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

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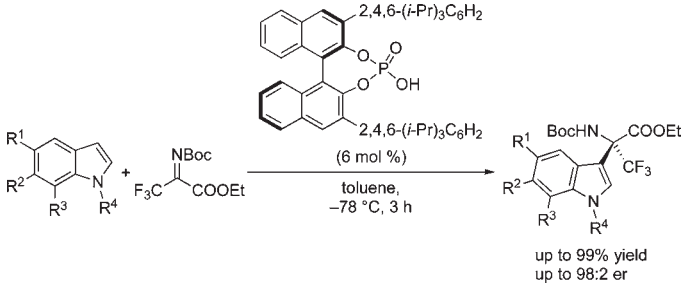
ABSTRACT



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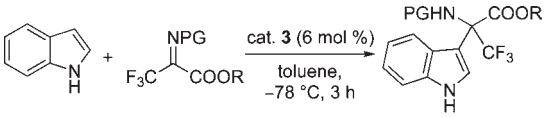
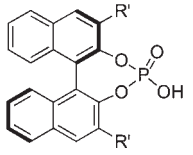
Table 1. Survey of Chiral Phosphoric Acids for the FC Reaction



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*-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.

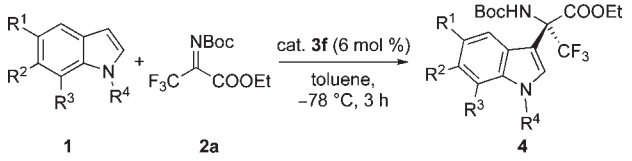
(14) Burger, K.; Höss, E.; Gaa, K. *Chem. Ztg.* **1989**, *113*, 243.

(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.

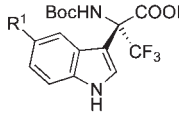
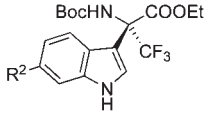
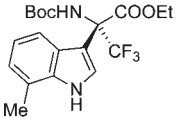
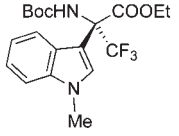
(16) No reaction was observed in the absence of a chiral phosphoric acid.

(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.

(18) Sheng, Y.-F.; Gu, Q.; Zhang, A.-J.; You, S.-L. *J. Org. Chem.* **2009**, *74*, 6899.

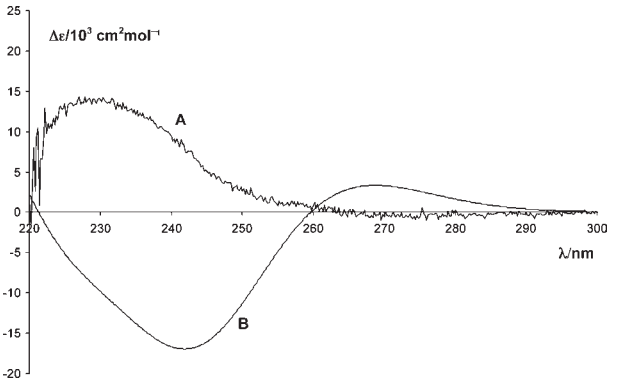


Figure 1. (A) Experimental ECD spectrum of **4a**. (B) Averaged calculated ECD spectrum of (*S*)-**4a**.

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).

(19) *Spartan, Version 02*; Wavefunction, Inc.: Irvine, CA, 2002.

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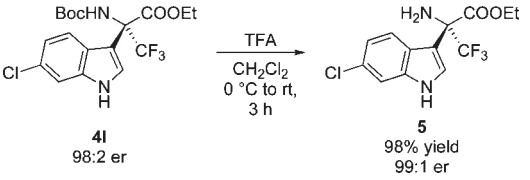
(23) The experimental ECD spectrum was recorded at room temperature using a 1.08×10^{-3} mol L^{-1} solution of **4a** (er = 96:4) in CH_3CN (path length 0.1 cm) on a AVIV 62DS circular dichroism spectrometer.

(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.

Acknowledgment. We are grateful to the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (DFG) within the SPP 1179 ("Organocatalysis") for financial support.

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.