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Towards an Asymmetric β-Selective Addition of Azlactones to Allenoates

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Abstract

We herein report the asymmetric organocatalytic addition of azlactones to allenoates. Upon using chiral quaternary ammonium salt catalysts, i.e. Maruoka's binaphthyl-based spirocyclic ammonium salts, the addition of various azlactones to allenoates proceeds in a β-selective manner with moderate levels of enantioselectivities (up to 83:17 e.r.). Furthermore, the obtained products can be successfully engaged in nucleophilic ring opening reactions, thus giving highly functionalized α-amino acid derivatives.

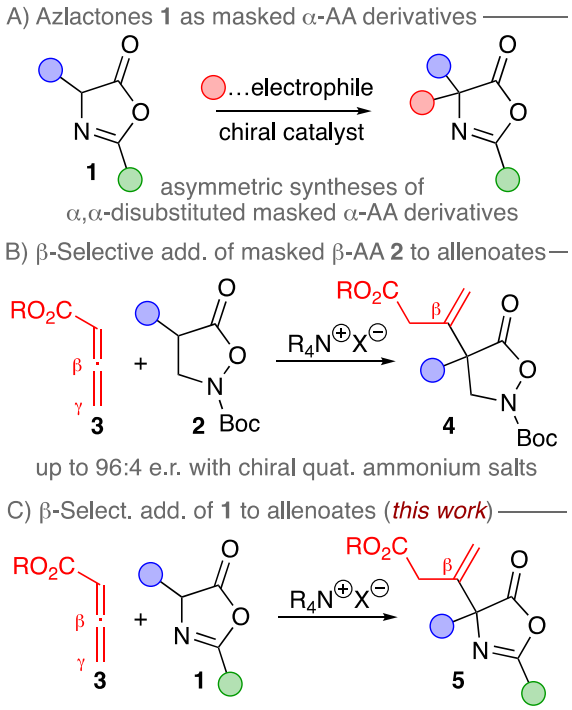
Keywords

organocatalysis; quaternary ammonium salt catalysis; azlactones; allenoates; amino acids

Introduction

The development of asymmetric syntheses routes to access non-natural amino acids has for decades been one of the most heavily investigated tasks in organic synthesis and catalysis-oriented research [1-13]. As a consequence, a broad variety of conceptually orthogonal strategies to access differently functionalized non-natural α-amino acids (α-AA) [2-7] as well as β-amino acids (β-AA) [8-13] have been introduced and there is still considerable interest in the development of new concepts and syntheses approaches. Our group has a longstanding focus on the development of asymmetric organocatalytic methods to access non-natural chiral α- and β-AA [14-19]. Hereby we are especially interested in utilizing simple (prochiral) starting materials and carry out stereoselective α-functionalizations by reacting them with suited C- or heteroatom electrophiles. α-Amino acid-derived azlactones **1** are amongst the most commonly utilized starting materials to access more diverse chiral α,α-disubstituted amino acids (Scheme 1A) [20-22]. More specifically, these compounds can be engaged for a variety of asymmetric α-carbo- and α-heterofunctionalization reactions by utilizing different catalysis strategies [20-22]. We have recently carried out systematic investigations concerning the syntheses of advanced β-AA by means of asymmetric α-carbofunctionalization reactions and during these studies we also realized that the masked β-AA derivatives **2** undergo enantioselective β-addition to allenoates **3** under chiral ammonium salt catalysis (Scheme 1B) [18]. Interestingly, hereby we also found that the use of alternative catalyst systems (i.e. tert. phosphines) allows for a γ-selective addition of **2** to the allenoate instead, thus resulting in two complementary catalyst-controlled pathways [18]. Based on these previous results, and also the well-documented different reactivity trends of allenoates **3** when using

different organocatalysts and activation modes [23-27], we were thus wondering if we could extend this ammonium salt catalyzed β-selective allenoate functionalization strategy to other amino acid classes. Azlactones **1** have previously been used for γ-selective additions to allenoates under chiral phosphine catalysis [28]. In addition, glycine Schiff base derivatives [29] as well as α-amino acid based thiazol-ones [30] have successfully been used for asymmetric β-selective additions to allenoates when using chiral ammonium salt catalysts or chiral organobase catalysts. However, to the best of our knowledge the β-selective asymmetric addition of azlactones **1** to allenoates **3** delivering highly functionalized α,α-disubstituted α-amino acid derivatives **5** has so far not been systematically addressed (for recent other β-selective additions of enolate precursors to allenoates please see Ref. [31-34]). Thus, we now became interested in testing this transformation under asymmetric ammonium salt catalysis [35-38] and the results of these investigations are outlined in this contribution (Scheme 1C).



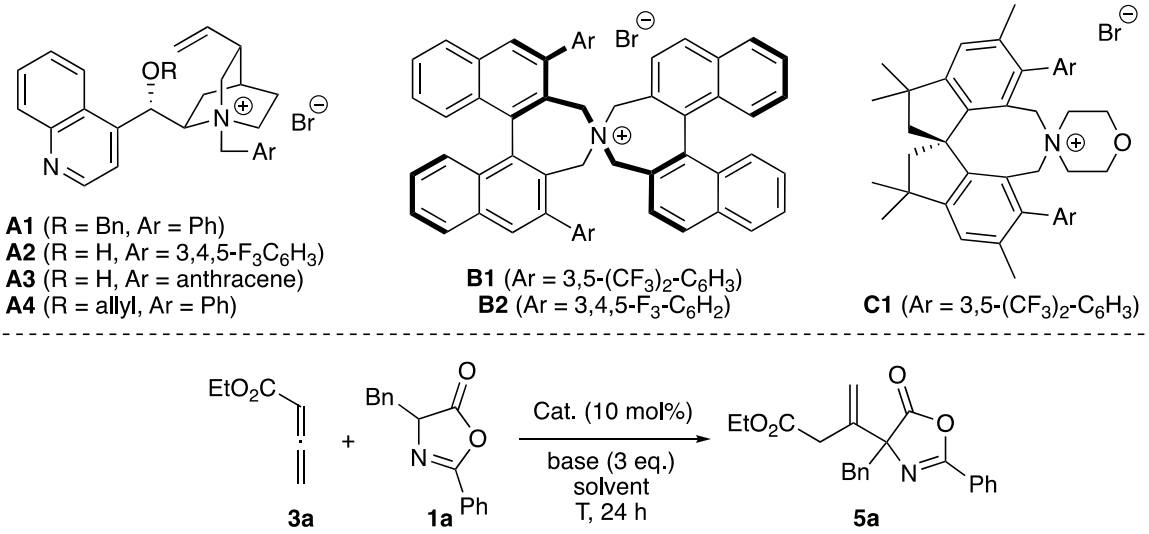
Scheme 1: General use of azlactones **1** to access more advance α–AA derivatives (A), our recently reported ammonium salt-catalyzed β-selective addition of compounds **2** to allenoates **3** (B), and the herein investigated β-selective addition of azlactones **1** to allenoates **3** (C).

Results and Discussion

We started our investigations by testing the quat. ammonium salt-catalyzed addition of azlactone **1a** to allenoate **3a** (Table 1 gives an overview of the most significant results obtained hereby). First experiments using Cinchona alkaloid-based quat. ammonium salts **A** showed that the expected β-addition product **5a** can be accessed under typical phase-transfer conditions, but with low selectivities and yields only when using these catalysts (entries 1-4, other Cinchona derivatives were tested too but did not allow for any improvement). Using the established and commercially available Maruoka catalysts **B1** and **B2** [39] next turned out to be more promising (entries 5-10). Testing the bis-CF_3-substitued **B1** first allowed for 75:25 e.r., but with moderate yield only when carrying out the reaction in toluene in the presence of 3 eq. of K_2CO_3 (entry 5). Lower amounts of base (entry 6) or other solvents, as exemplified for CH_2Cl_2 (entry 7, similar non-selective results were obtained when using THF), were found to be less-suited however. Testing the 3,4,5-trifluorobenzene-decorated catalyst **B2** with K_2CO_3 in toluene next (entry 8) allowed for a slightly higher selectivity but still gave a relatively low yield only. Spirobiindane-based salts **C** emerged as promising alternative quaternary ammonium salt scaffolds recently [40,41] and were also the catalysts of choice in our recently developed β-selective allenoate addition of isoxazolidinones **2** (compare with Scheme 1B [18]). Unfortunately, these catalysts were found to be less-suited for our azlactone protocol, as exemplified for derivative **C1** (entry 9).

Accordingly, we carried out our final optimization using Maruoka's catalyst **B2** (entries 10-14). By testing different bases and lower temperatures as well as lower catalyst loadings we identified the use of 3 eq. Cs_2CO_3 in toluene (0.05 M) at room temperature as the best-suited conditions (entry 13), allowing for the synthesis of **5a** in moderate yield (61%) and enantioselectivity (81:19 e.r.).

Table 1: Optimization of the addition of azlactone **1a** to allenoate **3a**[a].



Entry	Cat.	Base	solvent	T [°C]	Yield[b]	e.r.[c]
1	**A1**	K_2CO_3	toluene	25	41	58:42
2	**A2**	K_2CO_3	toluene	25	45	60:40
3	**A3**	K_2CO_3	toluene	25	40	58:42
4	**A4**	K_2CO_3	toluene	25	45	60:40
5	**B1**	K_2CO_3	toluene	25	55	75:25
6	**B1**	K_2CO_3 (1 eq.)	toluene	25	20	72:28
7	**B1**	K_2CO_3	CH_2Cl_2	25	33	51:49
8	**B2**	K_2CO_3	toluene	25	50	80:20
9	**C1**	K_2CO_3	toluene	25	40	68:32

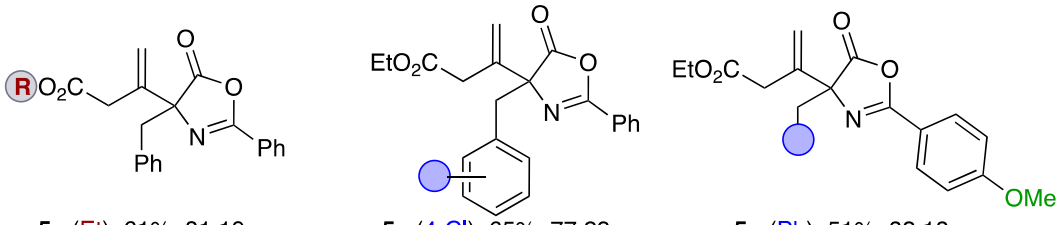
10	**B2**	K_2CO_3	toluene	0	45	80:20
11	**B2** (5%)	K_2CO_3	toluene	0	41	77:23
12	**B2**	K_3PO_4	toluene	25	55	81:19
13	**B2**	Cs_2CO_3	toluene	25	61	81:19
14	**B2**	Cs_2CO_3	toluene (0.1 M)	25	75	73:27

[a] Unless otherwise stated, all reactions were carried out by stirring **1a** (0.1 mmol), the allenoate (2 eq.), the indicated base and the catalyst, in the given solvent (0.05 M based on **1a**) at the given T for 24 h.

[b] Isolated yield.

[c] Determined by HPLC using a chiral stationary phase ((-)-**5a** was obtained as the major enantiomer when using the (*R*,*R*)-configurated catalysts **B**).

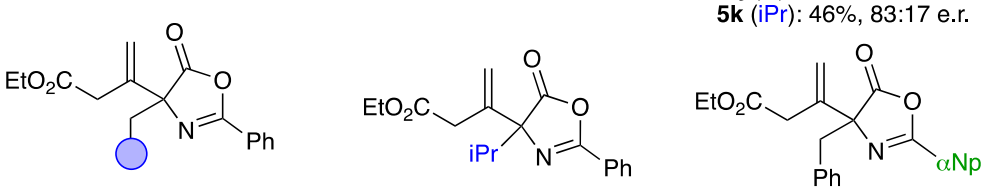
With optimized conditions for the synthesis of enantioenriched (-)-**5a** at hand, we next investigated the generality of this protocol. As outlined in Scheme 2, differently substituted allenoates were reasonably well tolerated (see products **5a**-**d**), albeit some erosion in enantioselectivity was observed when using a t-butyl ester containing allenoate (product **5d**). Various α-arylmethyl-substituted azlactones **1** performed similarly as compared to the parent system **1a** (products **5e**-**l**), and analogous α-alkyl-substituted derivatives were reasonably well accepted too (**5j**-**o**). When varying the aryl substituent in position **2** of the oxazolone core (compare products **5a**, **5g**, and **5p**) we found that increasing the steric bulk (**5p**) leads to a somewhat lower enantioselectivity, while the methoxy-substituent does not have a strong impact on the yield. It should however be stated that some of the methoxy-containing products, i.e. the α-alkyl-substituted **5j** and **5k** tend to undergo partial nucleophilic ring opening by residual water during column chromatography.



5a (Et): 61%, 81:19 e.r.
5b (Me): 67%; 80:20 e.r.
5c (Bn): 47%; 82:18 e.r.
5d (tBu): 56%; 67:33 e.r.

5e (4-Cl): 65%, 77:23 e.r.
5f (4-NO_2): 49%; 79:21 e.r.

5g (Ph): 51%, 82:18 e.r.
5h (4-ClC_6H_4): 80%, 81:19 e.r.
5i (4-$NO_2C_6H_4$): 80%, 78:22 e.r.
5j (H): 67%, 78:22 e.r.
5k (iPr): 46%, 83:17 e.r.



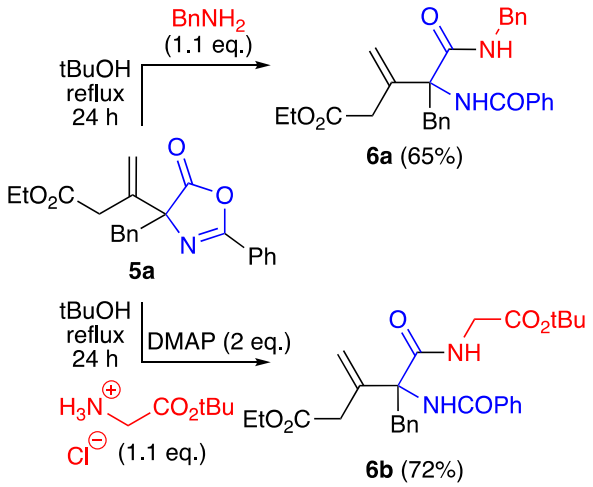
5l (Cy): 65%, 81:19 e.r.
5m (iPr): 70%, 79:21 e.r.
5n (H): 71%, 75:25 e.r.

5o: 81%, 74:26 e.r.

5p: 91%, 73:27 e.r.

Scheme 2: Application scope (conditions as detailed in entry 13, Table 1).

Finally, we also tested the suitability of products **5** to access acyclic α-AA derivatives by means of nucleophilic azlactone-opening reactions. Gratifyingly primary amines can be easily utilized under reflux conditions to access the amide derivatives **6a** and **6b** straightforwardly (Scheme 3), thus demonstrating the versatility of compounds **5** to access more complex acyclic α-AA derivatives in a straightforward manner.



6a (65%)

5a

6b (72%)

Scheme 3: Azlactone opening reactions.

Conclusion

The development of novel catalytic methods for the asymmetric synthesis of non-natural amino acid derivatives is a contemporary task and we herein introduce an organocatalytic protocol for the β-selective addition of various azlactones **1** to allenoates **3**. Upon using Maruoka's spirocyclic binaphthyl-based quaternary ammonium salts **B** as catalysts this transformation can be achieved with enantioselectivities up to 83:17 e.r.. Furthermore, the herein accessed cyclic products **5** could be successfully engaged in ring-opening reactions with different amines, thus giving access to the acyclic α-amino acid-based amides **6** straightforwardly.

Experimental

General details

^{1}H-,^{13}C- spectra were recorded on a Bruker Avance III 300 MHz spectrometer with a broad band observe probe. All NMR spectra were referenced on the solvent residual peak ($CDCl_3$: δ 7.26 ppm for ^{1}H NMR and δ 77.16 ppm for ^{13}C NMR). NMR data are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet), coupling constants (Hz).

High resolution mass spectra were obtained using a Thermo Fisher Scientific LTQ Orbitrap XL with an Ion Max API Source and analyses were made in the positive ionization mode if not otherwise stated.

HPLC was performed using a Shimadzu Prominence system with a diode array detector with a CHIRALPAK AD-H, CHIRAL ART Amylose-SA, (250 × 4.6 mm, 5 µm) chiral stationary phase. Optical rotations were recorded on a Schmidt + Haensch Polarimeter Model UniPol L1000 at 589 nm ([α]D values are listed in deg/(dm(g/cm^3)); concentration c is given in g/100 mL).

Unless otherwise stated, all chemicals were purchased from commercial suppliers and used without further purification. Dry solvents were obtained from an MBraun-SPS-800 solvent purification system. All reactions were carried out under argon atmosphere unless stated otherwise.

Azlactones 1 and allenoates **3** were synthesized according to previously published procedures [18,42-44].

General Procedure

An oven-dried Schlenk tube equipped with a stirring bar was charged with the azlactone **1** (0.05 – 0.1 mmol), catalyst **B2** (10 mol% related to 1), and Cs_2CO_3 (3 eq.). Then the respective allenoate **3** (2 eq.) and toluene (0.05 M with respect to **1**) were added and the mixture was stirred at room temperature for 24 h (Ar atmosphere). The crude product was passed through a short column of silicagel (rinsed with DCM and EtOAc), concentrated under reduced pressure, and subsequently purified by preparative TLC (silica gel, heptanes/EtOAc = 4/1) to obtain the products **2** in the given yields and enantiopurities.

Details for the parent compound 5a (details for the other targets can be found in the online supporting information)

Obtained as a colorless oil in 61% yield (81:19 e.r.) on 0.1 mmol scale. $[\alpha]_D^{22}$ = -11.4 (c 1.1, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$, 298.0 K): δ / ppm = 7.85 (2H, dd, *J* = 8.6, 1.4 Hz), 7.54 (1H, t, *J* = 7.4 Hz), 7.43 (2H, t, *J* = 7.53 Hz), 7.24-7.11 (5H, m), 5.79 (1H, s), 5.37 (1H, s), 4.14-3.90 (2H, m), 3-52-3.16 (4H, m), 1.15 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K): δ / ppm = 177.4, 171.0, 160.3, 139.1, 133.8, 132.6, 130.5, 128.6, 128.0, 127.8, 127.3, 125.6, 118.1, 75.9, 60.9, 44.9, 39.3, 13.9; HRMS (ESI) m/z: calculated for $[C_{22}H_{21}NO_4 + H]^+$: 364.1543; found: 364.1554, HPLC: (Chiralpak SA,

eluent: n-hexane:i-PrOH = 100/2, 0.5 mL· min-1, 20 °C, λ = 254 nm) retention times: t_{major} = 16.15 min , t_{minor} = 17.00 min.

Supporting Information

Full experimental and analytical details and copies of NMR spectra and HPLC traces can be found in the online supporting information.

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