CHEMISTRY
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**To be cited as:** *Chem. Eur. J.* 10.1002/chem.201901020

**Link to VoR:** http://dx.doi.org/10.1002/chem.201901020

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# Enantioselective Friedel-Crafts Alkylation Reaction of Heteroarenes with *N*-Unprotected Trifluoromethyl Ketimines by Means of Chiral Phosphoric Acid

Masamichi Miyagawa, Masaru Yoshida, Yuki Kiyota, Takahiko Akiyama*

**Abstract:** An enantioselective Friedel-Crafts alkylation reaction of pyrroles and indoles with *N*-unprotected trifluoromethyl ketimines by use of chiral phosphoric acid provided α-trifluoromethylated primary amines bearing chiral tetrasubstituted carbon centers in high yields and with high to excellent enantioselectivities. The present reaction is unique to *N*-unprotected trifluoromethyl ketimines. No reaction took place with *N*-*p*-methoxyphenyl (PMP)-substituted ketimine. Corresponding α-trifluoromethylated amines were transformed without loss of enantioselectivity.

The development of efficient synthetic reactions is one of the most challenging task in organic chemistry. Although the introduction of protecting groups sometimes improves functional group tolerance and stability of substrates, the requirement of protection and deprotection steps, in general, increases the number of steps and decreases chemical yields. In this regard, the development of protecting-group-free synthesis is highly desired from the standpoint of atom economy, low cost, and short reaction time, and will lead to the environmentally benign synthesis of organic compounds.[1]

The enantioselective introduction of a trifluoromethyl group has attracted much attention in pharmaceutical science and agrochemistry.[2] Because introduction of the trifluoromethyl group may increase lipophilicity and stability for the metabolism of fluorinated compounds, a number of synthetic methods have been developed for the preparation of trifluoromethylated compounds. Among the trifluoromethylated compounds, chiral α-trifluoromethylated amines have drawn increasing interest because of their intriguing biological activity.[3]

Much effort has been devoted to the enantioselective syntheses of α-trifluoromethylated amines. Examples include kinetic resolution using enzymes, nucleophilic addition using chiral substrates, and catalytic enantioselective nucleophilic addition.[4,5] Among these approaches, the catalytic enantioselective nucleophilic addition is superior in terms of substrate scope and preparation. Therefore, the development of catalytic enantioselective nucleophilic addition reaction is desired.

In regard to enantioselective nucleophilic addition reactions of ketimines, *N*-protected trifluoromethyl ketimines were generally used as substrates and the reaction gives α-trifluoromethylated secondary amines and the subsequent deprotection is necessary to furnish the primary amines.[6-8] *N*-unprotected ketimines are suitable electrophiles to obtain the primary amines directly by nucleophilic addition to ketimines.[9] *N*-Unprotected ketimines are, in general, unstable due to the electrophilicity of the carbon atom and the basicity of the nitrogen atom. Recently, *N*-unprotected trifluoromethyl ketimines have appealed to synthetic organic chemists as substrates for enantioselective reactions because these compounds lead to the efficient synthesis of α-trifluoromethylated primary amines. Due to the moderate stability of *N*-unprotected trifluoromethyl ketimines, their application to enantioselective reactions is still in its infancy.[10-11] Only one example of an enantioselective reduction of[12] and three examples of a nucleophilic addition to[13] *N*-unprotected trifluoromethyl ketimines have been reported.

As part of our continued work on chiral phosphoric acid catalysis,[14,15] we wish to report herein an enantioselective Friedel-Crafts alkylation reaction of pyrroles and indoles with trifluoromethyl ketimines, which gives rise to α-trifluoromethylated

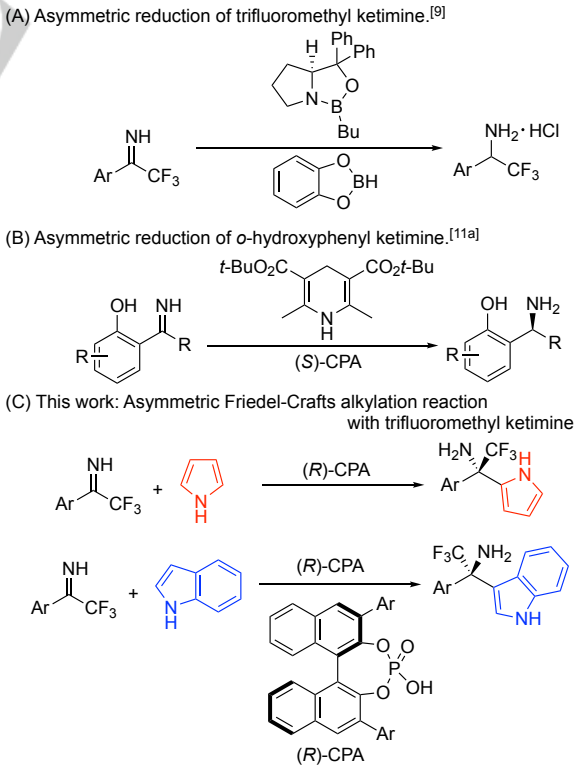


***Figure 1.*** Direct synthesis of chiral primary α-trifluoromethylated amines.

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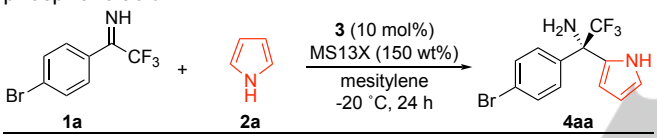
10.1002/chem.201901020




amines in good to high enantioselectivities. Indoles are, in general, suitable nucleophiles for the Friedel-Crafts alkylation reaction by means of chiral phosphoric acid, whereas pyrroles have not been extensively employed due to their low nucleophilicity.[16-17] Interestingly, pyrroles gave better results than indoles in the present reaction.

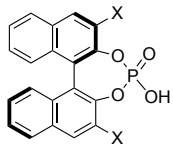
We commenced our investigation with the reaction between *N*-unprotected trifluoromethyl ketimine **1a** and pyrrole (**2a**) in the presence of a catalytic amount of chiral phosphoric acid **3** and molecular sieves 13X in mesitylene at –20 ˚C (Table 1). We confirmed that the enantioselective nucleophilic addition proceeded by means of chiral phosphoric acid **3**. Table 1 shows the results of examination of substituents at 3,3'-positions of **3**. Gratifyingly, the reaction gave chiral trifluoromethylated primary amine **4aa** in 96% yield with 27% ee when chiral phosphoric acid **3a** bearing triphenylsilyl groups at 3,3'-positions was employed (Entry 1). Further examination revealed that chiral phosphoric acid **3b** bearing 2,4,6-triisopropylphenyl groups furnished addition product **4aa** in 96% ee at –78 ˚C (Entry 7).

***Table 1:*** Optimization of substituents at 3,3'-positions of chiral phosphoric acid[a)]




**1a** **2a** **4aa**

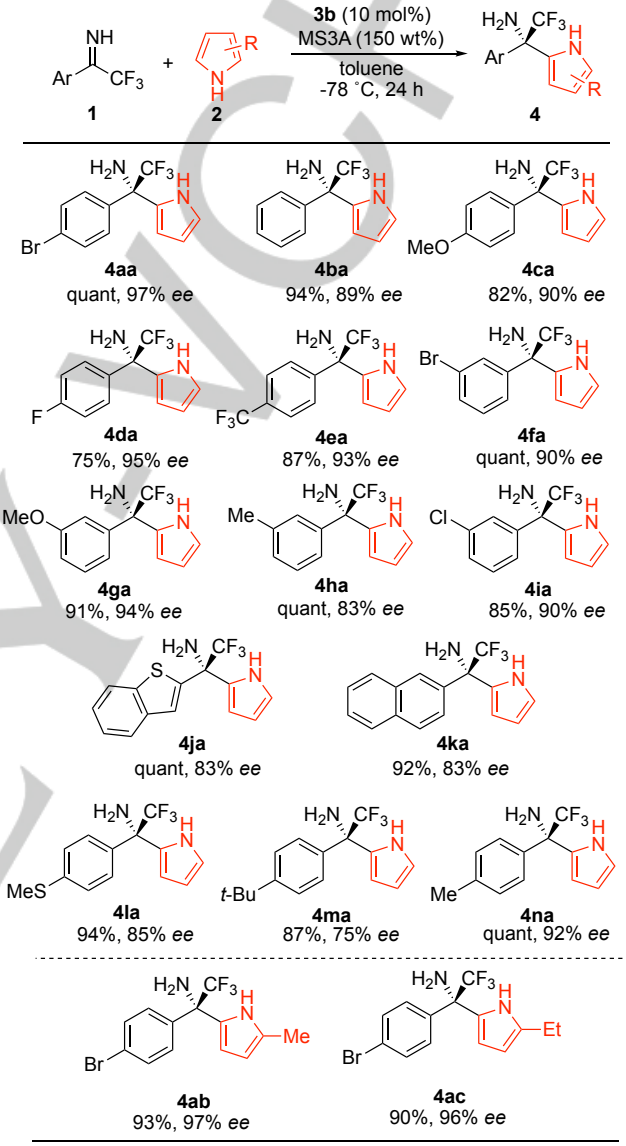
| entry | X | yield (%) | ee (%)[b)] |
|---|---|---|---|
| 1 | $SiPh_3$ | 96 | 27 |
| 2 | 2,4,6-($i$-Pr)$_3$C$_6$H$_2$ | 93 | 86 |
| 3 | $C_6F_5$ | 80 | -10 |
| 4 | 9-Anthryl | 84 | 65 |
| 5 | 2,4,6-$Cy_3C_6H_2$ | 87 | 79 |
| 6 | 2-Naphthyl | 78 | 27 |
| 7[c)] | 2,4,6-($i$-Pr)$_3$C$_6$H$_2$ | quant | 96 |




**3a**: X = $SiPh_3$
**3b**: X = 2,4,6-($i$-Pr)$_3$C$_6$H$_2$
**3c**: X = $C_6F_5$
**3d**: X = 9-anthryl
**3e**: X = 2,4,6-$Cy_3C_6H_2$
**3f**: X = 2-naphthyl

a) Reaction conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), **3** (10 mol%), MS13X (150 wt%), toluene (1.0 mL). b) Determined by chiral HPLC analysis. Detailed conditions are described in Supporting Information. c) In the presence of MS3A (150 wt%) at -78 ˚C in toluene.

We then evaluated the substrate scope of pyrroles (Scheme 1). First, the aryl group of trifluoromethyl ketimines was examined. Both electron-withdrawing and -donating groups were tolerant in this reaction, affording corresponding adducts **4** in high yields and with high to excellent enantioselectivities. Ketimines bearing *meta*- as well as *para*-substituted phenyl groups participated the reaction successfully. Ketimines having benzothienyl and 4-methylthiophenyl groups, both of which contain sulfur atom, also gave the adducts in excellent yields and with high enantioselectivities. 2-Naphthyl ketimine **1k** was also a suitable substrate. Substituted pyrroles **2b**–**c** also reacted with ketimine **1a** to provide **4ab**–**4ac** in high yields with excellent enantioselectivities. This reaction has wide tolerance for the substituents on pyrroles and the aryl group.




***Scheme 1.*** Substrate scope of pyrroles.

Next, we sought to expand the scope of the nucleophile to provide enantiomerically enriched α-trifluoromethylated primary amines. After the optimization, we found that indole derivatives **5** were also suitable nucleophiles that gave the corresponding products in good yields with good to high enantioselectivities (Scheme 2). Phenyl trifluoromethyl ketimine **1b** gave corresponding chiral primary amine **6ba** with 92% ee. Aryl trifluoromethyl ketimines gave corresponding adducts **6ca** and **6da** in good yields and with 86% ee.

We also investigated the substrate scope of indoles. 2-Methylindole (**5b**), 5-methoxyindole (**5c**), and 5-methylindole (**5d**)

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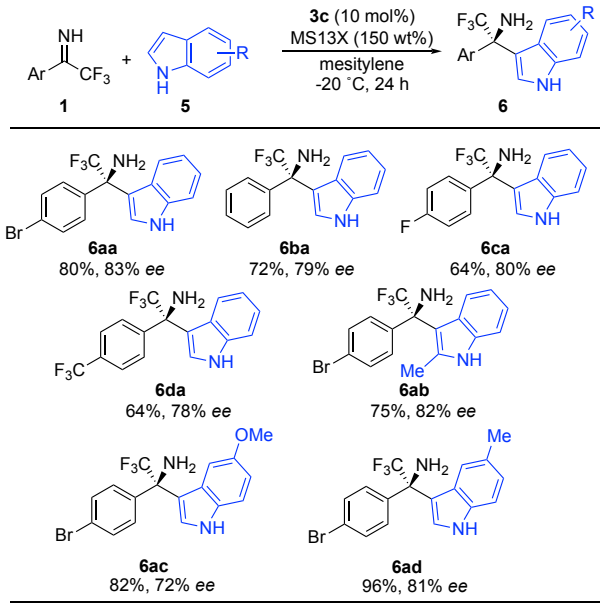
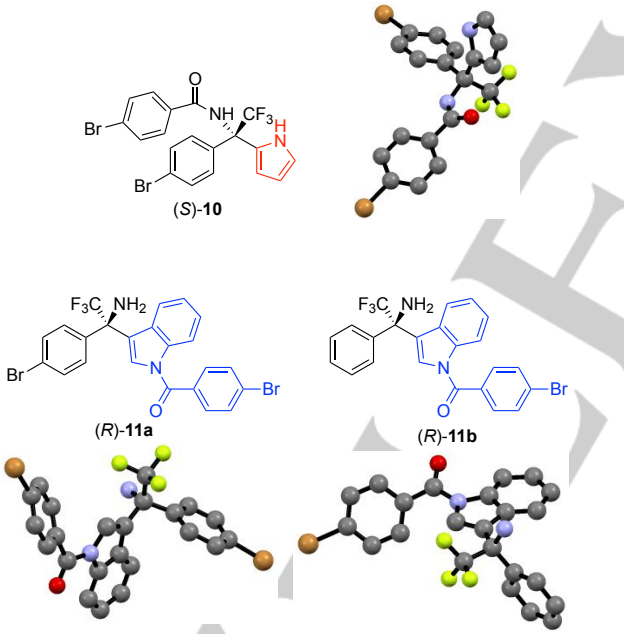
participated in the reaction successfully to furnish adducts **6ab**–**6ad** with good enantioselectivity.

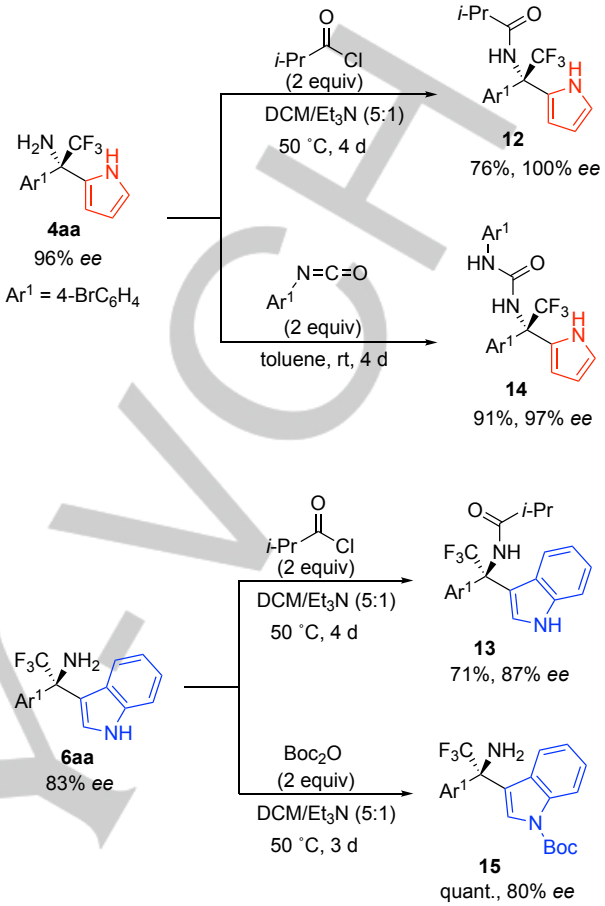



***Scheme 2.*** Substrate scope of indoles.



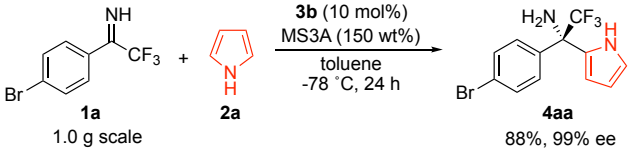

***Scheme 3.*** X-ray crystal analyses of indole- and pyrrole-substituted α-trifluoromethylated amines.

The absolute configurations of pyrrole- and indole-adducts were determined by X-ray analyses (Scheme 3). Adducts **4aa**, **6aa**, and **6ba** were acylated to **10**, **11a** and **11b**, respectively with benzoyl chloride derivatives.[18] X-ray analyses of them indicated that the absolute configuration of **4aa** was *S* and the ones of **6aa** and **6ba** were *R*. The configurations of all other products were surmised by analogy. Single-crystal X-ray analyses of pyrrole and indoles revealed that the absolute stereochemistries of adducts are different. The results suggested that the Friedel-Crafts reactions proceed with opposite face of the trifluoromethyl ketimine.[19]




***Scheme 4.*** Conversions of α-trifluoromethylated amines.

The resultant α-trifluoromethylated amines could be transformed into amides and ureas without loss of optical purity (Scheme 4). The acylation of primary amines proceeded smoothly. Treatment of **4aa** (96% ee) and **6aa** (83% ee) with isobutyryl chloride afforded amides **12** and **13** in 76% and 71% yields, respectively, with retention of ee. **4aa** reacted with 4-bromophenyl isocyanate to give urea **14** with retention of ee. Furthermore, the reaction of **6aa** with di-*tert*-butyl dicarbonate gave *N*-protected indole **15** in a quantitative yield with 80% ee. The difference between **13** and **15** of nitrogen atoms for acylation might be due to the steric hindrance of the acylating reagent. The reaction of **1a** was scaled up to 1.0 g (approximately 4.0 mmol) successfully to afford corresponding adduct **4aa** in 88% yield with 99% ee (Scheme 5).




***Scheme 5.*** Gram-scale enantioselective Friedel-Crafts alkylation reaction.

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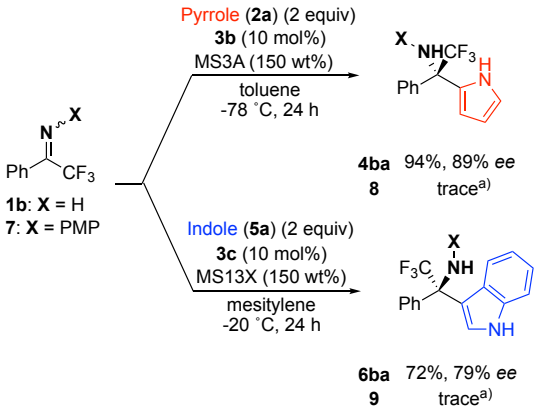
Finally, we compared the reactivity of *N*-H trifluoromethyl ketimine with that of *N*-PMP trifluoromethyl ketimine (Scheme 6). Interestingly, *N*-PMP trifluoromethyl ketimine **7** did not react with pyrroles and indoles at all under the optimized reaction conditions for *N*-H trifluoromethyl ketimines. It should be noted that no addition products were obtained even at room temperature, which is much higher temperature than that in the optimized reaction conditions. Moreover, the reaction did not proceed even in the presence of other chiral phosphoric acids at room temperature. These results clearly show that *N*-H trifluoromethyl ketimine is much more reactive than *N*-PMP trifluoromethyl ketimine.[20] We disclosed that the present Friedel-Crafts alkylation reaction is a specific reaction for *N*-unprotected trifluoromethyl ketimine.




***Scheme 6.*** Comparison of the reactivity between *N*-PMP trifluoromethyl ketimine and *N*-H trifluoromethyl ketimine. a) The reaction was conducted at room temperature.

In conclusion, we have developed an enantioselective Friedel-Crafts alkylation reaction of indoles and pyrroles with *N*-unprotected trifluoromethyl ketimines. The present reaction has wide functional group tolerance to provide a range of α-trifluoromethylated amines. The absolute configuration of the products was determined and the adducts were converted into *N*-acylated compounds without loss of ee. It is noted that *N*-unprotected trifluoromethyl ketimine is much more reactive than *N*-protected trifluoromethyl ketimine. We also revealed that the Friedel-Crafts alkylation reaction of indoles and pyrroles is specific to *N*-unprotected trifluoromethyl ketimines.

## Experimental Section

**General procedures for Friedel-Crafts alkylation reaction of pyrrole** Under a nitrogen atmosphere, a mixture of ketimine **1a** (0.10 mmol), pyrrole (**2a**) (0.20 mmol, 2.0 equiv), MS3A (150 wt%, activated), and chiral phosphoric acid **3b** (0.010 mmol, 10 mol%) in toluene (1.0 mL) was stirred at -78 ˚C for 24 h, and the reaction was monitored by TLC. After completion of the reaction, the reaction was quenched by adding saturated aqueous $NaHCO_3$. The crude mixture was extracted with EtOAc (x3) and the combined organic extracts were washed with brine, dried with $Na_2SO_4$, and concentrated *in vacuo*. The residue was purified by preparative TLC to give α-trifluoromethylated amine **4aa** (quantitatively with 96% ee).

## Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research on Innovative Areas “Advanced Transformation Organocatalysis” from MEXT, Japan, and a Grant-in-Aid for Scientific Research from JSPS (17H03060).

## Conflict of interest

The authors declare no conflict of interest.

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**Keywords:** trifluoromethyl ketimine • chiral phosphoric acid • nucleophilic addition • indole • pyrrole

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[18] The detailed reaction conditions are described in Supporting Information.

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[20] The Friedel-Crafts alkylation reaction of indole and pyrrole with *N*-PMP trifluoromethyl ketimine **1a** has not been reported to the best of our knowledge.

10.1002/chem.201901020

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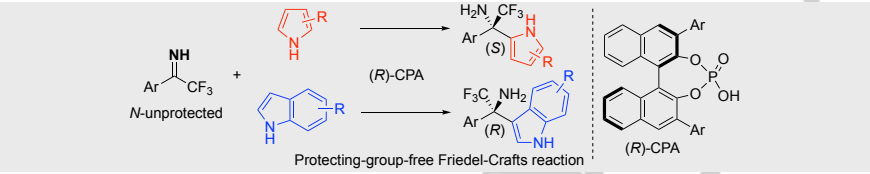


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**Enantioselective Friedel-Crafts Alkylation Reaction of Heteroarenes with *N*-Unprotected Trifluoromethyl Ketimines by Means of Chiral Phosphoric Acid**

Enantioselective Friedel-Crafts alkylation reaction of pyrroles and indoles with *N*-unprotected trifluoromethyl ketimines by use of chiral phosphoric acid provided α-trifluoromethylated primary amines bearing chiral tetrasubstituted carbon center. Present reaction is unique to *N*-unprotected trifluoromethyl ketimines and no reaction occurred with *N*-protected ketimines.