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An enantioselective synthesis of heteroaromatic *N*-tosyl α-amino acids

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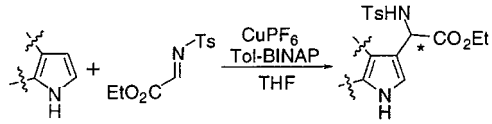
A new synthesis of optically active β-indolyl and pyrrolyl *N*-tosyl α-amino acids has been developed which uses readily available starting materials and proceeds with a high degree of enantioselection, giving the α-amino acids with up to 96% enantiomeric purity in 89% yield using 1–5 mol% of a chiral copper(I)–Tol-BINAP catalyst.

Within the last few years new catalysts have emerged for the classical and industrially very important Friedel–Crafts acylation of aromatics.[1] However, the addition of unsaturated compounds such as aldehydes and imines, which would lead to new and interesting compounds with stereogenic centers, has received only scant attention. Moreover, as far as the author is aware, the catalytic asymmetric version of such an addition has only one precedent the addition of ethyl pyruvate to 1-naphthol promoted by a chiral zirconium complex gave the addition product in 56% yield and with 84% ee.[2]

Recently considerable progress has been achieved with the long-standing problem of catalytic enantioselective addition of nucleophiles to imines.[3] This prompted us to investigate the enantioselective addition of a variety of aromatic compounds to imines. We now report our findings using a complex of copper(I) salts and Tol-BINAP[4] (the Lectka system)[3a] to catalyse the enantioselective addition of *N*-tosylimino esters of ethyl glyoxylate to electron-rich aromatics such as indole and pyrrole (Scheme 1).[5]

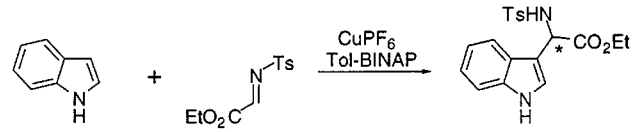


Scheme 1

Using as substrate furan we were able to isolate 15% of the desired aromatic addition product with 38% ee after 2 days at room temperature. This made us focus on the pyrrole and indole systems as these are known to be more active than furan in aromatic electrophilic substitution.[6] To our delight the reaction between indole **1a** and the imine **2** in THF was complete within a few hours, giving the 3-substitution product **3a** in almost quantitative yield and with 87% ee (Table 1, entry 1).[7] Running the reactions at lower temperatures (−20 and −78 °C) increased the enantioselectivity to 91 and 96% ee, respectively (entry 2, 3).[8] A simple recrystallisation gave the enantiopure *N*-protected α-amino acid **3a**.[9,10] Running the same reaction in CH_2Cl_2 gave a more sluggish conversion with more by-products and a lower enantioselection than in THF (entry 4). Finally, the amount of catalyst was reduced to 1 mol% almost without any change in yield or enantioselectivity [> 99% ee, 71% yield (recryst.)] (entry 5).

To test the scope of the reaction a variety of 5-substituted indole derivatives were screened.[11] As evident from Table 2 all the addition reactions give the 3-substituted indole derived amino acids.[12] The addition to the electron-rich methoxy-substituted substrate works particularly well, giving the product in 89% yield and more than 97% ee [> 99% ee, 73% yield (recryst)] (entry 2). The indole substrates with the electron-withdrawing substituents **1c,d** also react in a very enantioselective fashion, but a slightly higher reaction temperature was required in order to complete the reactions (entry 3,4). The 5-brominated indole reacts as the other indoles exclusively at the 3-position giving the addition product in 75% yield and with 88% ee [> 98 % ee, 55% yield (recryst.)] (entry 5).[13] The bromo product offers an interesting opportunity to test a variety C–C coupling reactions to give other enantiomerically pure 5-substituted indole alkaloids.[14]

Table 1 Enantioselective addition of imino ester **2** to indole **1a**



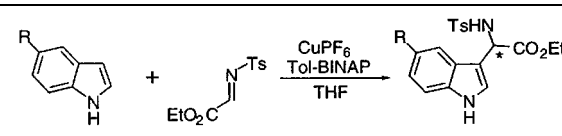
1a **2** **3a**

Entry	Catalyst/ mol%	Solvent	*T*/°C	Yield[a] (%)	Ee[bc] (%)
1	5	THF	room temp.	98	87
2	5	THF	−20	90	91
3	5	THF	−78	89	96
4	5	CH_2Cl_2	−78 to −10	57	78
5	1	THF	−78	89 (71)	94 (> 99)

[a] Yield after recrystallisation in parentheses. [b] Ee after recrystallisation in parentheses. [c] Ee determined by HPLC on a DAICEL OD-H or OJ column.

After having established the generality of the indole additions, focus was turned to the pyrrole systems. Two representative derivatives were chosen as model substrates, *viz.* *N*-methylpyrrole and 2-acetylpyrrole. The catalysed (5 mol% cat.) addition to *N*-methylpyrrole gives according to ^{1}H NMR approxiamtely a 1:1 mixture of the 2- and 3-substituted products **5** and **6**. After flash chromatographic separation, the two regioisomers were obtained in a total yield of 89%, the enantioselectivity being 84 and 56%, respectively. One recrystallisation of the 2-substituted product gave the enantiopure amino acid **6** [27% yield (recryst.)] (Scheme 2).

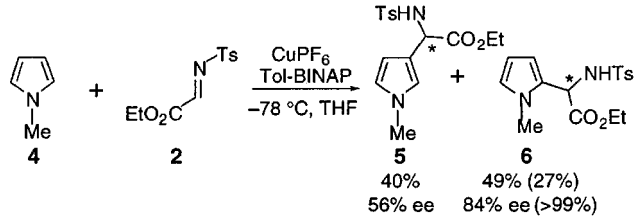
Table 2 Enantioselective addition of imino ester **2** to 5-substituted indoles **1a–e**



1a–e **2** **3a–e**

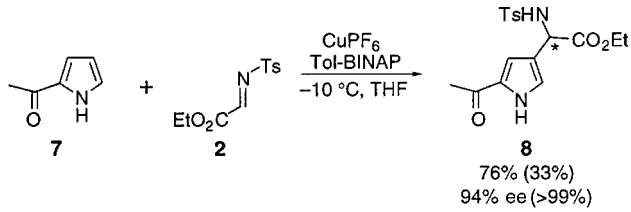
Entry	Catalyst/ mol%	R	*T*/°C	Yield[a] (%)	Ee[b] (%)
1	1	**1a** H	−78	89 (71)	96 (> 99)[c]
2	5	**1b** OMe	−78	89 (73)	97 (> 99)[c]
3	5	**1c** NO_2	−78 to −10	71	78
4	5	**1d** CO_2Me	−40	67 (52)	94 (> 98)[d]
5	5	**1e** Br	−10	75 (55)	88 (> 98)[d]

[a] Yield after recrystallisation in parentheses. [b] Ee after recrystallisation in parentheses. [c] Ee determined by HPLC on a DAICEL OD-H or OJ column. [d] Ee determined by ^{1}H NMR using a lanthanide shift reagent (ref. 13).



Scheme 2

In contrast to the *N*-methylated pyrrole **4**, the deactivated 2-acetylpyrrole **7** reacts primarily at the 4-position. The addition product was isolated in 76% yield, with a surprisingly high ee of 94% [> 99% ee, 33% yield (recryst.)] when compared to **5** (Scheme 3).



Scheme 3

Finally, it should be mentioned that the catalysed addition of **2** to pyrrole gives the *N*-addition product as the main product. It is the only case where we have observed this kind of amino acetal product during our investigation.

At present not much is known about the mechanism of the reaction. Earlier studies by Lectka *et al.* have shown the capability of the system to effect highly enantioselective imino aldol reactions.[3a,b] On the other hand we have found that the Mannich reaction of 1-morpholinocyclohex-1-ene with the tosyl imine **2** was very fast (< 1 min, −78 °C) giving the anticipated imino aldol product after hydrolysis. However, the enantiomeric excess was very low (< 10% ee). The fact that the enamine moiety of the substrates is a part of a heteroaromatic system is therefore crucial for the effectiveness of this new addition reaction. The present reaction should therefore most adequately be considered as an aromatic electrophilic substitution rather than a Mannich reaction.

In summary a novel synthesis of useful optically pure heteroaromatic α-amino acids has been developed. The procedure allows for the simple preparation of an array of electronically different indole α-amino acids. These might be used in the synthesis of natural products and pharmacologically interesting compounds as well as new chiral ligands for asymmetric catalysis. The presence of the different 5-substituents permits the systematic testing of the influence of electronics on the activity of the new indole derivatives. Simple pyrrole systems also worked well as substrates, giving access to new optically pure heteroaromatic α-amino acids.

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4 (*R*)-Tol-BINAP is the abbreviation for the commercial ligand (*R*)-(+)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl.

5 The optically pure heteroaromatic α-amino acids obtained this way are to the best of our knowledge all new compounds which are not easily accesible by any other synthetic route. They all give ^{1}H and ^{13}C NMR spectra in accordance with the assigned structures. It should be mentioned that a derivative of **3a** has previously been prepard *via* an enzymatic resolution (ref. 12). For some excellent reviews on the synthesis of α-amino acids, see: R. M. Williams, *Aldrichim. Acta*, 1992, **25**, 11; R. M. Williams, *Synthesis of Optically Active α-Amino Acids*, Pergamon, New York, 1989; R. O. Duthaler, *Tetrahedron*, 1994, **50**, 1539.

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8 *A representative experimental proceudre:* Synthesis of (1*H*-indol-3-yl)tosylaminoacetic acid ethyl ester **3a**. To a flame dried Schlenk tube was added $CuPF_6(MeCN)_4$ (ref. 15) (7.5 mg, 0.02 mmol) and (*R*)-Tol-BINAP (15 mg, 0.022 mmol) under N_2. The solids were dried on the vacuum line for 1 h before 1.5 ml of dry THF was added *via* syringe. The clear yellow solution was stirred for 1 h before cooling down to −78 °C. Indole **1a** (94 mg 0.80 mmol) and imino ester **2** (ref. 16) (96 mg, 0.40 mmol) dissolved in 0.2 ml dry THF were added and the reaction was stirred overnight. The product was purified by flash column chromatography (30% EtOAc in pentane) giving **3a** as a white solid in 89% yield (93 mg) and 96% ee detected by HLPC using a Chiralcel OD-H column (20% Pr^{i}OH–80% hexane, 0.5 ml min^{-1}); $[\alpha]_D^{rt}$ +102 (*c* 1.0, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 8.11 (br s, 1H, N*H*), 7.65 (d, 2H, *J* 8.0, Ar), 7.53 (d, 1H, *J* 8.0, Ar), 7.30 (d, 1H, *J* 8.5, Ar), 7.20–7.14 (m, 3H, Ar), 7.10–7.07 (m, 2H, Ar), 5.56 (d, 1H, *J* 8.0, CHN*H*Ts), 5.34 (d, 1H, *J* 8.0, C*H*NHTs), 4.09–3.97 (m, 2H, OCH_2CH_3), 2.36 (s, 3H, $ArCH_3$), 1.12 (t, 3H, *J* 7.0, CH_2CH_3); δ_c (75 MHz, $CDCl_3$) 170.5, 143.2, 137.0, 136.2, 129.2, 127.2, 125.2, 123.4, 122.7, 120.2, 119.1, 111.3, 110.5, 62.0, 53.1, 21.5, 13.9.

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