Organic LETTERS

Letter

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Direct Synthesis of *N*-Alkyl Arylglycines by Organocatalytic Asymmetric Transfer Hydrogenation of *N*-Alkyl Aryl Imino Esters

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Supporting Information

ABSTRACT: The organocatalytic asymmetric transfer hydrogenation of *N*-alkyl aryl imino esters for the direct synthesis of *N*-alkylated arylglycinate esters is reported. High yields and enantiomeric ratios were obtained, and 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 nonproteinogenic 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 semisynthetic 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,

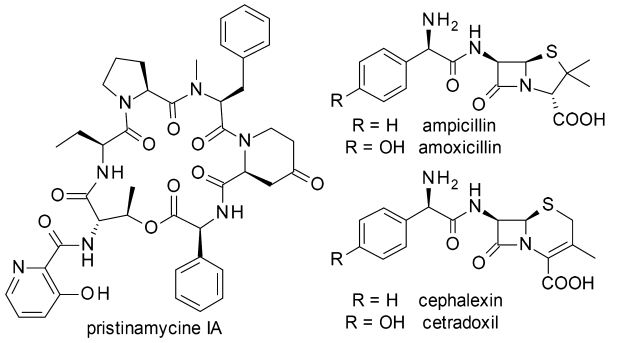


Figure 1. Arylglycine-containing pharmaceutical agents.

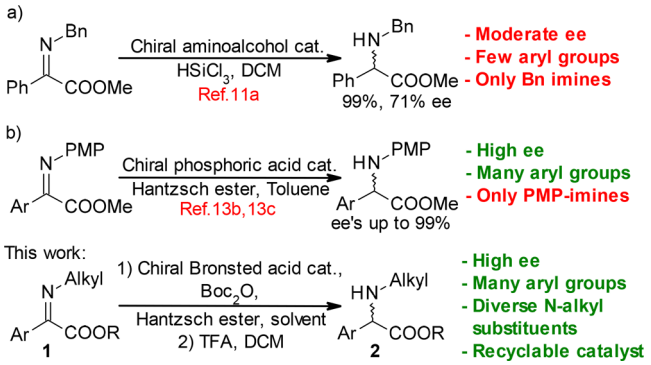
many of these methods either are lengthy and/or involve protection/deprotection sequences often associated with racemization of the sensitive stereocenter.[7] To our knowledge, only two asymmetric catalytic methodologies have been reported toward the direct synthesis of *N*-alkyl arylglycines.[11] Organocatalytic hydrosilylation of *N*-benzyl imino esters 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.

BINOL-derived chiral Brønsted acids have proved to be efficient catalysts for asymmetric imine transfer hydrogenation and reductive aminations of carbonyl compounds.[12] The

Received: August 24, 2017

DOI: 10.1021/acs.orglett.7b02627
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Asymmetric Catalytic Synthesis of Arylglycines



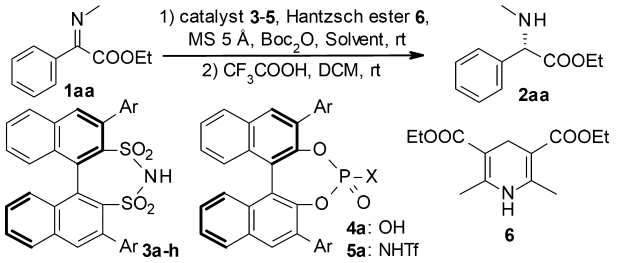
groups of You[13b] and Antilla[13c] reported the organocatalytic transfer hydrogenation of protected α-imino esters, obtaining α-amino esters with high yields and enantioselectivities (Scheme 1), but the substrate scope was limited to *N*-aryl imines. Inspired by the work of List using BINOL-derived 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 aryl imino esters **1**. We report herein the successful direct synthesis of enantioenriched arylglycines **2** bearing diverse functionalized *N*-alkyl substituents (Scheme 1).

Gratifyingly, we found that reduction of aryl imino ester **1aa** using **3a** as the catalyst, Hantzsch ester **6** as a hydrogen donor, and Boc_2O in toluene in the presence of 5 Å 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 a trapping agent is needed to achieve high yields.[14] Other trapping groups could be used maintaining comparable levels of selectivity (see Supporting Information).

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).

With the optimal reaction conditions in hand, we next examined the generality of this transformation, commencing with reduction of various *N*-methyl aryl imino esters. 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). Imino ester **1ea** with

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]^{1}H NMR yield of the corresponding Boc-protected amino ester using dibromomethane as internal standard. [c]Determined by ^{1}H NMR adding (*R*)-TBPTA. [d]Isolated yield of the amino ester. [e]Reaction run at 0 °C for 24 h.

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 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 aryl imino esters, delivering varied *N*-alkyl arylglycine esters directly with good to excellent selectivities.

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 amino acid **8**, which could potentially be

DOI: 10.1021/acs.orglett.7b02627
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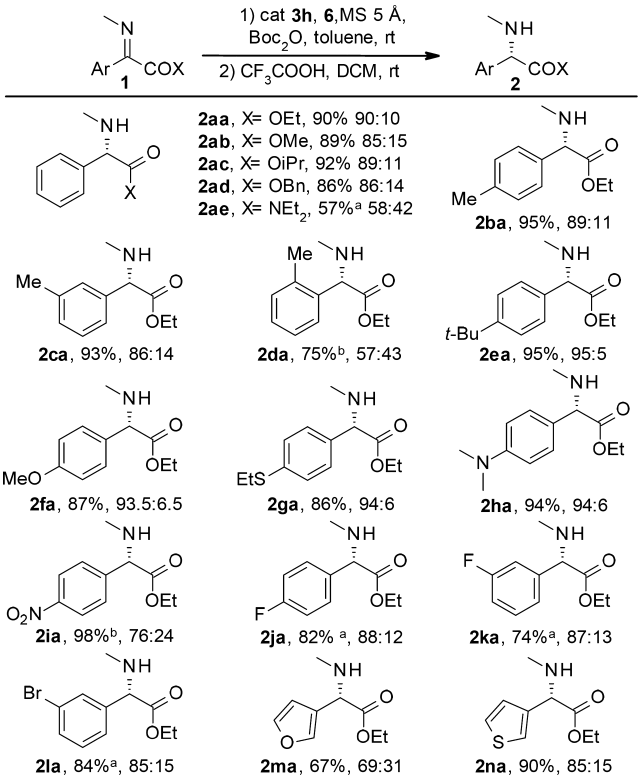

Figure 2. Substrate scope in the transfer hydrogenation of *N*-methyl aryl imino esters. Reaction conditions: (1) **1** (0.2 mmol), **1**/**3h**/**6**/Boc_2O (1:0.05:1.4:1.2) with 100 mg 5 Å molecular sieves in 6 mL of toluene for 16 h at rt. (2) TFA/DCM 3:1 for 2 h at rt. [a] Reaction run for 3 d. [b]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

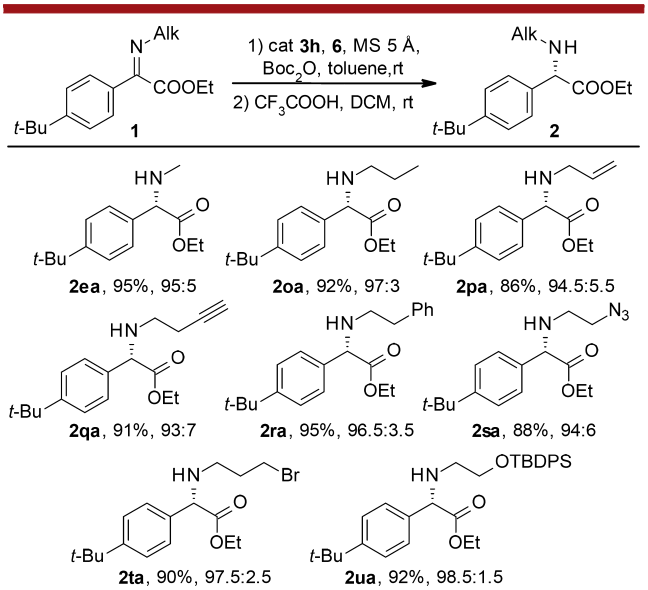

Figure 3. Substrate scope in the transfer hydrogenation of *N*-alkyl aryl imino esters. Reactions conditions: (1) **1** (0.2 mmol), **1**/**3h**/**6**/Boc_2O (1:0.05:1.4:3) with 100 mg 5 Å molecular sieves in 6 mL of toluene for 3 d at rt. (2) TFA/DCM 3:1.

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

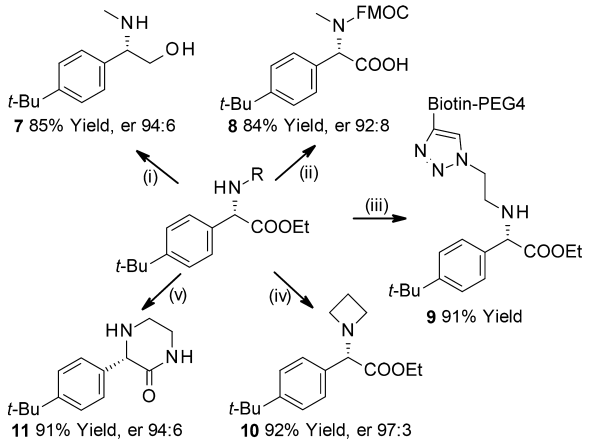

Figure 4. Preparation of diverse building blocks from functionalized *N*-alkylated arylglycine derivatives. Conditions: (i) $LiAlH_4$, THF (from **2ea**). (ii) (a) FMOC-Cl, DIPEA, THF. (b) MgI_2, THF (from **2ea**). (iii) Na-ascorbate, $CuSO_4$, *t*BuOH, H_2O (from **2qa**). (iv) DIPEA, CAN (from **2ta**).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

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).

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]

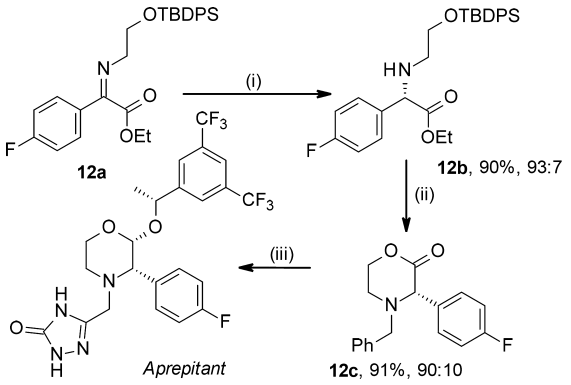

Figure 5. Formal asymmetric synthesis of *Aprepitant*. Conditions: (i) (a) **3h**, **6**, 5 Å molecular sieves, Boc_2O, toluene; (b) TFA, DCM; (ii) BnBr, TBAI, K_2CO_3, DMF; (iii) ref 19.

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

DOI: 10.1021/acs.orglett.7b02627
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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** (0.5 mmol), **1ea**/**3h**/**6**/Boc_2O (1:0.05:1.4:1.2) with 200 mg 5 Å molecular sieves in 15 mL of 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.

protocol for the recovery and reuse of a chiral Brønsted acid catalyst and should find wider applicability.

In summary, we have developed an organocatalytic transfer hydrogenation of *N*-alkylated aryl imino 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 functionalized *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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02627.

Experimental methods, materials used, synthetic characterization, and data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank AstraZeneca Gothenburg and the AstraZeneca PostDoc programme for financial support. Dr. Thomas Cogswell (AstraZeneca) is acknowledged for the help in the preparation of chiral Brønsted acids.

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DOI: 10.1021/acs.orglett.7b02627
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