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Formation of Optically Active Aromatic *α*-Amino Acids by Catalytic Enantioselective Addition of Imines to Aromatic Compounds**

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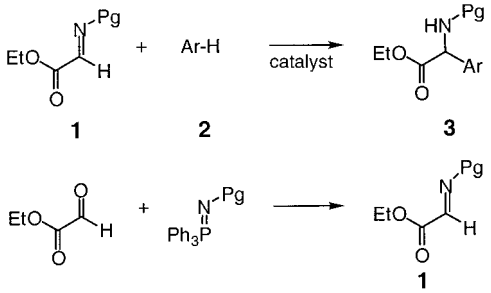
Optically active *α*-amino acids are vital to life as building blocks of peptides, proteins, and many other natural products. Amino acids are also applied extensively as food additives, pharmaceuticals, and agrochemicals. Furthermore, amino acids are widely used in organic synthesis as targets, and as constituents for reagents and/or catalysts in asymmetric synthesis.

The synthesis of optically active nonproteinogenic *α*-amino acids is an interesting and important research field which has received much attention[1] and the application of asymmetric catalysis towards formation of these compounds from simple starting materials is a fundamental challenge.

Recently, catalysts have been developed for enantioselective addition reactions to imines, including processes such as the ene[2], Mannich-type,[3] allylation,[4] and aza-Diels–Alder reactions.[5] Reports on the catalytic enantioselective addition of imines to aromatics are very few, and, according to our knowledge, only one example of the addition of an imine to indole and pyrrole systems has been reported.[6] Recently, several catalytic asymmetric Strecker reactions have emerged for the synthesis of optically active, natural, as well as unnatural, aromatic and aliphatic *α*-amino acids.[7]

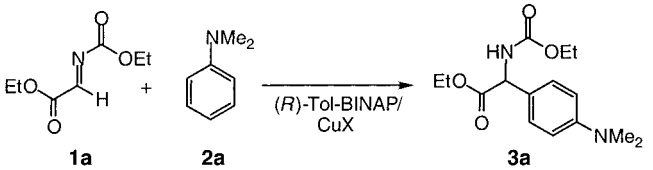
In this paper we present the development of a catalytic enantioselective addition reaction of imines **1** to electron-rich aromatic compounds **2** leading to protected optically active aromatic *α*-amino acids **3**[8] (Scheme 1). An advantage of this reaction is that **1** is prepared by an aza-Wittig reaction[9] and used directly without further purification (Scheme 1).



Scheme 1. Top: Addition of imines **1** to electron-rich aromatic compounds **2** to form protected aromatic *α*-amino acids **3**. Bottom: Synthesis of the protected imine starting materials **1**. Pg = protecting group.

The combination of $CuClO_4$ and (*R*)-Tol-BINAP catalyzed the reaction of the *α*-imine ester **1a** with *N,N*-dimethylaniline (**2a**) in THF at room temperature to give the protected aromatic *α*-amino acid **3a** in 81% yield and with 14% *ee* (see Equation (1) and Table 1, entry 1). Lowering the reaction temperature to −78 °C caused a substantial improvement in

Table 1. Optimisation results for the reaction of imine **1a** and *N,N*-dimethylaniline (**2a**) with (*R*)-Tol-BINAP/CuX as the catalyst.



Entry	CuX	Cat. concentration [mol%]	Solvent	*T* [°C]	Yield[a] [%]	*ee* [%]
1	$CuClO_4$	10	THF	RT	81	14
2	$CuClO_4$	10	THF	−78	81	87
3	$CuClO_4$	10	CH_2Cl_2	−78	82	85
4	$CuClO_4$	5	THF	−78	78	93
5	$CuPF_6$	5	THF	−78	75	96
6	$CuPF_6$	1	THF	−78	79	81
7[b]	$CuPF_6$	5	THF	−78	76	93

[a] Yield of isolated products. [b] Large scale reaction with 8.0 mmol of starting material.

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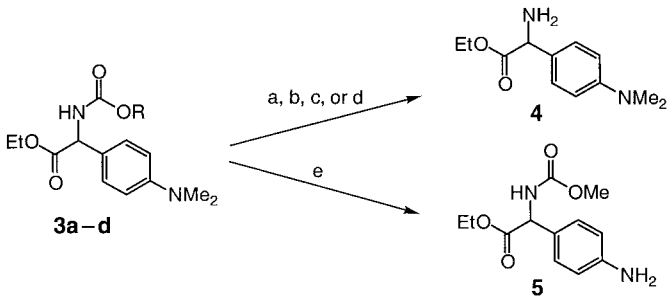
the *ee* value (87%) while maintaining the high yield (81%; entry 2). The optimum catalytic conditions presented in entry 5 gave **3a** in 75% yield with an excellent enantiomeric excess value of 96%. For this catalyst combination, a reduction of the loading to 1 mol% leads also to satisfactory results (entry 6). It should be noted that the reaction is highly regioselective, as only the *para*-substituted product is formed.

To broaden the applicability and scope of the present enantioselective reaction a number of imines with different N-protecting groups were tested, and the results are presented in Table 2. Entries 2 and 3 show that the *N*-methoxy- and *N*-benzyloxycarbonyl α-imino esters **1b**, **c** both react with **2a** giving the aromatic substitution adducts **3b**, **c** in good yields and excellent enantioselectivities (93% *ee* in both reactions). The reaction of the *N*-Boc protected α-imine ester **1d** with **2a** gave the desired product **3d** in high yield, however, even with optimised solvent, counterion, and temperature conditions, only a moderate enantioselectivity of 64% ee was obtained (entries 4–6). The *N*-tosyl α-imino-ester **1e**[10] also reacts with **2a** giving **3e** in high yield, but with slightly lower enantioselectivity (entry 7) compared to the products **3a**–**c**, which also have N-protecting groups which are readily removed (see below).

Explaining the mode of coordination of the imines **1a**–**e** to the catalyst is an intriguing problem as the absolute configurations of the products depend on the imine protecting group. Using the (*R*)-Tol-BINAP–Cu^{I} complex as the catalyst, the *N*-ethoxy-, *N*-methoxy-, and *N*-benzyloxycarbonyl protected imines **1a**–**c** gave the *R* enantiomers of **3a**–**c**, while use of the more bulky *N*-Boc and *N*-tosyl protected imines gave the *S* enantiomers of **3d** and **3e**, respectively. At the present stage of investigation we can not account for this observation. Most notable are the results in entry 6 and the dramatic temperature dependency of the reaction (Table 1, entries 1 and 2), which indicate that two competitive coordination modes with opposite chiral induction might be involved.

An important application of the products obtained from the present enantioselective catalytic reaction is, for example, the synthesis of novel nonproteinogenic optically active electron-rich aromatic α-amino acids, and readily removable protecting groups are therefore highly desirable. In Scheme 2, the synthetic procedure is illustrated for the removal of the four different N-protecting groups in **3a**–**d** to give **4** in high yield



Scheme 2. a) When R = Et: TMSI, CH_3CN, 82 °C, 20 min, then EtOH, 82 °C, 3 min, 83%; b) when R = Me: TMSI, CH_3CN, 80 °C, 15 min, then MeOH, 25 °C, 10 min, 90% (isolated as the HI salt); c) when R = Bn: H_2, 20% $Pd(OAc)_2$, EtOH, RT, 1 h, 98%; d) when R = *t*Bu: 25% TFA in CH_2Cl_2, 25 °C, 30 min, quantitative; e) PhIO, $TMSN_3$, CH_2Cl_2, −40 °C, 3 h, then work-up in sat. $NaHCO_3$ (aq.), THF (1:1), RT, 48 h, 92%. TMS = trimethylsilyl, Bn = benzyl, TFA = trifluoroacetic acid.

without detectable racemization; it is also shown that the *N,N*-dimethyl substituent on, for example, **3b** can be deprotected selectively to **5** by a one step procedure.[11, 12] With the free amino group in **5**, it is now possible to introduce a variety of different new electron-donating and electron-withdrawing substituents on to the aromatic nucleus.

With the conditions for the catalytic addition of imines **1a**–**e** to **2a** and for the selective deprotection of the products in hand, we examined a variety of electron-rich aromatic compounds with a large structural diversity as potential substrates (Table 3). Mono- and disubstituted, mono- and polyaromatic compounds react in a regioselective reaction, as only one regioisomer of the aromatic electrophilic substitution product is formed. The product **3f** obtained by reaction of imine **1b** with **2b** was isolated in 88% yield and with 86% *ee* (entry 2) and contains a pyrrolidine unit, which is susceptible to further elaboration.[13] The disubstituted aromatic compound **2c** reacts selectively in the *para* position, relative to the *N,N*-dimethylamino substituent, to give **3g** in good yield and with up to 79% *ee* (entries 3–5). Bicyclic, naphthalene- and anthracene-based substrates also react in a highly enantioselective fashion, giving access to a series of novel optically active aromatic α-amino acid derivatives. The reaction of imine **1b** with *N*-methylindoline (**2d**) gives an almost enantiopure product **3h** (up to 98% *ee*; entries 7 and 8). The aromatic substitution adduct **3h** is interesting as novel optically active 5-indolyl α-amino acids are accessible by

Table 2. Reaction of different N-protected imines **1a**–**e** with *N,N*-dimethylaniline (**2a**) catalyzed by (*R*)-Tol-BINAP/$CuPF_6$.[a]

Entry	Imine/Pg	Cat. concentration [mol%]	Solvent	*T* [°C]	Product	Yield [b] [%]	*ee* [%] (configuration[c])
1	**1a**/CO_2Et	5	THF	−78	**3a**	75	96 (*R*)
2	**1b**/CO_2Me	5	CH_2Cl_2	−78	**3b**	75	93 (*R*)
3	**1c**/CO_2Bn	5	CH_2Cl_2	−78	**3c**	68	93 (*R*)
4	**1d**/Boc	10	DCE	RT	**3d**	84	64 (*S*)
5	**1d**/Boc	1	DCE	RT	**3d**	72	64 (*S*)
6	**1d**/Boc	10	THF	−50	**3d**	22	14 (*R*)
7	**1e**/Ts	5	THF	−78	**3e**	91	88 (*S*)

[a] Abbreviations: Pg = protecting group, RT = room temperature, Bn = benzyl, Boc = *tert*-butoxycarbonyl, DCE = 1,2-dichloroethane, Ts = tosyl = toluene-4-sulfonyl, Cbz = benzyloxycarbonyl, DMAP = 4-dimethylaminopyridine. [b] Yield of isolated products. [c] The configuration of **3c** is derived from a crystalline camphanic acid derivative of **3c**, which was analysed by X-ray crystallography; see the Supporting Information for further details. The configurations of the other products were assigned by deprotection (see Scheme 2) followed by standard transformations (CbzCl, Et_3N, DMAP/TsCl, DMAP) and comparison of the samples obtained with **3c**.

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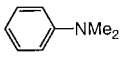
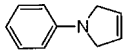
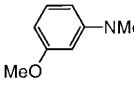
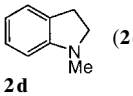
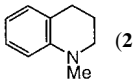
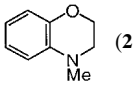
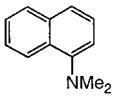
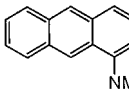
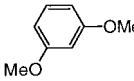
Table 3. Results for the reaction of the imines **1b**, **c**, **e** with the substrates **2a–i** using (*R*)-Tol-BINAP/$CuPF_6$ as the catalyst.[a]

Entry	Imine	Substrate	Cat. concentration [mol%]	Product	Yield[b] [%]	*ee* [%]
1	**1b**	 (**2a**)	5	**3b**	75	93
2	**1b**	 (**2b**)	5	**3f**	88	86
3	**1b**	 (**2c**)	5	**3g**	68	72
4	**1b**	**2c**	10	**3g**	79	76
5[c]	**1b**	**2c**	5	**3g**	56	79
6	**1b**	 (**2d**)	10	**3h**	63	97
7	**1b**	**2d**	20	**3h**	79	98
8	**1b**	 (**2e**)	5	**3i**	82	87
9	**1b**	 (**2f**)	10	**3j**	44	52
10	**1b**	 (**2g**)	5	**3k**	75	92
11	**1c**	 (**2h**)	5	**3l**	65	89
12[c]	**1e**	 (**2i**)	10	**3m**	83	79

[a] All reactions were performed at −78 °C, except the reaction in entry 12 which was performed at 0 °C. All reactions were performed with CH_2Cl_2 as the solvent, except for the reactions in entries 5 and 12 which were performed in THF. The observed most active position for aromatic electophilic substitution in all these substrates is the 4-position, relative to the nitrogen substituent. The major product from substrate **2i** is also addition in the 4-position. [b] Yield of isolated products.

oxidation of the indoline moiety using mild procedures.[14] *N,N*-Dimethyl-1-aminonaphthalene (**2g**) and *N,N*-dimethyl-1-aminoanthracene (**2h**) also react in an enantioselective reaction giving the corresponding aromatic α-amino acids in good yields and with high *ee* values (92% and 89%, respectively; entries 10 and 11).

The catalytic reaction shows high substrate tolerance, as a series of diverse products are formed in generally good yields and with excellent *ee* values (up to 98%). The optically active aromatic α-amino acids are formed with easily removable protecting groups on the amino functionality and show potential and applicability in various fields of chemistry.

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