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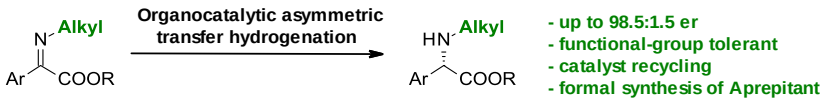
Direct synthesis of *N*-alkyl arylglycines by organocatalytic asymmetric transfer hydrogenation of *N*-alkyl aryl imino esters

Javier Mazuela[1]*, Thomas Antonsson[1], Magnus J. Johansson[1], Laurent Knerr[1], Stephen P. Marsden[2]

[1] Cardiovascular and Metabolic Diseases, Innovative Medicines and Early Development, AstraZeneca R&D, Pepparedsleden 1, Mölndal, SE-431 89, Sweden.

[2]School of Chemistry, University of Leeds, Leeds, LS2 9JT, UK.

Supporting Information Placeholder



ABSTRACT: The organocatalytic asymmetric transfer hydrogenation of N-alkyl arylimino esters for the direct synthesis of N-alkylated arylglycinate esters is reported. High yields and enantiomeric ratios were obtained, and the tolerance to a diverse set of functional groups facilitated the preparation of more complex molecules as well as intermediates for active pharmaceuticals. A simple recycling protocol was developed for the Brønsted acid catalyst which could be reused through five cycles with no loss of activity or selectivity.

Despite considerable recent interest in peptides as candidate drugs thanks to their potential for tackling complex targets (e.g. protein-protein interaction modulation) and improved selectivity and toxicity profiles, their use is strongly hampered by their poor pharmacokinetic profile, including short circulating plasma half-life and poor potential for oral absorption. Thus, the development of novel chemical strategies to stabilize peptides and improve their pharmacokinetic properties has gained in profile.[1] Among the strategies developed to circumvent these limitations,[1,2] the incorporation of N-alkylated amino acids is considered an effective way to enhance metabolic stability, lipophilicity and membrane-permeability.[2] For example, the clinically-used immunosuppressive natural product cyclosporine A features seven N-methylated residues and, although violating the Lipinski rules for oral bioavailability, has an excellent pharmacokinetic profile.[3] N-Alkylation modifies the steric constraints of the peptide chain and the hydrogen bond patterns, offering opportunities for broader conformational design.[2,4] Moreover, N-allylated amino acids have been used in approaches to stabilize secondary structures such as Arora's hydrogen bond surrogate strategy,[5] and in the preparation of stapled peptides.[6] In view of these developments, there is significant interest in the development of new methods to provide optically pure N-alkyl amino acids.

Arylglycines belong to a family of non-proteinogenic amino acids[7] which are present in a wide range of natural products of pharmaceutical relevance (such as the pristinamycines[8] and ramoplanines[9] Figure 1) as well as semi-synthetic drugs (such as penicillins and cephalosporins, Figure 1).[10] Classical methodologies for the preparation of N-alkylated arylglycines can be grouped into three processes: reductive amination, reductive ring opening of 5-oxazolidinones and N-alkylation.[2a] However, many of these methods are either lengthy and/or involve protection/deprotection sequences often associated with racemization of the sensitive stereocentre.[7] To our knowledge, only two asymmetric catalytic methodologies have been reported towards the direct synthesis of N-alkyl arylglycines.[11] Organocatalytic hydrosilylation of N-benzyl iminoesters was reported with moderate enantioselectivity (up to 71% ee, Scheme 1),[11a] while an asymmetric Rh-catalyzed hydrogenation of aldimines proceeding via dynamic kinetic resolution gave moderate-to-low enantiomeric ratios.[11b] In this context, the development of a modular asymmetric catalytic methodology for the preparation of a wide range of arylglycines bearing different N-alkyl chains is still needed.

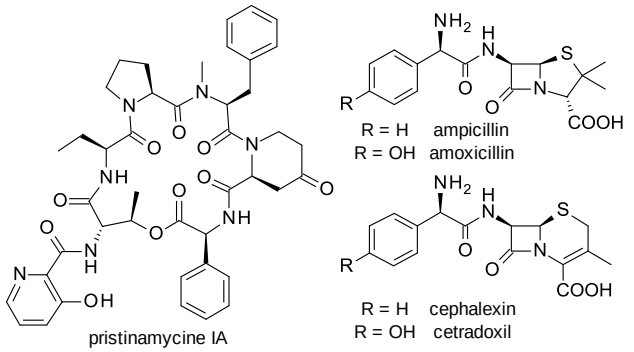
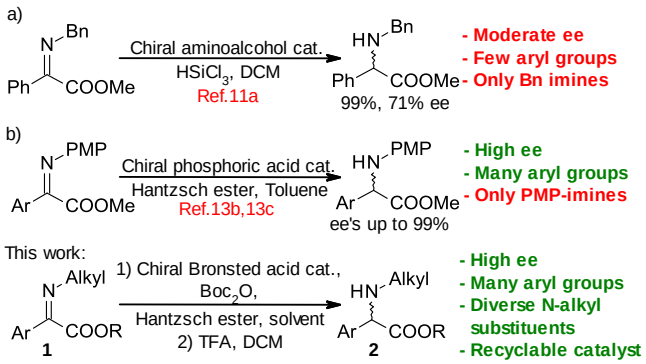


Figure 1. Arylglycine-containing pharmaceutical agents.

BINOL-derived chiral Brønsted acids have proved to be efficient catalysts for asymmetric imine transfer hydrogenation and reductive aminations of carbonyl compounds.[12] The groups of You[13b] and Antilla[13c] reported the organocatalytic transfer hydrogenation of protected α-iminoesters, obtaining α-amino esters with high yields and enantioselectivities (Scheme 1), but the substrate scope was limited to N-aryl imines. Inspired by the work of List using BINOL-derived disulfonimides **3** to promote the asymmetric transfer hydrogenation of N-alkyl ketimines,[14] we set out to examine the use of chiral Brønsted acids as catalysts for the transfer hydrogenation of N-alkyl aryliminoesters

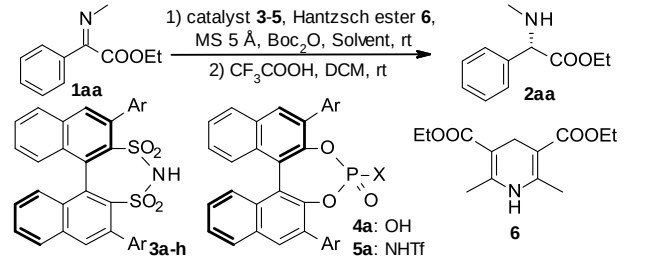
1. We report herein the successful direct synthesis of enantioenriched arylglycines **2** bearing diverse functionalized N-alkyl substituents (Scheme 1).

Scheme 1. Asymmetric catalytic synthesis of arylglycines.



Gratifyingly, we found that reduction of arylimino ester **1aa** using **3a** as the catalyst, Hantzsch ester **6** as hydrogen donor and Boc_2O in toluene in the presence of 5Å molecular sieves furnished the desired Boc-protected N-methyl amino ester in a 95% NMR yield with a high enantiomeric ratio (e.r. = 81:19, Table 1, Entry 1). It was observed that apolar solvents are needed to obtain both high yields and enantiomeric ratios, but the best result was obtained in toluene (Table 1, entries 1-6). Different hydrogen donors were also tested and the best results were obtained using Hantzsch ester **6** (see Supporting Information). As reported by List, the presence of Boc_2O as an trapping agent is needed to achieve high yields.[14] Other trapping groups could be used maintaining comparable levels of selectivity (see Supporting Information).

Table 1. Optimization of the reaction conditions[a].



entry	cat	Ar	solvent	yield[b] (%)	er[c]
1	**3a**	3,5-$(CF_3)_2C_6H_3$	Toluene	95	81:19
2	**3a**	3,5-$(CF_3)_2C_6H_3$	Mesitylene	94	81:19
3	**3a**	3,5-$(CF_3)_2C_6H_3$	DCM	95	70:30
4	**3a**	3,5-$(CF_3)_2C_6H_3$	Et_2O	48	75:25
5	**3a**	3,5-$(CF_3)_2C_6H_3$	cC_6H_{12}	55	73:27
6	**3a**	3,5-$(CF_3)_2C_6H_3$	MeOH	0	-
7	**4a**	3,5-$(CF_3)_2C_6H_3$	Toluene	57	53:47
8	**5a**	3,5-$(CF_3)_2C_6H_3$	Toluene	85	51:49
9	**3b**	4-CF_3-C_6H_4	Toluene	97	86:14
10	**3c**	4-CN-C_6H_4	Toluene	84	89:11
11	**3d**	4-SF_5-C_6H_4	Toluene	85	82:18
12	**3e**	3,5-Ph_2-C_6H_3	Toluene	68	80:20
13	**3f**	4-Me-3,5-$(NO_2)_2$-C_6H_2	Toluene	87	89:11
14	**3g**	4-OMe-C_6H_4	Toluene	66	84:16
14	**3h**	4-NO_2-C_6H_4	Toluene	95 (90)[d]	90:10
15[e]	**3h**	4-NO_2-C_6H_4	Toluene	47	93:7

(a) Reactions conditions: 1) **1aa** (0.1 mmol), **1aa**/cat/**6**/Boc_2O (1:0.05:1.4:1.2) with 50 mg 5 Å molecular sieves in 3 mL solvent for 16 h at room temperature. 2) TFA:DCM 3:1 for 2 h at rt. (b) ^1H NMR yield of the corresponding Boc-protected aminoester using dibromomethane as internal standard. (c) Determined by ^1H NMR adding (R)-TBPTA. (d) Isolated yield of the amino ester. (e) Reaction run at 0 °C for 24 h.

BINOL-derived phosphoric acid **4a** and triflyl phosphoramide **5a** gave only moderate yields and low selectivities (entries 7-8). The effect of the substituent in the 3/3'-position of the binaphthyl moiety of the catalyst was investigated. Aryl substituents with electron-withdrawing groups in the para position gave the highest levels of enantioselectivity (entries 1, 9-14), with the best result obtained with para-nitrophenyl substituted disulfonimide **3h**, affording the Boc-protected amino ester in a 95% NMR yield and 90:10 enantiomeric ratio; deprotection gave a 90% isolated yield of N-methyl amino ester **2aa**.[15] The e.r. could be further increased by decreasing the reaction temperature to 0°C (entry 15).

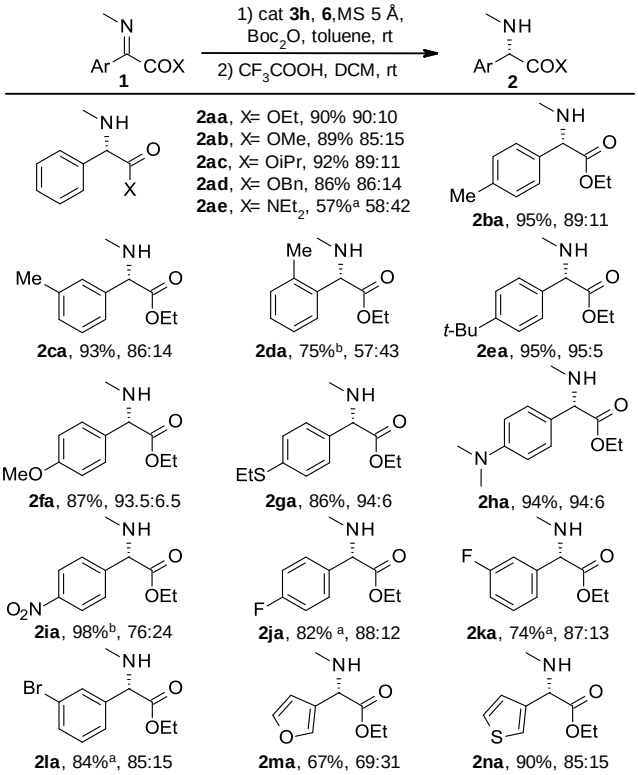


Figure 2. Substrate scope in the transfer hydrogenation of N-methyl aryliminoesters. Reaction conditions: 1) **1** (0.2 mmol), **1**/**3h**/**6**/Boc_2O (1:0.05:1.4:1.2) with 100 mg 5 Å mol. sieves in 6 mL toluene for 16 h at rt. 2) TFA:DCM 3:1 for 2 h at rt. (a). Reaction run for 3 d. (b) Reaction run for 2 d.

With the optimal reaction conditions in hand, we next examined the generality of this transformation, commencing with reduction of various N-methyl iminoesters. Different ester groups were well tolerated, with ethyl esters affording the best results (Figure 2). The replacement of the ester functionality by a tertiary amide gave the corresponding amide but with low yield

and enantioselectivity. Variation in the aryl substituent was probed. Both para and meta substituents on the aryl ring were well tolerated but the introduction of ortho substituents led to a decrease in both activity and enantioselectivity (Figure 2). Iminoester **1ea** with a tert-butyl substituent in the para position performed particularly well and the N-methyl arylglycine **2ea** could be prepared on gram-scale maintaining the excellent yield and enantioselectivities (Supporting Information). Electron-donating groups on the aryl ring led to an increase in the enantiomeric ratio while electron-withdrawing substituents decreased both activity and selectivity (Figure 2). Finally, the organocatalytic transfer hydrogenation was compatible with the introduction of heteroaromatic rings into the imino ester; however, only moderate enantioselectivities were obtained (Figure 2).

The effect of various N-alkyl groups was then investigated (Figure 3). Pleasingly a range of substituents with different chain lengths and bearing a variety of functional groups (allyl, homopropargyl, azide, bromo, silyl ether) were very well tolerated, maintaining excellent enantioselectivities albeit that longer reaction times were needed. Notably, the ready access to N-allyl, homopropargyl and azidoalkyl amino acids will facilitate the preparation of stapled peptides. Together, these results represent the first asymmetric transfer hydrogenation of N-alkylated arylimino esters, delivering varied N-alkyl arylglycine esters directly with good to excellent selectivities.

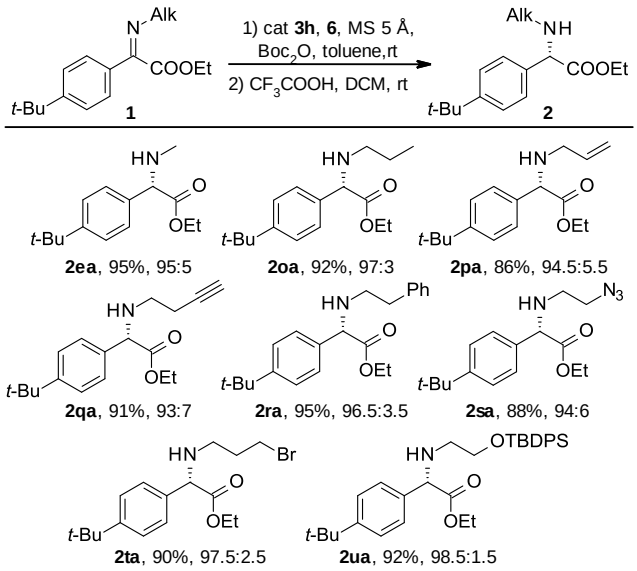


Figure 3. Substrate scope in the transfer hydrogenation of N-alkyl aryliminoesters. Reactions conditions: 1) **1** (0.2 mmol), **1**/**3h**/**6**/Boc_2O (1:0.05:1.4:3) with 100 mg 5 Å mol. sieves in 6 mL toluene for 3 d at rt. 2) TFA:DCM 3:1.

Furthermore, the functional groups present on the N-alkyl substituents could be used for further transformations to construct more complex chiral compounds. For example, ester reduction afforded amino alcohol **7** in good yield, while the Fmoc-protected aminoacid **8**, which could potentially be directly used in the construction of synthetic peptides, was easily prepared from amino ester **1ea** (Figure 4).[16] We were also able to perform a Cu-catalyzed click reaction of azide containing amino ester **1sa** to afford the biotinylated compound **9** in high yield, offering the potential for incorporation in bioactive peptides and use as a tool in chemical biology (Figure 4).[17] N-Heterocycles could also be elaborated from N-alkyl amino esters. Azetidine containing amino ester **10** was generated by internal nucleophilic substitution of an alkyl bromide, while piperazone **11** was obtained by reductive cyclization of azido ester **2sa**. In all cases the products were obtained maintaining the excellent enantioselectivities (Figure 4).

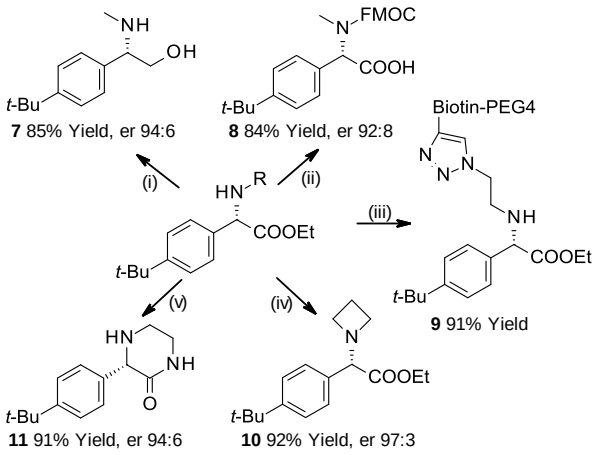


Figure 4. Preparation of diverse building blocks from functionalised N-alkylated arylglycine derivatives. Conditions: (i) $LiAlH_4$, THF (from **2ea**). (ii) a) FMOC-Cl, DIPEA, THF. b) MgI_2, THF (from **2ea**). (iii) Na-ascorbate, $CuSO_4$, tBuOH, H_2O (from **2qa**). (iv) DIPEA, CAN (from **2ta**). (v) Pd/C, H_2, MeOH (from **2sa**).

Finally, we demonstrated the applicability of our method to the direct synthesis of a marketed drug, by completing the synthesis of morpholinone **12c** which is an intermediate for the preparation of the antiemetic drug Aprepitant (Figure 5).[18,19] This is the first catalytic asymmetric method developed to date for the preparation of compound **12c**.[20]

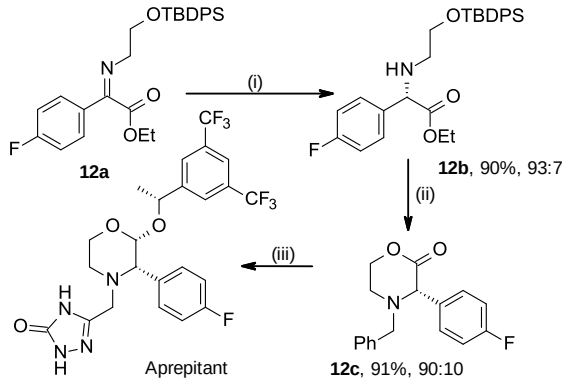
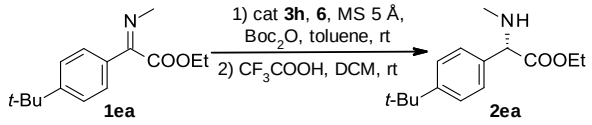


Figure 5. Formal asymmetric synthesis of Aprepitant. Conditions: (i) a) **3h**, **6**, 5 Å MS, Boc_2O, Toluene. b) CF_3COOH, DCM. (ii) BnBr, TBAI, K_2CO_3, DMF. (iii) Ref. 19.

In our effort to increase the applicability and sustainability of the process, we developed a protocol for the recovery and reuse of the chiral Brønsted acid catalyst (Table 2). Simply by transferring the crude reaction mixture to a commercially available anion exchange resin column followed by solvent elution allowed us to recover the Boc-protected amino ester. A final acid wash of the column eluted the Brønsted acid catalyst, which could be recovered nearly quantitatively. In this way, the catalyst was reused up to five times while maintaining excellent yields and selectivities. This represents the first successful protocol for the recovery and reuse of a chiral Brønsted acid catalyst, and should find wider applicability.

Table 2.Catalyst recovery and recycling experiments[a].



run	yield[b] (%)	er[c]	cat. rec.[d] (%)
1	91	95:5	95
2	93	95:5	94
3	90	94:6	95
4	88	94:6	90
5	90	94:6	95

(a) Reactions conditions: 1) **1ea**/**3h**/**6**/Boc_2O (1:0.05:1.4:1.2) with 200 mg 5 Å molecular sieves in 15 mL toluene for 16 h at rt. 2) TFA:DCM 3:1. (b) Isolated yield of the amino ester **2ea** (c) Determined by ^1H NMR adding (R)-TBPTA. (d) Catalyst recovery.

In summary, we have developed an organocatalytic transfer hydrogenation of N-alkylated arylimino esters which gives direct access to N-alkyl arylglycines. Excellent yields and enantiomeric ratios were achieved for a wide range of substrates with a range of (hetero)aryl substituents as well as diverse functionalised N-alkyl chains. The broad synthetic applicability of these products, combined with the opportunity for catalyst recycling offers great potential utility.

ASSOCIATED CONTENT

Supporting Information

Experimental methods, materials used, synthetic characterization and data are available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

*Javier.MazuelaAragon@astrazeneca.com

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final manuscript.

Notes

The authors declare no competing financial interest.

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