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Enantioselective Organocatalytic Synthesis of Quaternary α-Amino Acids Bearing a CF_3 Moiety

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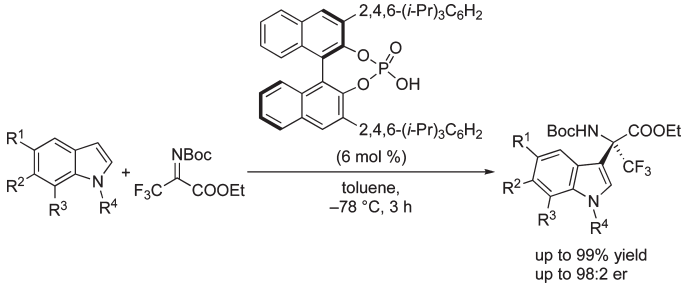
ABSTRACT



A highly enantioselective Friedel−Crafts reaction catalyzed by a chiral phosphoric acid was developed. *N*-Boc-protected ethyl trifluoropyruvate imine was activated by 6 mol % of catalyst and reacted with a wide variety of indole derivatives to afford quaternary α-amino acids in excellent yields (up to 99%) and high enantioselectivities (up to 98:2 er).

The synthesis of quaternary carbon stereogenic centers remains a challenging goal in organic synthesis.[1] Also, the development of synthetic methods to produce trifluoromethylated compounds in an enantioselective fashion is highly desirable.[2] The catalytic asymmetric Friedel−Crafts (FC) reaction constitutes an important C−C bond-forming transformation,[3] and several examples with trifluoromethyl ketones as electrophiles catalyzed by chiral hydrogen donor catalysts have been published.[4]

Directed hydrogen bond interactions represent an important mode of activation for asymmetric organocatalysis.[5]

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Since the landmark discovery of Jacobsen in 1998, where thiourea derivatives catalyzed the asymmetric Strecker reaction,[6] chiral Brønsted acid catalysis has gained much attention in the field. After the TADDOL-catalyzed hetero-Diels–Alder reaction reported by Rawal,[7] much stronger hydrogen bond donors such as phosphoric acids were found to catalyze Mannich-type reactions.[8] A wide variety of BINOL-derived phosphoric acids have been developed since then, serving as versatile catalysts to perform highly enantioselective organocatalytic transformations.[9]

Numerous protocols for FC reactions to the indole moiety with electrophiles such as carbonyl compounds,[4] α,β-unsaturated carbonyl derivatives,[10] imines,[4,11] and nitroolefins[12] catalyzed by chiral Brønsted acids are known. However, to the best of our knowledge, no FC reactions with trifluoropyruvate-derived imines catalyzed by chiral BINOL-derived phosphoric acids have been described. Here, we present an enantioselective aminoalkylation of indole derivatives giving quaternary α-amino acids in good to excellent yields and high enantioselectivities.[13]

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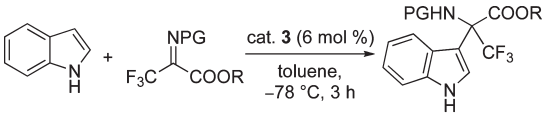
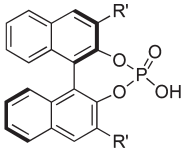
Table 1. Survey of Chiral Phosphoric Acids for the FC Reaction



1a **2a**: PG = Boc, R = Et; **2b**: PG = Cbz, R = Et; **2c**: PG = Bz, R = Et; **2d**: PG = Boc, R = Me — **4a-d**



3a: R' = 4-MeOPh; **3b**: R' = 3,5-$(CF_3)C_6H_3$; **3c**: R' = 4-*t*-BuPh; **3d**: R' = 9-Phenanthryl; **3e**: R' = $SiPh_3$; **3f**: R' = 2,4,6-$(i\text{-}Pr)_3C_6H_2$

entry[a]	catalyst	product	yield (%)[b]	er[c]
1	**3a**	**4a**	25	37:63
2	**3b**	**4a**	16	37:63
3	**3c**	**4a**	39	30:70
4	**3d**	**4a**	78	56:44
5	**3e**	**4a**	37	51:49
6	**3f**	**4a**	**99**	**96:4**
7	**3f**	**4b**	71	87:13
8	**3f**	**4c**	96	50:50
9	**3f**	**4d**	73	91:9

[a] Reaction conditions: **1a** (1 equiv), **2** (1.2 equiv), and **3** (0.06 equiv) in toluene (0.1 M) at −78 °C for 3 h. [b] Yield after column chromatography. [c] The *R*:*S* ratio was determined by HPLC analysis on a chiral stationary phase.

Initially, we investigated the reaction of indole with *N*-Boc-protected 3,3,3-trifluoropyruvate imine[14] in the presence of a chiral phosphoric acid catalyst in toluene (Table 1). The reaction proceeded at −78 °C and was complete after 3 h.[15–17] Catalysts with various substitution patterns on the 3,3′ position of the binaphthyl scaffold were examined (entries 1–6) and the 2,4,6-triisopropylphenyl-substituted catalyst (TRIP,[15] entry 6) was found to be the best in terms of yield and enantioselectivity. Substrates with alternative protecting groups on the imine nitrogen were also tested. The Cbz-protected imine gave the desired product in good yield (71%, entry 7), but with only moderate er (87:13). The imine with a benzoyl protecting group reacted well to give the quaternary amino acid derivative in high yield (96%, entry 8) but surprisingly as a racemate. Use of the methyl imino ester (entry 9) resulted in a lower yield (73%) and an er of 91:9.

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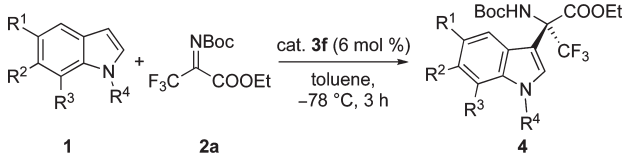
(15) The free acid catalysts were prepared according to literature procedures: Klussmann, M.; Ratjen, L.; Hoffmann, S.; Wakchaure, V.; Goddard, R.; List, B. *Synlett* **2010**, 2189.

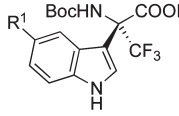
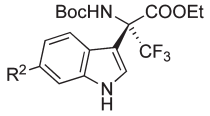
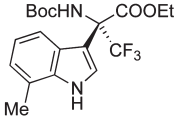
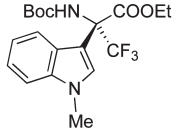
(16) No reaction was observed in the absence of a chiral phosphoric acid.

(17) Special care should be taken in collecting the entire product after column chromatography because self-disproportionation of enantiomers can occur. No such effect was observed upon sublimation under high vacuum at room temperature. For such phenomena, see: (a) Soloshonok, V. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 766. (b) Soloshonok, V. A.; Ueki, H.; Yasumoto, M.; Mekala, S.; Hirschi, J. S.; Singleton, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 12112.

Table 2. Scope of the Catalytic Enantioselective FC Reaction



1 2a 4

entry[a]	indole 4		yield (%)[b]	er[c]
1		R^1 = F (**4e**)	99	96:4
2		Cl (**4f**)	99	95:5
3		Br (**4g**)	85	96:4
4		Me (**4h**)	99	94:6
5		OMe (**4i**)	99	93:7
6		COOMe (**4j**)	65[d]	95:5
7		R^2 = F (**4k**)	97	95:5
8		Cl (**4l**)	98	98:2
9		(**4m**)	99	94:6
10		(**4n**)	22	54:46

[a–c] As in Table 1. [d] A longer reaction time (10 h) was needed for full conversion.

The optimized conditions were then employed to examine the reaction scope (Table 2). Use of 5-halogenated indole derivatives afforded the products in excellent yields. However, in the case of 5-bromoindole the yield was slightly lower (85%, entry 3) as compared to the 5-fluoro- or 5-chloro-substituted indoles (99% in both cases, entries 1 and 2). The enantiomeric ratios of the adducts **4e** and **4g** were 96:4 and that for **4f** was 95:5. Electron-rich indoles also reacted readily. 5-Methyl- and 5-methoxyindole furnished the desired products in excellent yields (99% in both cases, entries 4 and 5) and high enantioselectivities (94:6 for **4h** and 93:7 for **4i**). Methyl indole-5-carboxylate needed a prolonged reaction time for full conversion and yielded 65% of product with an enantiomeric ratio of 95:5 (entry 6). With 6-fluoro-, 6-chloro-, and 7-methyl-substituted indoles (entries 7–9) the reaction went smoothly, giving the best result in terms of enantioselectivity (98:2 er) for **4l**. *N*-Methylindole gave the product in low yield and in an almost racemic form (entry 10). This is in accordance with findings by Zhou[13b] and You[18] confirming the necessity of the free N–H of the indole to interact with the chiral phosphoric acid.

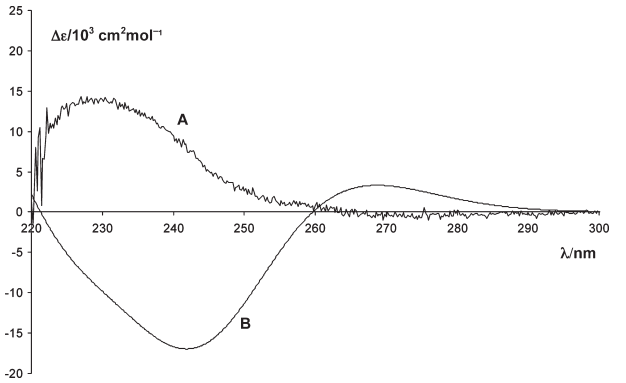


Figure 1. (A) Experimental ECD spectrum of **4a**. (B) Averaged calculated ECD spectrum of (*S*)-**4a**.

The absolute configuration of a representative product was determined by comparison of calculated and measured ECD spectra (Figure 1). A conformational search for (*S*)-**4a** was performed using the program Spartan '02.[19] Geometry optimizations of all conformers and TD-DFT[20] calculations applying the B3LYP functional[21] and the 6-311++G** basis set were accomplished with the program Gaussian 09[22] to obtain the theoretical ECD spectrum (**B** in Figure 1). The Boltzmann weighted spectrum of (*S*)-**4a** is close to the mirror image of the experimental spectrum (**A** in Figure 1),[23] revealing the absolute configuration of **4a** to be most likely *R*. On the basis of analogy and considering the same algebraic sign of the optical rotation, the absolute configurations of products **4b** and **4d–n** were also assigned as *R*.[24]

Deprotection of the 6-chloro derivative **4l** was effected with trifluoroacetic acid in dichloromethane. After basic workup, the desired free amino ester was obtained in 98% yield without affecting the stereochemisty (Scheme 1).

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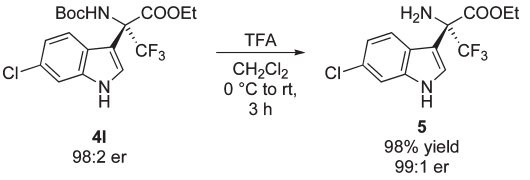
(23) The experimental ECD spectrum was recorded at room temperature using a 1.08×10^{-3} mol L^{-1} solution of **4a** (er = 96:4) in CH_3CN (path length 0.1 cm) on a AVIV 62DS circular dichroism spectrometer.

(24) See Supporting Information for optical rotation values.

Scheme 1. Amino Acid Ester **5** by Deprotection of **4l**



4l
98:2 er

5
98% yield
99:1 er

In summary, we developed the first chiral Brønsted acid catalyzed FC reaction to form quaternary α-amino acids bearing a CF_3 group.[25] The *N*-Boc-protected trifluoropyruvate-derived imine proved most effective in terms of yield and stereoselectivity. A wide variety of substituents in the 5-, 6-, and 7-positions of the indole were tolerated. The absolute configuration of a representative product was determined by comparison of calculated and experimental ECD spectra. Deprotection of the Boc-derivative was accomplished giving the amino acid ester in excellent yield while retaining the stereochemical information.

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Supporting Information Available. Experimental and computational procedures as well as spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(25) During the preparation of this manuscript, an elegant organocatalytic enantioselective Strecker synthesis of quaternary α-trifluoromethyl amino acids was described: Enders, D.; Gottfried, K.; Raabe, G. *Adv. Synth. Catal.* **2010**, *352*, 3147.