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Triflic Acid-Catalyzed Highly Stereoselective Friedel–Crafts Aminoalkylation of Indoles and Pyrroles

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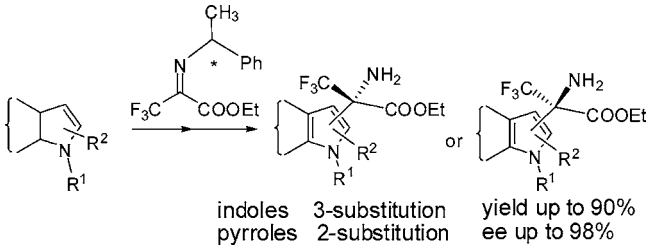
ABSTRACT



A simple and efficient synthesis to both enantiomers of highly enantiomerically enriched α-trifluoromethyl-α-(heteroaryl)-glycine derivatives via highly stereoselective aminoalkylation of indoles and pyrroles is described. The triflic acid-catalyzed reaction of enantiomeric 3,3,3-trifluoro-pyruvate-α-methylbenzyl imines with indoles and pyrroles and the subsequent Pd-catalyzed hydrogenolysis of the methylbenzyl group provided the products in high yields and excellent enantioselectivities.

The discovery of the beneficial effects of fluorine incorporation into organic molecules[1] has drawn extensive attention to synthetic organofluorine chemistry.[2] Among organofluorine compounds, trifluoromethyl group-containing products are especially important.[3] Fluorinated amino acids represent new prospects in the construction of hyperstable protein folds and in the production of highly specific protein−protein interfaces. The CF_3 group also serves as a reporting group in ^{19}F NMR studies.[4] The expansion of their applications, however, is strongly hindered by the very limited number of synthetic procedures.

The electrophilic aminoalkylation of aromatic compounds with α-iminoesters, a type of the well-known Friedel−Crafts reaction,[5] is a viable approach for the synthesis of aminoacids.[6] Asymmetric Friedel−Crafts reactions have been developed using chiral electron-deficient metal complexes,[7] organocatalysts,[8] and most recently chiral Brønsted acid catalysts.[9] Despite these efforts, there is no direct asymmetric

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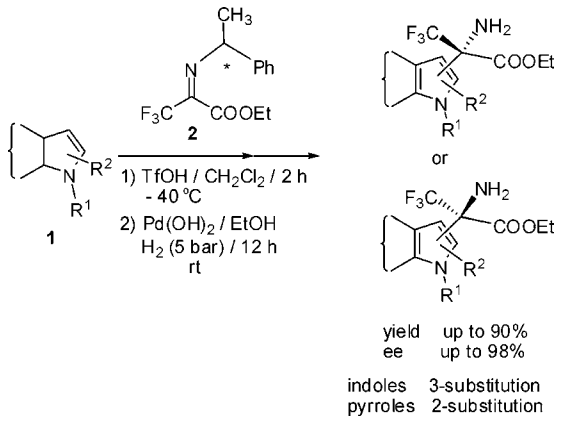
Friedel−Crafts method available for the synthesis of fluorinated aminoacid derivatives, although few racemic processes have been reported.[10] The sporadic asymmetric Friedel−Crafts reactions of imines and enamines focus on electron-rich imines and produce amines.[9]

Our success in enantioselective Friedel−Crafts hydroxyalkylations with ethyl trifluoropyruvate (ETFP),[11] prompted us to extend the use of this valuable synthon. Herein, we describe the first superacid-catalyzed chiral Friedel−Crafts aminoalkylation with chiral imines derived from ethyl trifluoropyruvate. We demonstrate that, with the application of enantiomeric 3,3,3-trifluoro-pyruvate-α-methylbenzyl imines in the reaction with substituted 5-membered *N*-heteroaromatics (indoles and pyrroles), the synthesis of both enantiomeric products is possible (Scheme 1).

Scheme 1. Synthesis of Chiral 3,3,3-Trifluoro-2-(Indol-3-yl)-2-Amino-Propionic Acid Esters via Stereoselective Friedel−Crafts Aminoalkylation



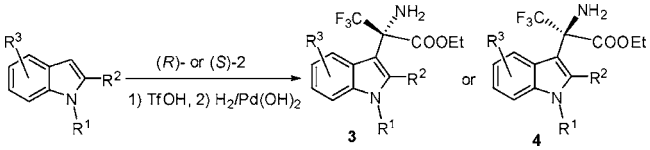
To synthesize chiral α-trifluoromethylated-α-(*N*-heteroaryl)-glycines through a simple approach, we have chosen α-methylbenzylamine, which is commercially available in both enantiomeric forms. The enantiomeric imines (**2**) were synthesized by K-10 montmorillonite-catalyzed condensation of the amines with ETFP. This convenient method made possible the bulk preparation of the starting material (**2**) in excellent yields (98%).

Our approach is based on the Friedel−Crafts aminoalkylation of 5-membered *N*-heteroaromatics with these imines to produce *N*-phenylethyl-α-trifluoromethyl-α-(*N*-heteroaryl)-glycine esters. In the last step, the benzyl group is cleaved by Pd-catalyzed hydrogenolysis to obtain the target compounds (**3**−**6**).

Optimization of the reaction conditions with indole as the aromatic starting material identified the nonoxidizing, superacidic trifluoromethanesulfonic acid (TfOH, triflic acid) as the catalyst of choice for the aminoalkylation.[12] We have found that the expected products could be synthesized under mild conditions in high yields (usually 90−94%).

The removal of the benzylic group was executed by Pd-catalyzed hydrogenolysis.[13] In the hydrogenolysis step the Pearlman's catalyst ($Pd(OH)_2/C$) provided the best yields (usually >90%). After determination of the optimum conditions, we carried out the reaction sequence (Scheme 1) using both (*R*)- and (*S*)-enantiomers of **2**, respectively, with several indole and pyrrole derivatives. The results are tabulated in Tables 1 and 2.

Table 1. Synthesis of Chiral 3,3,3-Trifluoro-2-(Indol-3-yl)-2-Amino-Propionic Acid Esters via Stereoselective Friedel−Crafts Aminoalkylation[a]



entry	R^1	R^2	R^3	**2**	product	yield [%][b]	ee [%][c]
1	H	H	H	(*R*)	**3a** (*S*)	83	92
2	H	H	H	(*S*)	**4a** (*R*)	82	90
3	H	H	5-OMe	(*R*)	**3b** (*S*)	83	93
4	H	H	5-OMe	(*S*)	**4b** (*R*)	73	90
5	H	H	5-CO_2Me	(*R*)	**3c** (*S*)	75	93
6	H	H	5-CO_2Me	(*S*)	**4c** (*R*)	85	90
7	H	H	5-Me	(*R*)	**3d** (*S*)	82	93
8	H	H	5-Me	(*S*)	**4d** (*R*)	75	94
9	Me	H	H	(*R*)	**3e** (*S*)	85	85
10	Me	H	H	(*S*)	**4e** (*R*)	84	86
11	Me	Me	H	(*R*)	**3f** (*S*)	86	87
12	Me	Me	H	(*S*)	**4f** (*R*)	73	93
13	H	H	6-iPr	(*R*)	**3g** (*S*)	86	97
14	H	H	6-iPr	(*S*)	**4g** (*R*)	90	97
15	H	H	7-Me	(*R*)	**3h** (*S*)	85	96
16	H	H	7-Me	(*S*)	**4h** (*R*)	84	96
17	H	CO_2Et	H	(*R*)	**3i** (*S*)	75	80[d]
18	H	CO_2Et	H	(*S*)	**4i** (*R*)	79	60

[a] Reactions were carried out with 1.1 mmol of **2**, 1 mmol of indole, and 1.6% (w/v) triflic acid in 4.5 mL CH_2Cl_2 at −40 °C; the hydrogenolysis took place on 10% $Pd(OH)_2/C$ in 5 mL EtOH at rt under 5 bar H_2. [b] Isolated overall yields. [c] Determined by chiral HPLC. [d] X-ray analysis

The data in Tables 1−2 show that the aminoalkylation took place in high yields with very high stereoselectivity.

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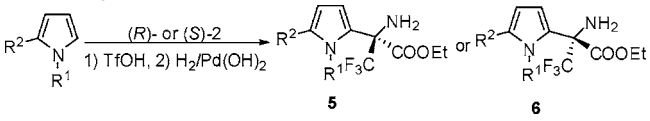
Table 2. Synthesis of Chiral 3,3,3-Trifluoro-2-(Pyrrol-2-yl)-2-Amino-Propionic Acid Esters via Stereoselective Friedel−Crafts Aminoalkylation[a]



entry	R^1	R^2	**2**	product	yield [%][b]	ee [%][c]
1	H	H	(*R*)	**5a** (*S*)	82	97
2	H	H	(*S*)	**6a** (*R*)	75	94
3	Me	H	(*R*)	**5b** (*S*)	77	84
4	Me	H	(*S*)	**6b** (*R*)	72	98
5	H	Et	(*R*)	**5c** (*S*)	81	91
6	H	Et	(*S*)	**6c** (*R*)	74	84

[a] Reactions were carried out with 1.1 mmol of **2**, 1 mmol of pyrrole, and 1.6% (w/v) triflic acid in 4.5 mL CH_2Cl_2 at −40 °C; the hydrogenolysis took place on 10% $Pd(OH)_2/C$ in 5 mL EtOH at rt under 5 bar H_2. [b] Isolated overall yields. [c] Determined by chiral HPLC.

The overall isolated yields after the two steps were in the 72−90% range, indicating that the individual steps occurred in about 90% yield each. The diastereomeric excesses (de) of the intermediates were usually excellent (>97%) except when using 2-carbethoxyindole, where the bulky substituent in the 2 position resulted in decline in the de. More importantly, the final enantiomeric excesses (ee) after hydrogenolysis were mostly excellent (up to 97% and 98% ee for the enantiomeric products). Although the yields are slightly lower with substituted pyrroles, the enantiomeric excess values are very high with both indoles and pyrroles. The lower yields are most likely due to the higher acid sensitivity of pyrroles.

The stereoselective aminoalkylation showed practically no limitation in using substituted indoles and pyrroles. However, it is worth mentioning that although the Friedel−Crafts aminoalkylation occurred with very high stereoselectivity with 5-halo-indoles (Cl, Br, I), the use of Pd catalyst in the hydrogenolysis step resulted in the complete loss of the halogens from the carbocyclic ring. In these cases, **3a** and **4a** were isolated, respectively, rather then the desired halogenated products. Further investigations are underway to solve this problem.

To characterize the stereochemistry of the products, the absolute configuration of the (indol-3-yl)-trifluoromethyl glycine ester **3i** has been determined by X-ray crystallography. The optical purity of **3i** was improved to 100% ee via fractional crystallization. The X-ray crystal structure of **3i** is shown in Figure 1. The analysis of the structure leads to an assignment of the chiral center formed in the reaction as (*S*) (Figure 1).

At this point in our studies, discussion of the detailed mechanism leading to the observed enantioselectivity is premature. Preliminary theoretical calculations indicated that steric factors generated by the chiral auxiliary are primarily responsible for the almost exclusive product formation. In the case of (*R*)-α-trifluoromethyl-α-ketimino-ester, the heteroaromatic compounds attack from the *Re* face, yielding a new chiral center in the product with predominantly (*S*)-configuration.

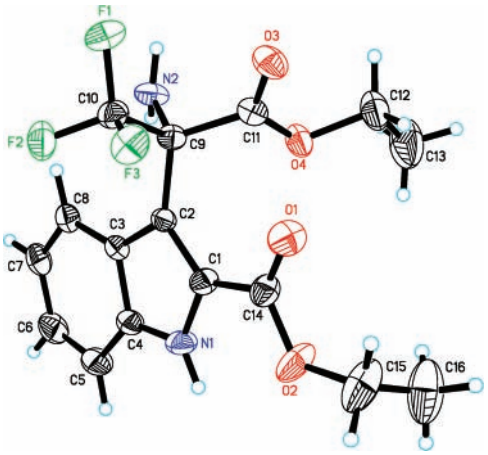


Figure 1. X-ray crystal structure of **3i** for determination of the absolute configuration of the chiral center formed in the aminoalkylation.

In conclusion, we have developed an efficient synthesis to both enantiomers of highly enantiomerically enriched α-trifluoromethyl-α-(heteroaryl)-glycine derivatives. Besides the high yields and enantioselectivities, the major advantages of the process are clean and fast reactions and the commercial availability of the chiral auxiliaries and catalyst, allowing selective synthesis of both enantiomers of the products. The new trifluoromethylated aminoacid derivatives represent a potentially important new class of compounds with possible extension to the synthesis of fluorinated peptides and other compounds.

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Supporting Information Available: Complete experimental details along with spectroscopic data for all compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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