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Asymmetric phase-transfer catalysed β-addition of isoxazolidin-5-ones to MBH carbonates†

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A novel high yielding, *enantio*- and diastereoselective protocol for the synthesis of α-allylated highly functionalised β-amino acid derivatives by adding isoxazolidin-5-ones to MBH carbonates under asymmetric phase-transfer catalysis has been developed.

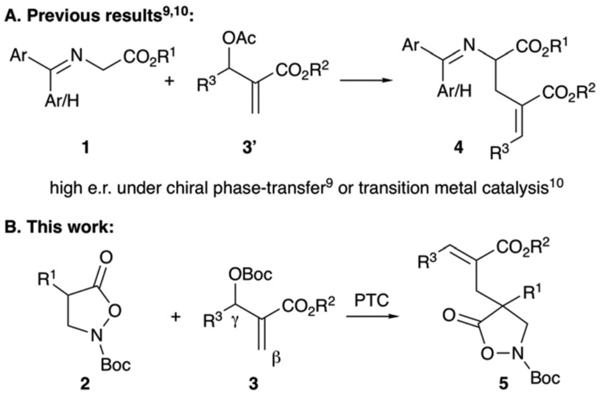
Introduction

Chiral phase-transfer catalysis is one of the most powerful strategies to achieve the catalytic non-covalent asymmetric control of prochiral nucleophiles in stereoselective transformations (*i.e.* C–C bond forming reactions *via* alkylations or conjugate additions and heterofunctionalization reactions).[1] Among the many enantioselective applications that rely on the use of chiral phase-transfer catalysts (PTCs), asymmetric syntheses of chiral natural and non-natural amino acids have attracted maybe the most interest.[2] Here asymmetric α-functionalization reactions of glycine Schiff bases **1** to access chiral α-amino acids have been a very thoroughly investigated topic.[2–4] On the other hand, the synthesis of chiral β-amino acids under chiral phase-transfer catalysis has so far mainly been associated with Mannich type approaches,[1] while the use of simple isoxazolidin-5-ones **2** as starting materials for the asymmetric syntheses of α,α-difunctionalized β-amino acids emerged only recently as a powerful and complementary strategy.[5–7] While Briere and co-workers have used compounds **2** as starting materials in asymmetric PT-catalysed transformations,[5] the groups of Shibasaki and Cossy independently developed asymmetric transition metal-catalysed allylation approaches by using these interesting pronucleophiles.[6]

In general, also the use of easily available Morita–Baylis–Hillman adducts **3** under asymmetric organocatalysis allows for highly enantioselective allylation reactions,[8] thus resulting in a complementary strategy to transition metal-catalysed allylation approaches. Very interestingly, more than 10 years ago O'Donnell's group already demonstrated that the use of chiral Cinchona alkaloid-based PTCs allows for the highly enantioselective β-addition of glycine Schiff bases **1** to allylic acetates **3′** (Scheme 1A).[9,10] Besides this inspiring initial report,[9] it was also impressively shown that, based on the nature of the employed catalyst, the nucleophilic attack on allylic substrates **3** can either occur in the β- or in the γ-position.[11,12]

Our groups have over the last years focused on the syntheses of chiral amino acids by using asymmetric phase-transfer catalysis,[4] and we were now interested in the achievement of the stereoselective α-allylation of β-amino acid precursors **2** by reacting them with the simple MBH-carbonates **3** under asymmetric phase-transfer conditions (Scheme 1B).

Inspired by the work of O'Donnell,[9] we rationalized that the PT-catalysed addition of **2** should also predominantly occur to the β-position of acceptor **3**, which would thus result in a complementary protocol (compared to the previous reports by



Scheme 1 Known reaction of glycine Schiff bases **1** with MBH acetates **3′** and targeted reaction of β-amino acid-based compounds **2** with MBH carbonates **3**.

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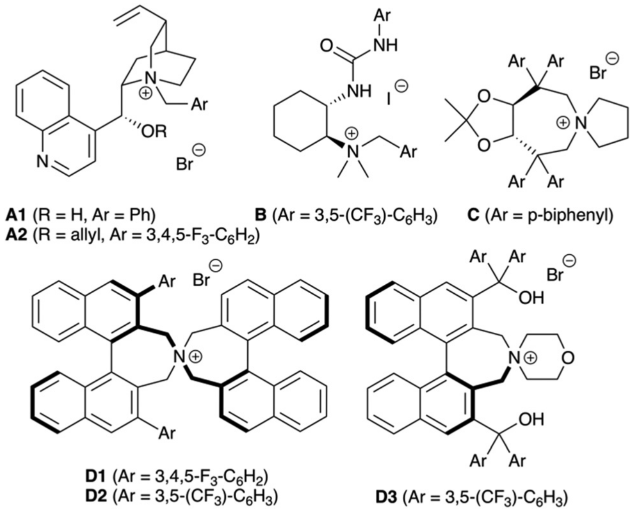


Fig. 1 Chiral PTCs used in this study.

Cossy and Shibasaki[6]) for the allylation of the masked β-amino acids **2**.

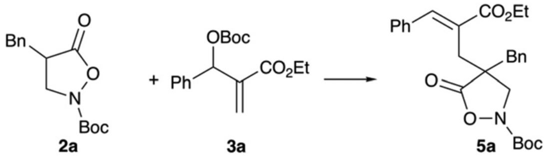
As chiral catalysts we focused on the use of easily available Cinchona derivatives **A**,[1] our own bifunctional system **B**,[13] our tartaric acid-based ammonium salt **C**,[4] and on the commercially available Maruoka catalysts **D**[14] (Fig. 1).

Results and discussion

We started our screening by investigating the reaction between the benzyl-substituted isoxazolidin-5-one **2a** and the parent MBH carbonate **3a** (Table 1 gives an overview of the most significant results obtained using the chiral PTCs **A–D** under a variety of different conditions). The first reactions were carried out with tetrabutylammonium bromide (TBAB) as an achiral PTC. As anticipated the addition of **2a** to the conjugated acceptor **3a** occurs exclusively to the β-position, giving the (*E*)-configurated product **5a** as the main product (entry 1). By focusing on chiral Cinchona alkaloid-based PTCs **A** next, we unfortunately realized that, independent of the solvent and/or the nature/amount of the base, only racemic product can be obtained (entries 2–6). Interestingly also, the amount of base has a crucial effect on the conversion rate (compare entries 2 and 5). Based on our recent progress in the design and use of bifunctional ammonium salts like compound **B**,[13] we next tested this catalyst, but again no enantioenrichment could be observed (entry 7). Intriguingly, the reaction proceeded significantly faster even with only 1.1 equiv. of base compared to the reactions with catalysts **A**.

Briere and co-workers recently described several asymmetric phase-transfer catalysed transformations of compounds **2** and in these reports[5] they also found that catalyst classes **A** and **B** are not suited to achieve any face-differen-

Table 1 Identification of the most selective catalyst and the optimum reaction conditions



Entry[a]	Cat.	Solvent	Base	T [°C]	t [h]	Yield[b] [%]	E/Z[c]	e.r.[d]
1	TBAB (10%)	THF	Cs_2CO_3 (20 eq.)	25	16	94	5 : 1	—
2	**A2** (5%)	THF	Cs_2CO_3 (20 eq.)	25	16	84	6 : 1	48 : 52
3	**A2** (5%)	CH_2Cl_2	Cs_2CO_3 (20 eq.)	25	16	39	5 : 1	49 : 51
4	**A2** (5%)	CH_2Cl_2	K_3PO_4 (20 eq.)	25	16	43	3 : 1	46 : 54
5	**A2** (5%)	THF	Cs_2CO_3 (1.1 eq.)	25	16	<5	—	—
6	**A1** (5%)	THF	Cs_2CO_3 (1.1 eq.)	25	72	54	4 : 1	51 : 49
7	**B** (5%)	THF	Cs_2CO_3 (1.1 eq.)	25	48	75	5 : 1	50 : 50
8	**C** (5%)	THF	Cs_2CO_3 (3 eq.)	25	24	60	6 : 1	49 : 51
9	**D1** (5%)	THF	Cs_2CO_3 (3 eq.)	25	24	86	6 : 1	74 : 26
10	**D1** (2%)	THF	Cs_2CO_3 (3 eq.)	25	72	73	6 : 1	71 : 29
11	**D1** (10%)	THF	Cs_2CO_3 (3 eq.)	25	24	95	7 : 1	75 : 25
12	**D2** (5%)	THF	Cs_2CO_3 (3 eq.)	25	24	82	5 : 1	85 : 15
13	**D3** (5%)	THF	Cs_2CO_3 (3 eq.)	25	24	26	5 : 1	50 : 50
14	**D2** (5%)	THF	Cs_2CO_3 (1.1 eq.)	25	24	<5	—	—
15	**D2** (5%)	CH_2Cl_2	Cs_2CO_3 (1.1 eq.)	25	96	60	3 : 1	78 : 22
16	**D2** (5%)	THF	K_2CO_3 (3 eq.)	25	24	<5	—	—
17	**D2** (5%)	MTBE	Cs_2CO_3 (3 eq.)	25	72	86	7 : 1	83 : 17
18	**D2** (5%)	iPr_2O	Cs_2CO_3 (3 eq.)	25	48	90	7 : 1	87 : 13
19	**D2** (5%)	iPr_2O	Cs_2CO_3 (3 eq.)	−20	96	90	10 : 1	94 : 6
20	**D2** (5%)	iPr_2O	Cs_2CO_3 (3 eq.)	−30	96	50	12 : 1	94 : 6
21	**D2** (5%)	THF	Cs_2CO_3 (3 eq.)	−40	96	23	7 : 1	96 : 4
22	**D1** (5%)	THF	Cs_2CO_3 (3 eq.)	−40	96	39	7 : 1	85 : 15

[a] Using 0.1 mmol **2a** and 0.15 mmol **3a** (c = 0.05 M). [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by HPLC using a chiral stationary phase.

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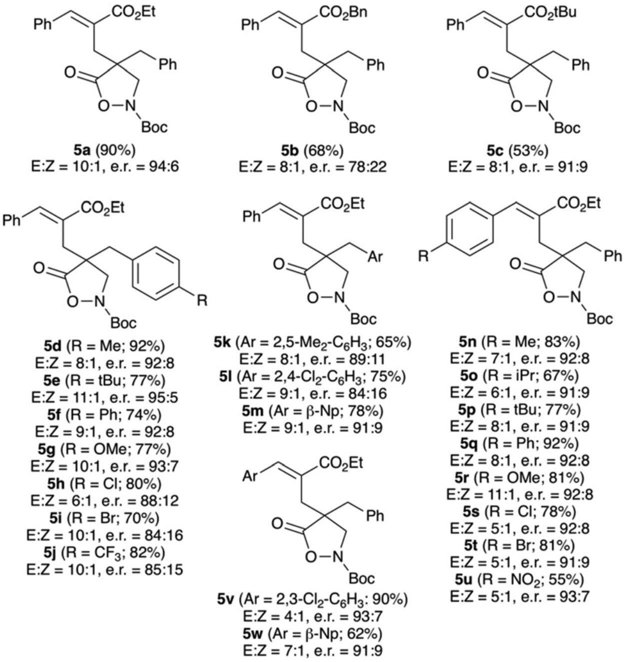
tiation with this unique pronucleophile. In contrast, the more rigid Maruoka catalysts **D** were found to be much better suited in their case studies, and we therefore tested the commercially available derivatives **D1–3** as well as our own tartaric acid-based spiroammonium salt **C**[4] next.

While ammonium salt **C** was found to be not selective (entry 8), the first experiment carried out with catalyst **D1** gave product **5a** in high yield and with a promising initial e.r. of 74 : 26 (entry 9). Carrying out the reaction with different catalyst loadings showed no pronounced effect (entries 9–11) and we thus used 5 mol% of catalyst for the further optimization. Also, different concentrations and stoichiometric ratios of the reagents were tested at that point (not given in the table), but no notable change in performance was observed. Testing catalysts **D2** and **D3** next, we found that the spiro-bis-binaphthyl-based derivative **D2** allows for a clear increase in the selectivity (entry 12), while the bifunctional **D3** did not give any asymmetric induction at all (entry 13). It was also found that 3 equiv. of Cs_2CO_3 in an ether solvent is the combination of choice to achieve reasonable yields and selectivities with catalyst **D2** (entries 14–16) and we therefore screened different ethers next. While MTBE did not result in any improvement, diisopropylether (iPr_2O) allowed for a slightly higher e.r. at room temperature (entry 18). The selectivity could be further improved by lowering the temperature from −20 to −40 °C (entries 19–22), although the reaction slowed down significantly at temperatures below −20 °C (no product formation in iPr_2O at −40 °C and only a very slow reaction in THF at −40 °C).

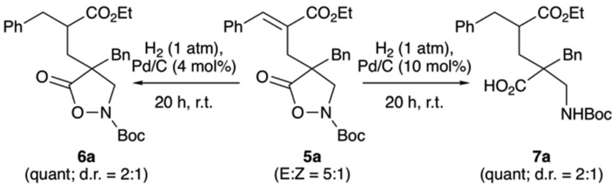
Based on that extensive screening, we thus chose the conditions given in entry 19 (5 mol% of **D2** in iPr_2O at −20 °C) to carry out the investigation of the application scope next (Scheme 2).

It turned out that the reaction performs best with ethyl ester-based MBH-carbonates **3** (compare products **5a–c**). Structural changes on the nucleophile **2** were relatively well tolerated (see products **5d–m**), although some reduced enantioselectivities were observed when accessing the halide- and CF_3-substituted products **5h**, **5i**, **5j**, **5l**. On the other hand, variations on the acceptor **3** turned out to have a rather minor effect only (products **5n–w**), thus resulting in an overall satisfyingly robust protocol to obtain these novel highly functionalized β-amino acid derivatives shown in Scheme 2 with reasonable yields and high diastereo- and enantioselectivities. The only real limitation that we observed so far was when we carried out the reaction with an α-i-propyl containing isoxazolidin-5-one **2**, which did not result in any product formation at all (under the racemic as well as the asymmetric reaction conditions).

Concerning the absolute configuration of products **5** it must be admitted that we have not yet been able to obtain crystals of satisfying quality of the enantioenriched products. We only obtained good crystals of racemic **5f** which also proved the (*E*)-double bond configuration (which is in accordance to NMR investigations).[15]



Scheme 2 Application scope for the asymmetric reaction of β-amino acid-based compounds **2** with MBH carbonates **3** (all reactions were carried out under the conditions shown in entry 19, Table 1; the *E* : *Z* ratios were determined by NMR of the crude product mixture; the enantiomeric ratios are given for the major diastereomere and were measured by HPLC using a chiral stationary phase).



Scheme 3 Heterogenous atmospheric pressure hydrogenation of compound **5a**.

Finally, we also investigated the atmospheric pressure hydrogenation of compound **5a** under heterogeneous conditions (using Pd/C, Scheme 3). Here we found that double bond hydrogenation to obtain compound **6** occurs easily, albeit with some erosion of d.r., followed by N–O cleavage to **7** when using a slightly larger amount of hydrogenation catalyst.

Conclusions

We developed a novel metal-free α-allylation protocol to access highly functionalized β-amino acid derivatives **5** by carrying out the asymmetric phase-transfer catalysed addition of isoxazolidin-5-ones **2** to MBH carbonates **3**. Very interestingly, a variety of commonly employed asymmetric PTCs did not give any noteworthy levels of enantioselectivities for this new transformation, while the reaction proceeds with satisfying *enantio-*

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and diastereoselectivities only when using the commercially available Maruoka type catalyst **D2**.

Experimental details[16]

General procedure

The Baylis–Hillman carbonates **3a–m** (1.5 eq., 0.15 mmol), benzyl-substituted isoxazolidin-5-ones **2a–k** (1.0 eq., 0.10 mmol) and catalyst **D2** (0.05 eq., 0.005 mmol, 5.4 mg) were charged to a Schlenk tube (under argon atmosphere), dissolved in 2.0 ml of isopropyl ether, and the mixture cooled to −20 °C. After 20 minutes, Cs_2CO_3 (3.0 eq., 0.30 mmol, 98 mg) was quickly added and the mixture was stirred at −20 °C for 96 h (1000 rpm). Then, the mixture was filtered over a pad of Na_2SO_4, washed with DCM, the solvent evaporated and the residue dried *in vacuo*. The resulting crude product was purified by chromatography (silica gel, heptane–ethyl acetate, 15/1 to 10/1) to afford enantioenriched products **5a–w**.

Analytical data for 5a

$[\alpha]_D^{25} = 43.9°$ (c = 0.41, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 298 K) δ 7.83 (s, 1H), 7.30–7.06 (m, 8H), 7.04–6.94 (m, 2H), 4.21 (q, J = 7.1 Hz, 2H), 3.82–3.70 (m, 2H), 3.06 (s, 2H), 2.96 (d, J = 13.9 Hz, 1H), 2.58 (d, J = 13.9 Hz, 1H), 1.40 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 298 K) δ 175.5, 167.7, 154.9, 143.5, 134.9, 134.9, 130.4, 128.9, 128.8, 128.7, 128.7, 128.0, 127.4, 83.6, 61.4, 54.4, 49.8, 40.8, 31.7, 28.1, 14.1 ppm; IR (film): ν (cm^{-1}) 2977, 2938, 1794, 1712, 1454, 1369, 1254, 1202, 1146, 1095, 1022, 848, 754, 701; HRMS (MALDI-FT ICR): m/z calcd for $C_{27}H_{31}NNaO_6$ $[M + Na]^+$ = 488.20456, found: 488.20359; The enantioselectivity was determined by HPLC (Chiralpak AD-H column, n-hexane : i-PrOH = 95 : 5, 0.5 mL min^{-1}, 10 °C, t_{major} = 46.8 min, t_{minor} = 61.4 min).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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15 CCDC 1870182† contains the supplementary crystallographic data for **5f**.

16 Full experimental and analytical details can be found in the online ESI.†

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