*-acetal forms an equilibrium with the imine, which is protonated and activated by the chrial phosphoric acid to shield the *Si* face of the imine. Subsequently, the indole attacks mainly from the *Re* face of the imine to give the corresponding product with an *R* configuration, and the chiral catalyst is regenerated (Figure 2). Thus, the phosphoric acid provides a chiral environment, as well as positioning the reaction partners in close proximity and with the correct relative geometry to facilitate this reaction in a synergistic manner.

This methodology was further extended to difluoroacetaldehyde methyl hemiacetal to demonstrate the scope of this one-pot, three-component reaction. We found that the solvent influenced the reaction rate and selectivity. Dichloromethane did not lead to full conversion, and resulted in a less than 75% *ee* value.

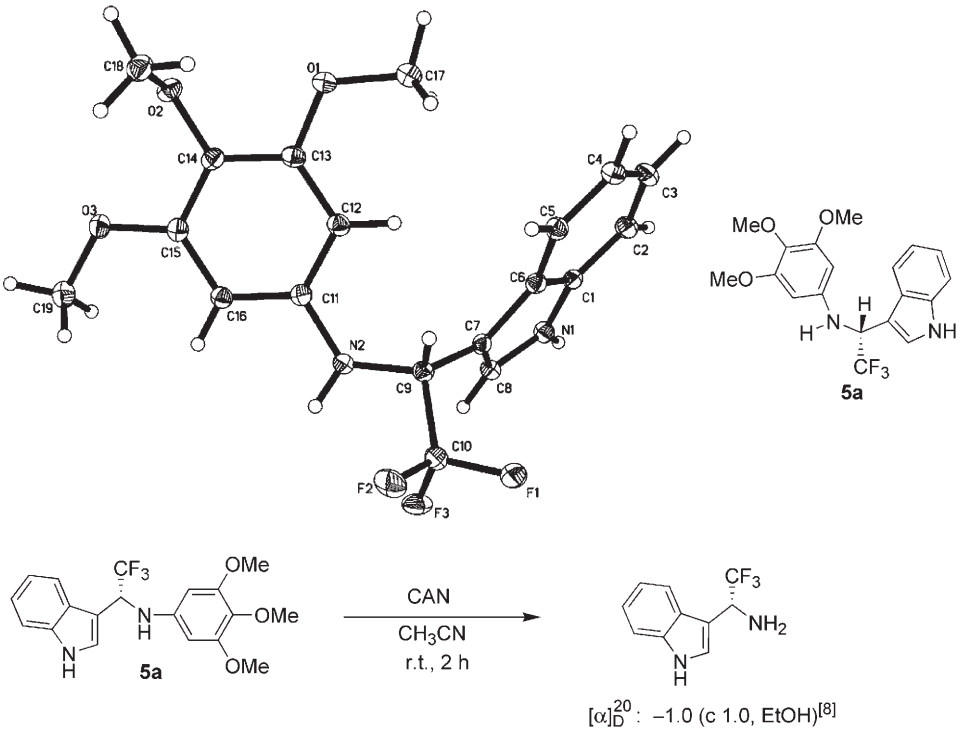


Figure 1. X-ray structure of (*R*)-**5a** and deprotection of (*R*)-**5a**.

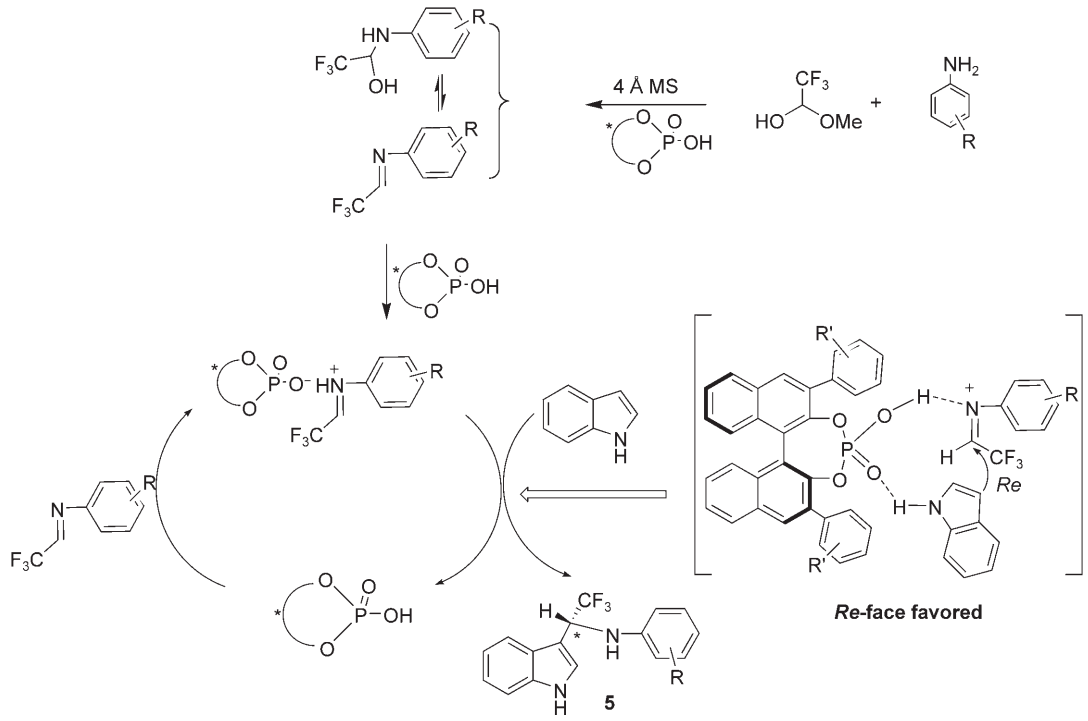
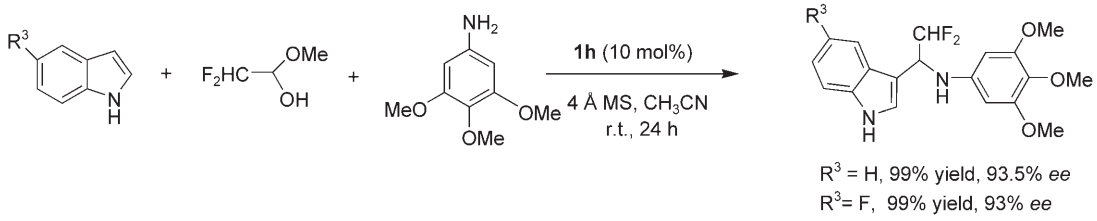


Figure 2. Proposed reaction mechanism.



Scheme 2. Organocatalytic enantioselective synthesis of difluoromethyl-containing compounds.

However, a considerable improvement was observed with acetonitrile. The reactions performed in this solvent exhibited improved quantitative yields and excellent enantioselectivities (Scheme 2).

In conclusion, we have developed an asymmetric, catalytic, one-pot, three-component Friedel–Crafts-type reaction by employing chiral phosphoric acids as efficient catalysts. The use of trifluoroacetaldehyde hemiacetal as a stable, easily handled, and commercially available prochiral trifluoromethyl-containing source, in combination with the advantages of organocatalysis, allows this simple protocol. A series of indole derivatives can be aminoalkylated in high yield with excellent enantioselectivity. High enantioselectivity is also achieved with difluoroacetaldehyde hemiacetal. Further studies on the application of these chiral trifluoromethyl and difluoromethyl compounds to other areas of chemistry and chemical synthesis are currently underway in our laboratory.

Experimental Section

Typical Pocedure

Brønsted acid catalyst **1h** (18.8 mg, 0.025 mmol) was added to a mixture of indole (43.8 mg, 0.37 mmol), trifluoroacetaldehyde methyl hemiacetal (48.8 mg, 0.37 mmol), 3,4,5-trimethoxyaniline (45.7 mg, 0.25 mmol) and powdered 4 Å molecular sieves (50 mg) in dichloromethane (1.0 mL). The resulting mixture was stirred at room temperature for 24 h. Then, the reaction solution was concentrated under vacuum, and the residue was purified by silica gel flash column chromatography (petroleum ether/AcOEt: 15:1) to give the desired product **5a** as a white solid; yield: 94.3 mg (99%, 94% *ee*).

Acknowledgements

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[10] A mixture of indole (43.8 mg, 0.37 mmol), trifluoroacetaldehyde methyl hemiacetal (48.8 mg, 0.37 mmol), Brønsted acid **1h** (0.025 mmol) and powdered 4 Å molecular sieves (50 mg) in toluene (1.0 mL) was stirred at room temperature for 96 h. No reaction occurred.

When the reaction mixture was stirred at 80 °C for 72 h, the hydroxyalkylated indole was obtained in 87% yield with a 3% *ee* value.

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[12] CCDC 672342 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.

