Enantioselective β-Selective Addition of Isoxazolidin-5-ones to Allenoates Catalyzed by Quaternary Ammonium Salts

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Dedicated to Prof. Cristina Nevado on the occasion of her reception of the 2021 Dr. Margaret Faul Women in Chemistry Award (and thanks for being one of the best friends one can imagine ever since we wrestled with the Iejimalides Cris!!).

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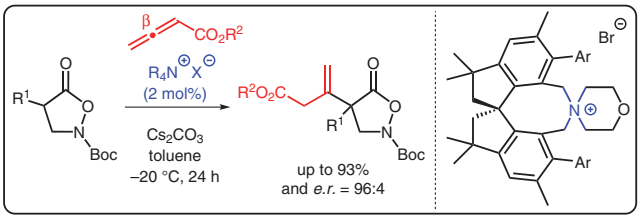
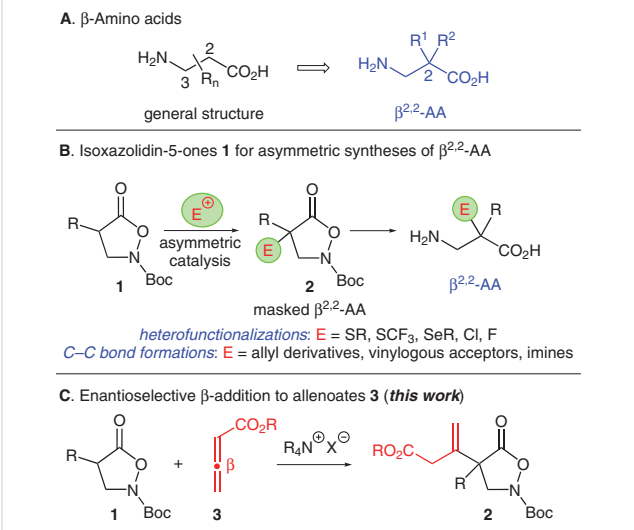
Abstract The enantioselective addition of isoxazolidin-5-ones to the β-carbon of allenoates has been carried out by using a novel spirobiindane-based quaternary ammonium salt catalyst. This protocol, which proceeds under classical liquid-solid phase-transfer conditions, gives access to unprecedented highly functionalized $\beta^{2,2}$-amino acid derivatives with good enantioselectivities and in high yields, and further manipulations of these products have been carried out as well.

Key words ammonium salt catalysis, organocatalysis, β-amino acids, heterocycles, allenoates

Enantioselective non-natural amino acid syntheses[1,2] have for decades been amongst the most important transformations and the value of the thereby accessed chiral target molecules inspired the development and introduction of a variety of broadly applicable synthesis and catalysis concepts.[3,4] Nowadays, numerous often routinely employed strategies to access a multitude of differently functionalized non-natural α-amino acids (α-AA)[3] and β-amino acids (β-AA)[4] have been introduced and the field is still a very heavily investigated one. Next to the general focus on the development of broadly applicable novel catalysis concepts and synthesis strategies, also the introduction and utilization of carefully designed synthetically useful AA-precursors (or masked AA derivatives) has been of major interest and value. Besides the more 'traditional' focus on α-AA and α-AA-based peptides,[3] non-natural β-AA have emerged as valuable targets, as the introduction of β-AA into the peptides, as well as the preparation of chiral β-AA-based heterocycles, can lead to peptidomimetics with outstanding biological properties.[4,5] Depending on their substitution pattern, different classes of β-AA can be defined (Scheme 1A), and efficient synthesis strategies to access these individual families have been developed.[4] Amongst them, the enantioselective syntheses of $\beta^{2,2}$-AA remained challenging until recently,[6–12] when Brière's group introduced the direct synthesis of isoxazolidin-5-ones **1** starting from easily accessible Meldrum's acid derivatives.[6] Compounds **1** have since then been established as versatile β-AA surrogates, which can be reacted in an asymmetric manner with different electrophiles to access the masked cyclic $\beta^{2,2}$-AA deriva-





Scheme 1 β-Amino acids (A), the recently established isoxazolidin-5-one strategy to access $\beta^{2,2}$-AA (B), and the herein investigated addition of compounds **1** to allenoates **3** (C)

tives **2** straightforwardly (Scheme 1B).[7–11] These highly functionalized chiral heterocycles provide a straightforward entry to free β[2,2]-AA and small peptides as well as for heterocyclic amino acid derivatives.[13]

Our group has been interested in these versatile heterocycles for a few years now and so far we have succeeded in introducing chiral quaternary ammonium salt-catalyzed approaches[14] for asymmetric α-C–C-bond formations[9] as well as α-heterofunctionalizations.[11] In ongoing attempts to expand the use of compounds **1** to access novel chemical space by targeting highly functionalized enantioenriched heterocycles **2** via asymmetric α-functionalization reactions, we now became interested in using allenoates **3** as possible C_{sp}-electrophiles (undergoing β-addition).[15–19] Interestingly, the acceptor properties of allenoates **3** can be tuned by nature of the catalyst system.[15] While the use of (chiral) phosphine catalysts usually allows for γ-additions, it has also been reported that the use of simple inorganic Brønsted bases,[17] chiral organobases,[19] or the use of chiral quaternary ammonium salt catalysts under classical phase-transfer conditions[18] allow for β-selective additions of C-nucleophiles (i.e., in situ generated enolate species) with promising enantioselectivities.[18,19] Based on these inspiring contributions, that is, Jørgenson's seminal report[18] on the use of allenoates as β-acceptors under asymmetric ammonium salt catalysis, we thus became interested in exploring the enantioselective β-addition of pronucleophiles **1** to allenoates **3** by using chiral quaternary ammonium salt catalysts (Scheme 1C).

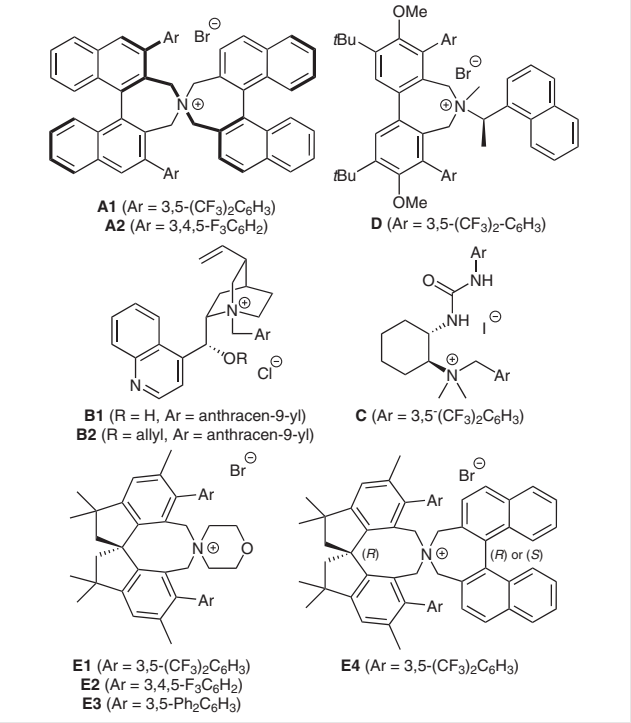


Figure 1 Chiral ammonium salt catalysts used herein

We started our investigations by focusing on the addition of the parent isoxazolidin-5-one **1a** to ethyl allenoate **3a** in the presence of known (**A–D**)[14,20–22] and new (**E**) chiral ammonium salt catalysts (Figure 1). Table 1 gives an overview of the most significant results obtained in a detailed screening of different catalysts and conditions.

Initial trials with Maruoka's binaphthyl-based catalysts **A**[20] showed that the intended β-addition is proceeding well under the chosen biphasic phase-transfer conditions (giving product **2a** in over 70% yield) but with very little enantioenrichment only (Table 1, entries 1 and 2). These low se-

Table 1 Identification of the Best-Suited Catalyst and Conditions for the Enantioselective Addition of **1a** to **3a**[a]

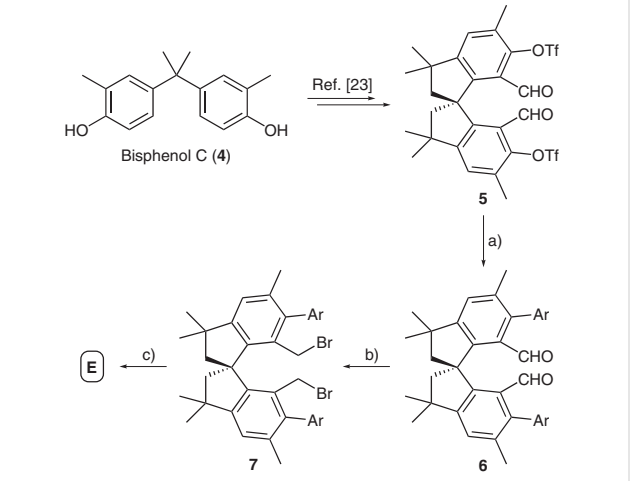
Entry	Catalyst	Base	Solvent	Temp (°C)	Yield (%)[b]	*e.r.*[c]
1	**A1**	Cs_2CO_3	toluene	25	77	38:62
2	**A2**	Cs_2CO_3	toluene	25	71	46:54
3	**B1**	Cs_2CO_3	toluene	25	65	54:46
4	**B2**	Cs_2CO_3	toluene	25	53	55:45
5	**C**	Cs_2CO_3	toluene	25	49	50:50
6	**D**	Cs_2CO_3	toluene	25	88	84:16
7	**D**	Cs_2CO_3	toluene	–20	87	88:12
8	**E1**	Cs_2CO_3	toluene	25	82	84:16
9	**E2**	Cs_2CO_3	toluene	25	76	69:31
10	**E3**	Cs_2CO_3	toluene	25	74	58:42
11	(*R*,*R*)-**E4**	Cs_2CO_3	toluene	25	94	35:65
12	(*R*,*S*)-**E4**	Cs_2CO_3	toluene	25	85	30:70
13	**E1**	K_2CO_3	toluene	25	85	75:25
14	**E1**	K_2HPO_4	toluene	25	16	81:19
15	**E1**	Cs_2CO_3	CH_2Cl_2	25	78	60:40
16	**E1**	Cs_2CO_3	MTBE	25	80	70:30
17	**E1**	Cs_2CO_3	*o*-xylene	25	89	82:18
18	**E1**	Cs_2CO_3	toluene	–20	80	89:11
19	**E1** (2%)	Cs_2CO_3	toluene	–20	86	89:11
20	**E1** (1%)	Cs_2CO_3	toluene	–20	92	87:13
21	**E1** (0.1%)	Cs_2CO_3	toluene	–20	85	86:14
22	**E1** (2%)	Cs_2CO_3	toluene[d]	–20	78	91:9
23[e]	**E1** (2%)	Cs_2CO_3	toluene[d]	–20	90	91:9

[a] All reactions were run for 20–24 h using 0.1 mmol **1a**, 0.12 mmol **3a**, 0.11 mmol base and 5 mol% of the catalyst in the indicated solvent (*c* = 0.1 M with respect to **1a**) at the given temperature, unless otherwise stated.
[b] Isolated yields.
[c] Measured by HPLC using a chiral stationary phase, given as the ratio of (+):(–)-enantiomer.
[d] *c* = 0.05 M with respect to **1a**.
[e] Using 3 equiv base and 5 equiv allenoate **3a**.

lectivities came as a surprise as we,[9,11] as well as others,[10] found these ammonium salt catalysts being well-suited for asymmetric α-functionalizations of compounds **1** in the past. As we were not able to overcome this obstacle by variation of the conditions, we next tested other catalyst scaffolds. While cinchona alkaloid-based salts **B**[14,18] and our own bifunctional ammonium salt **C**[21] failed (entries 3–5), Lygo's biphenyl-based catalyst **D**[22] gave good levels of enantioselectivity (up to *e.r.* = 88:12 when lowering the temperature to –20 °C; entries 6 and 7).

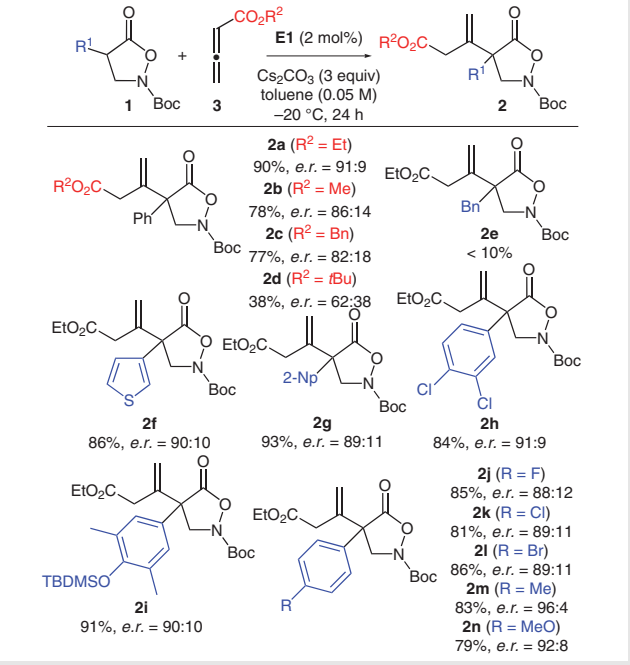
During the initial period of these investigations, we also started a project aiming on the design of spirobiindane-based ammonium salts **E** in our group. Relying on recent reports describing the straightforward synthesis of enantio-enriched dialdehyde **5** starting from bisphenol C (**4**),[23] we were able to develop a procedure to access ammonium salts **E** as summarized in Scheme 2.[24] Very interestingly, during our initial studies to establish this route for catalysts **E**, we became aware of a very similar approach reported by the groups of Xu and Bai,[25] who utilized bisphenol A (lacking the two aromatic methyl groups) to access analogous catalyst systems. Remarkably, they showed that these catalysts can be very successfully used already for asymmetric α-alkylations, thus demonstrating the potential of this new quaternary ammonium salt catalyst scaffold.[25] Gratifyingly, already the first attempt with the morpholine-based ammonium salt **E1** showed very promising initial results in our study (Table 1, entry 8) with enantioselectivity (*e.r.* = 84:16) and yield (82%) in the same range as the Lygo catalyst **D** (compare with entry 6). Inspired by this first hit, we next screened the analogous derivatives **E2** and **E3**, which, however, gave lower selectivities only (entries 9 and 10). In addition, we also prepared and tested the binaphthyl-spirobiindane hybrid system **E4** (using the *R*,*R* as well as the *R*,*S* stereoisomers; entries 11 and 12). Unfortunately, these interesting scaffolds were found to be not as selective as initially hoped for (considering the potential of Maruoka's catalysts) and for this reason we carried out the final optimization with the novel catalyst derivative **E1**[26] (entries 13–22). Testing different inorganic bases and solvents next (entries 13–17), we realized that the initial combination of solid Cs_2CO_3 (1.1 equiv) and toluene was already the most promising one. The enantioselectivity could be increased slightly when lowering the temperature (entry 18) and remained almost constantly high when lowering the catalyst loading (entries 19–21). Finally, carrying out the reaction under slightly more diluted conditions in the presence of 2 mol% **E1** resulted in a good *e.r.* of 91:9 with an acceptable isolated yield of 78% after 24 hours reaction time (entry 22) and the yield could be increased to 90% when using a larger excess of base and allenoate **3a** (entry 23).

Lower temperatures and higher dilution were screened as well, but no further improvement was possible anymore, and for that reason we investigated the application scope



Scheme 2 Syntheses[24] of catalysts **E**: *Reagents and conditions*: a) $ArB(OH)_2$, $Pd(PPh_3)_4$ (10 mol%), K_3PO_4 (2 equiv), KBr (10 mol%), DME/H_2O, reflux, 20 h; b) $NaBH_4$ (4 equiv), THF/MeOH, 0 °C, 90 min followed by HBr in AcOH (excess), reflux, 90 min; c) respective amine (1.5 equiv), $NaHCO_3$ (1.5 equiv), MeCN, 70 °C, 3 days

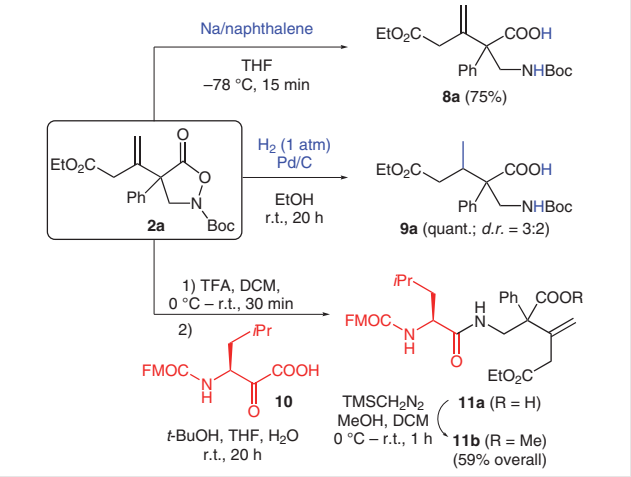
with the set of conditions outlined in entry 23, Table 1 next (Scheme 3; the excess of base and allenoate was used to ensure good conversion also in the case of starting materials **1** containing an electron-rich aryl substituent as those are usually less reactive). As can be seen from the results summarized in Scheme 3, a broad variety of different allenoates **3** and α-arylisoxazolidin-5-ones **1** were generally well-tolerated, albeit *tert*-butyl allenoates were found to be less



Scheme 3 Enantioselective application scope

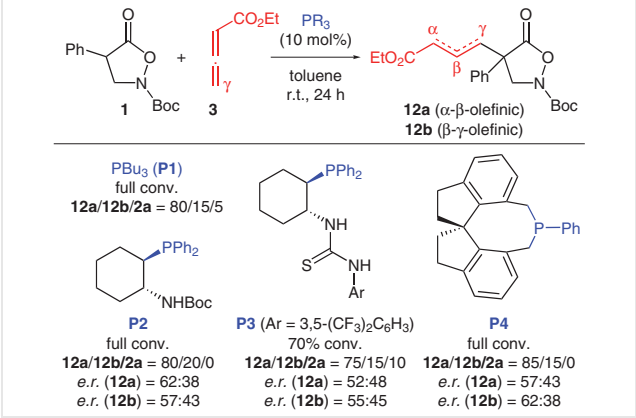
suited than sterically less demanding esters (compare products **2a–d**). The only real limitation that we, however, encountered was when we used α-Bn-containing compounds **1** instead of the α-aryl derivatives, as exemplified for compound **2e**, which was formed with rather low yield only (resulting from the well-documented[11] lower reactivity of the corresponding starting material **1**). Unfortunately, neither of the products **2** yielded crystals of sufficient quality for X-ray analysis and we were therefore not able to assign the absolute configuration of these novel compounds so far.

After investigating the asymmetric application scope, we also tested if compound **2a** can be transferred into the corresponding acyclic $\beta^{2,2}$-AA derivatives **8a** or **9a**. Gratifyingly, N–O reduction to product **8a** could be carried out selectively by using Na/naphthalene as the reducing agent.[8c] In contrast, the Pd-catalyzed heterogeneous hydrogenation of **2a** delivered product **9a** as a mixture of diastereomers instead (Scheme 4). Furthermore, it was possible to subject **2a** to an α-ketoacid-hydroxylamine (KAHA)-type ligation[8b,9b,27] with the α-ketoacid **10**, thus providing access to the mixed α-AA-β-AA dipeptide **11a** (which was isolated as its methyl ester **11b**; *d.r.* of **11b** equals the *e.r.* of the used starting material **2a**).



Scheme 4 Further manipulations of **2a**

As stated in the introductory part, the acceptor behavior of allenoates **3** can be influenced by the nature of the used organocatalysts.[15] As it has been well-established that the use of (chiral) tertiary phosphines leads to a preferred γ-attack of C-nucleophiles,[15] we also briefly tested the reaction between pronucleophiles **1** and allenoates **3** in the presence of (chiral) phosphine catalysts (Scheme 5). First racemic experiments with PBu_3 showed that γ-addition giving the α,β-unsaturated product **12a** is indeed the preferred pathway (accompanied by small quantities of the double bond isomer **12b** and the β-addition product **2a**). Attempts to render this reaction enantioselective next were unfortunately not very successful. A variety of easily available or commercially accessible chiral tertiary phosphines (mono- or bifunctional) were tested but, as exemplified for derivatives **P2–P4**, neither of them allowed for reasonable enantioselectivities. Thus, despite the general feasibility of this γ-addition process, the limited enantiocontrol that we obtained so far stopped us from investigating this reaction in more detail.



Scheme 5 Phosphine-catalyzed γ-addition

In conclusion, we have been able to develop a robust protocol for the asymmetric quaternary ammonium salt-catalyzed β-addition of isoxazolidin-5-ones **1** to allenoates **3**. The hereby accessible cyclic masked $\beta^{2,2}$-AA derivatives **2** could be obtained with good enantioselectivities and in high yields by using the novel spirobiindane-based ammonium salt catalyst **E** under liquid-solid biphasic phase-transfer conditions. The cyclic products **2** can be transferred in the acyclic $\beta^{2,2}$-AA derivatives **8** and **9** under reductive conditions then and undergo KAHA-type ligations as well (giving dipeptide **11**). In addition, we also succeeded in obtaining a first proof-of-concept for the γ-addition of compounds **1** to allenoates **3** under tertiary phosphine catalysis, albeit with low enantioselectivities only.

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance III 300 MHz spectrometer with a broad band observe probe and a sample changer and, on a Bruker Avance DRX 500 MHz spectrometer with an Ascend magnet and TCI cryoprobe, which are both the property of the Austro Czech NMR Research Center 'RERI uasb'. NMR spectra were referenced on the solvent peak and chemical shifts are given in ppm. High-resolution mass spectra were obtained using a Thermo Fisher Scientific LTQ Orbitrap XL with an Ion Max API Source. Analyses were made in the positive ionization mode, if not otherwise stated. Purine (exact mass for $[M + H]^+$ = 121.050873) and 1,2,3,4,5,6-hexakis(2,2,3,3-tetrafluoropropoxy)-1,3,5,2,4,6-triazatriphosphinane (exact mass for $[M + H]^+$ = 922.009798) were used for internal mass calibration. HPLC was performed using a Thermo Scientific Dionex Ultimate 3000 or a Shimadzu Prominence system with diode array detector with a Chiralpak AD-H, OD-H, Chiral ART Amylose-SA, Cellulose-SB, or Cellulose-SZ (250 × 4.6 mm, 5 µm) chiral stationary phase. Optical rotations were recorded on a Schmidt + Haensch Polarimeter Model UniPol L1000 at 589 nm. All chemicals were purchased from

commercial suppliers and used without further purification, unless otherwise stated. Isoxazolidin-5-ones **1**[8,10,11] and allenoates **3**[28] were synthesized as described previously. Anhydrous solvents were obtained from an MBraun-SPS-800 solvent purification system. All reactions were carried out under argon atmosphere, unless otherwise stated.

Synthesis Sequence to Access Catalysts E

Enantioenriched intermediate **5** was synthesized from Bisphenol C as reported previously.[23,24]

Synthesis of Dialdehydes 6; General Procedure

A pressure Schlenk tube was charged with compound (*R*)-**5** (3.5 equiv), boronic acid (2 equiv), K_3PO_4, and 10 mol% KBr in dimethoxyethane/H_2O (3:1). The mixture was degassed by performing three freeze-pump thaw cycles. $Pd(PPh_3)_4$ (10 mol%) was added and the reaction mixture was stirred at 90 °C for 17 h. The mixture was cooled to r.t., H_2O (20 mL) was added and the aqueous phase was extracted with EtOAc (4 × 15 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered over cotton; and the solvent was evaporated.

Analytical Details for Dialdehyde 6a (en Route to Catalyst E1)[24]

Obtained by starting from compound (*R*)-**5** (162 mg, 0.25 mmol) as a light-yellow foam; yield: 142 mg (73%); $[\alpha]_D^{23}$ –63.7 (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 9.46 (s, 2 H), 7.86 (s, 2 H), 7.57 (d, *J* = 4.3 Hz, 4 H), 7.34 (s, 2 H), 2.56 (s, 4 H), 2.03 (s, 6 H), 1.51 (s, 6 H), 1.48 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 191.1, 154.5, 149.3, 141.6, 140.3, 136.8, 131.8 (dq, *J* = 33.4, 10.2 Hz), 129.8, 129.5, 125.2 (d, *J* = 7.3 Hz), 121.5 (d, *J* = 7.4 Hz), 121.3, 59.1, 58.5, 43.3, 32.6, 32.0, 29.2, 22.8, 20.7, 14.2.

^{19}F NMR (282 MHz, $CDCl_3$, 298 K): δ = –62.7 (s), –62.9 (s).

HRMS (ESI): *m*/*z* calcd for $C_{41}H_{36}F_{12}NO_2^+$: 802.2549 $[M + NH_4]^+$; found: 802.2546.

Synthesis of Dibromides 7; General Procedure

Cross-coupling product (*R*)-**6** was dissolved in THF/MeOH (1:1, 0.025 M) and cooled to 0 °C. $NaBH_4$ (4 equiv) was slowly added and the reaction mixture was stirred for 1.5 h at 0 °C. The reaction was quenched by the addition of H_2O and the organic solvents were evaporated. The residue was extracted with EtOAc (4 ×) and the combined organic phases were washed with brine (1 ×). The organic phase was dried (Na_2SO_4), filtered over cotton, and the solvent was evaporated. The residue was taken up in HBr in AcOH (33%, 0.08 M) and refluxed for 1.5 h. After cooling to r.t., H_2O was added and the aqueous phase was extracted with EtOAc (4 ×). The combined organic phases were washed with H_2O (3 ×), sat. aq $NaHCO_3$ (1 ×), and brine (1 ×). The organic phase was dried (Na_2SO_4), filtered over cotton, and the solvent is evaporated.

Analytical Details for Dibromide 7a (en Route to Catalyst E1)[24]

Obtained by starting from (*R*)-**6a** (71 mg, 0.1 mmol) as a greenish brown oil; yield: 76 mg (93%); $[\alpha]_D^{24}$ +117.8 (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.90 (s, 2 H), 7.81 (s, 2 H), 7.66 (s, 2 H), 7.13 (s, 2 H), 3.86 (q, *J* = 10.2 Hz, 4 H), 2.68 (d, *J* = 13.6 Hz, 2 H), 2.45 (d, *J* = 13.6 Hz, 2 H), 1.97 (s, 6 H), 1.49 (s, 6 H), 1.43 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 153.2, 145.1, 141.3, 140.3, 137.1, 131.7 (dq, *J* = 33.3, 8.3 Hz), 131.3, 130.6, 130.4, 128.9 (d, *J* = 8.8 Hz), 125.5, 125.3 (d, *J* = 8.8 Hz), 121.7 (d, *J* = 8.8 Hz), 121.4, 118.0 (d, *J* = 8.8 Hz), 59.2, 56.8, 43.4, 32.7, 30.1, 29.9, 29.2, 21.3.

^{19}F NMR (282 MHz, $CDCl_3$, 298 K): δ = –62.8 (s), –63.0 (s).

Synthesis of Catalysts E; General Procedure

A pressure Schlenk tube was charged with catalyst precursor (*R*)-**7** and Na_2CO_3 (2 equiv) in MeCN (0.025 M). Amine (morpholine or binaphthylamine, 3 equiv) was added and the reaction mixture was stirred at 70 °C for 66 h. The mixture was cooled to r.t., filtered, and washed with DCM. The filtrate was evaporated to dryness. The crude product was purified by silica gel column chromatography (DCM, DCM/MeOH 10:1).

Analytical Details for Catalyst E1[24]

Obtained by starting from (*R*)-**7a** (161 mg, 0.18 mmol) as an off-white solid; yield: 159 mg (80%); $[\alpha]_D^{24}$ +96.5 (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.96 (s, 2 H), 7.84 (s, 2 H), 7.80 (s, 2 H), 7.32 (s, 2 H), 4.89 (d, *J* = 13.9 Hz, 2 H), 4.19 (d, *J* = 13.9 Hz, 2 H), 3.38–3.32 (m, 2 H), 3.11–3.09 (m, 2 H), 2.70–2.68 (m, 2 H), 2.64–2.50 (m, 4 H), 2.22 (d, *J* = 13.0 Hz, 2 H), 2.10 (s, 6 H), 1.58 (s, 6 H), 1.49 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 153.6, 149.6, 140.7, 140.3, 138.1, 133.6, 133.2, 132.8, 132.3, 131.6, 131.3, 129.0, 125.2, 124.8, 122.4, 118.0, 61.3, 61.0, 57.5, 56.9, 42.2, 32.6, 30.3, 21.8.

^{19}F NMR (282 MHz, $CDCl_3$, 298 K): δ = –62.3 (s), –62.8 (s).

HRMS (ESI): *m*/*z* calcd for $C_{45}H_{42}F_{12}NO^+$: 840.3069 $[M]^+$; found: 840.3070.

Addition Reactions of Compounds 1 to Allenoates 3; Asymmetric Synthesis of Products 2; General Procedure

A thermostatically controlled double-walled and oven-dried Schlenk tube equipped with a stirring bar was charged with catalyst **E1** (1.8 mg, 2 mol%), isoxazolidin-5-one **1** (0.1 mmol) and anhyd toluene (2 mL, 0.05 M with respect to **1**). The mixture was stirred until all components were completely dissolved to give a colorless solution, which was cooled to –20 °C. Cs_2CO_3 (97.7 mg, 3 equiv) and allenoate **3** (5 equiv) were added and the reaction mixture was stirred for 24 h under an argon atmosphere. After completion, the crude product was concentrated under reduced pressure and subsequently subjected to column chromatography (silica gel, heptanes/Et_2O 2:1) to obtain the β-addition products **2** in the given yields and enantiopurities.

Details for the Parent Product 2a[24]

Following the general procedure, the β-addition of **1a** (25.8 mg, 0.098 mmol) to **3a** (58 µL, 5 equiv) gave **2a** as a colorless oil; yield: 33 mg (90%, 0.088 mmol); *e.r.* = 91:9; R_f (heptanes/Et_2O 2:1) 0.27; $[\alpha]_D^{24}$ +120.2 (*c* 0.96, $CHCl_3$).

HPLC: YMC Chiral ART Amylose-SA, eluent: *n*-hexane/*i*-PrOH (20:1), 0.7 mL·min^{-1}, 20 °C, λ = 210 nm); t_R = 17.4 min (major), t_R = 15.1 min (minor).

^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.43–7.30 (m, 5 H), 5.43 (s, 1 H), 5.40 (s, 1 H), 4.62 (d, *J* = 12.0 Hz, 1 H), 4.57 (d, *J* = 12.0 Hz, 1 H), 4.01 (2 dq, *J* = 10.8, 7.2 Hz, 2 H), 3.06 (dd, *J* = 16.2, 0.9 Hz, 1 H), 2.98 (dd, *J* = 16.2, 0.9 Hz, 1 H), 1.37 (s, 9 H), 1.18 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 173.8, 170.6, 155.9, 138.5, 135.1, 129.1, 128.8, 127.5, 119.6, 84.2, 61.1, 58.0, 57.9, 38.4, 27.9, 14.2.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{29}N_2O_6^+$: 393.2020 [M + NH_4]$^+$; found: 393.2021.

Synthesis of Products 12; General Procedure

A reaction vial equipped with a stirring bar was charged with phosphine catalyst (10 mol%), *N*-Boc 4-phenylisoxazolidin-5-one **1a** (26.3 mg, 0.1 mmol), and toluene (1 mL, 0.1 M with respect to **1a**). Ethyl 2,3-butadienoate (**3a**; 14 µL, 1.2 equiv) was added and the resulting solution was stirred for 24 h at rt. After completion (determined by TLC analysis), the crude product was concentrated under reduced pressure and purified by preparative TLC (silica gel, heptanes/Et_2O 2:1) to obtain γ-addition products **12**.

Details of the Major Product 12a[24]

Obtained as a colorless oil, which solidified upon storage in a refrigerator when using 10 mol% of PPh_3; yield: 31.4 mg (84%, 0.084 mmol); R_f (heptanes/Et_2O 2:1) = 0.17.

^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.44–7.31 (m, 5 H), 6.68 (dt, *J* = 15.6, 7.6 Hz, 1 H), 5.86 (dt, *J* = 15.6, 1.3 Hz, 1 H), 4.69 (d, *J* = 11.9 Hz, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 4.06 (d, *J* = 11.9 Hz, 1 H), 2.83 (2 ddd, *J* = 14.6, 7.6, 1.3 Hz, 2 H), 1.31 (s, 9 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 174.8, 165.6, 155.9, 140.7, 135.4, 129.3, 128.8, 126.5, 84.3, 60.7, 57.8, 52.0, 39.9, 27.9, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{29}N_2O_6^+$: 393.2020 [M + NH_4]$^+$; found: 393.2017.

Further Transformations of Compound 2a

Reductive N–O Cleavage with Na/Naphthalene; Product 8a

To a flame-dried Schlenk tube equipped with a stirring bar were added recrystallized naphthalene (320 mg, 2.5 mmol) and anhyd THF (5 mL) under argon atmosphere. Na (63 mg, 2.7 mmol, 1.1 equiv) was added and the mixture was stirred for 30 min to provide a dark-green solution of sodium naphthalide. The freshly prepared reductant solution was added dropwise, via syringe, to a second Schlenk tube containing **2a** (34.6 mg, 0.092 mmol) in anhyd THF (3.4 mL, 0.03 M) at –78 °C, until the dark-green color of the reaction mixture persisted for at least 5 min. The reaction was quenched with deionized H_2O and warmed to rt. The pH value was lowered to 2 with aq 1 N HCl before it was extracted with DCM (3 ×). The collected organic phases were washed with brine, dried (anhyd Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography with gradient elution (silica gel, DCM/MeOH 1:0–10:1) to obtain **8a** as a colorless oil; yield: 26 mg (75%, 0.074 mmol).

^{1}H NMR (500 MHz, CD_3OD, 298 K): δ = 7.34–7.21 (m, 6 H), 5.35 (s, 1 H), 5.30 (s, 1 H), 4.05 (q, *J* = 7.2 Hz, 2 H), 3.87–3.76 (m, 2 H), 3.07 (s, 2 H), 1.31 (s, 9 H), 1.20 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (125 MHz, CD_3OD, 298 K): δ = 178.4, 174.6, 158.5, 144.2, 141.4, 130.6, 129.9, 128.9, 119.8, 81.0, 64.4, 62.7, 47.4, 41.7, 29.5, 15.3.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{27}NO_6Na$: 400.1731 [M + Na]$^+$; found: 400.1732.

Reductive N–O Cleavage and Double Bond Hydrogenation; Product 9a

A flame-dried Schlenk tube equipped with a magnetic stirrer was charged with 10% Pd/C (11.0 mg, 10 mol%). The flask was evacuated and backfilled with argon (3 ×) and a solution of **2a** (38.4 mg, 0.102 mmol) in EtOH (2 mL, 0.05 M) was added under a counterflow of argon. The reaction mixture was degassed by means of 3 freeze-pump-thaw cycles, filled with H_2 gas and vigorously stirred for 20 h at rt. After completion (determined by TLC analysis), the mixture was filtered through a pad of Celite, washed with DCM, and concentrated under reduced pressure to give **9a** as a colorless oil; yield: 38.4 mg (99%, 0.101 mmol); *d.r.* = 3:2.

^{1}H NMR (500 MHz, CD_3OD, 298 K): δ = 7.33–7.22 (m, 5 H), 4.09 (q, *J* = 7.2 Hz, 2 H), 3.82–3.58 (m, 2 H), 2.89–2.78 (m, 1 H), 2.58 and 2.46 (*major*: d, *J* = 15.4 Hz, *minor*: d, *J* = 16.2 Hz, 1 H), 2.24 and 2.00 (*minor*: dd, *J* = 16.2, 10.9 Hz, *major*: dd, *J* = 15.4, 10.9 Hz, 1 H), 1.36 and 1.29 (*major*: s, *minor*: s, 9 H), 1.24–1.20 (m, 3 H), 1.03 and 0.97 (*minor*: d, *J* = 6.7 Hz, *major*: d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, CD_3OD, 298 K): δ = 178.4, 178.1, 176.1, 175.6, 158.7, 158.6, 141.5, 141.0, 130.1, 130.0, 129.9, 128.9, 128.8, 81.1, 80.9, 62.4, 62.3, 61.8, 60.8, 47.5, 45.9, 40.5, 39.7, 37.0, 36.9, 29.5, 17.5, 17.0, 15.4.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{29}NO_6Na$: 402.1887 [M + Na]$^+$; found: 402.1889.

KAHA-Ligation; Product 11

To a solution of compound **2a** (31.2 mg, 0.083 mmol, *e.r.* = 83:17) in anhyd DCM (1 mL, 0.1 M) was added TFA (0.5 mL) dropwise at 0 °C. The reaction mixture was warmed to rt and stirred for 30 min, whereupon it was concentrated under reduced pressure and dried in *vacuo* to give the deprotected isoxazolidin-5-one as a colorless oil. To a solution of the *N*-deprotected **2a** in *t*BuOH/THF/H_2O (1:1:1, 1.5 mL in total) was added Fmoc-Leu-CO_2H (35.2 mg, 1.1 equiv) portionwise (gas evolution) and left to stir for 20 h at rt. H_2O and DCM were added and the phases were separated. The aqueous phase was extracted with DCM (3 ×) and the combined organic phases were dried (anhyd Na_2SO_4), filtered through a short pad of silica gel, washed with DCM/MeOH (10:1, 25 mL in total) and concentrated under reduced pressure to give crude **11a** as a white foam. To a solution of the ligation product in anhyd DCM (2 mL, 0.05 M) was added MeOH (28 µL, 7 equiv) and cooled in an ice-bath. A solution of $TMSCH_2N_2$ in hexane (0.6 mol·L^{-1}, 0.8 mL, 5 equiv) was added and the reaction mixture was stirred for 30 min at rt. The reaction was quenched by dropwise addition of AcOH/Et_2O (9:1) until complete discoloration of the mixture. After removal of all volatiles under reduced pressure, the crude product was purified via preparative TLC (silica gel, heptanes/EtOAc 2:1) to obtain methyl ester **11b** as a colorless oil in an overall 59% yield (30.6 mg, 0.049 mmol).

^{1}H NMR (500 MHz, CD_3OD, 298 K): δ = 7.78 (d, *J* = 7.5 Hz, 2 H), 7.67–7.56 (m, 2 H), 7.38 (t, *J* = 7.5 Hz, 3 H), 7.32–7.25 (m, 4 H), 7.24–7.19 (m, 3 H), 5.39 (s, 1 H), 5.30 (s, 1 H), 4.41–4.29 (m, 2 H), 4.18 (t, *J* = 6.7 Hz, 1 H), 4.04–3.90 (m, 5 H), 3.66 (s, 3 H), 3.03 (d, *J* = 16.5 Hz, 1 H), 2.96 (d, *J* = 16.5 Hz, 1 H), 1.55–1.46 (m, 1 H), 1.39–1.30 (m, 2 H), 1.16 (t, *J* = 7.2 Hz, 3 H), 0.87 (d, *J* = 6.5 Hz, 3 H), 0.84 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (125 MHz, CD_3OD, 298 K): δ = 175.8, 175.2, 174.1, 159.2, 146.2, 146.0, 143.4, 142.5, 140.1, 130.3, 130.2, 129.6, 129.5, 129.0, 127.1, 121.8, 121.7, 68.8, 63.6, 62.8, 55.8, 53.9, 49.3, 45.6, 42.4, 41.4, 26.6, 24.3, 22.6, 15.3.

HRMS (ESI): *m*/*z* calcd for $C_{37}H_{42}N_2O_7Na$: 649.2884 [M + Na]$^+$; found: 649.2887.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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