Enantioselective β-selective addition of isoxazolidin-5-ones to allenoates catalyzed by quaternary ammonium salts

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The enantioselective addition of isoxazolidin-5-ones to the β-carbon of allenoates has been carried by using a novel spirobiindane-based quaternary ammonium salt catalyst. This protocol, which proceeds under classical liquid-solid phase-transfer conditions, gives access to highly functionalized β2,2-amino acid derivatives with good enantioselectivities and in high yields.

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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 β2,2-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 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. Numerous nowadays often routinely employed strategies to access a multitude of differently functionalized non-natural α-amino acids (α-AA) and β-amino acids (β-AA) 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 design 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, 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. 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. Amongst them, the enantioselective syntheses of β2,2-AA remained challenging until recently, when Brière’s group introduced the direct synthesis of isoxazolidin-5-ones starting from easily accessible Meldrum’s acid derivatives. 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 β2,2-AA derivatives straightforwardly (Scheme 1B). These highly functionalized chiral heterocycles provide a straightforward entry to free β2,2-AA and small peptides as well as for heterocyclic amino acid derivatives.
Our group has been interested in these versatile heterocycles for a few years now and so far we succeeded in introducing chiral quaternary ammonium salt-catalyzed approaches for asymmetric α-C-C-bond formations as well as α-heterofunctionalizations. In ongoing attempts to expand the use of compounds to access novel chemical space by targeting highly functionalized enantioenriched heterocycles, we became interested in using allenoates as simple inorganic Brønsted bases, or the use of chiral quaternary ammonium salt catalysts under classical phase-transfer conditions allow for β-selective additions of C-nucleophiles (i.e. in situ generated enolate species) with promising enantioselectivities. Based on these inspiring contributions, we started our investigations by focusing on the addition of the parent isoxazolidin-5-one to ethyl allenoate, giving product 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 and our own bifunctional ammonium salt failed (entries 3-5), Lygo's bipheronial catalyst gave good levels of enantioselectivity (up to e.r. = 88:12 when lowering the temperature to -20 °C; entries 6 and 7).

Initial trials with Maruoka's binaphthyl-based catalyst showed that the intended β-addition is proceeding well under the chosen biphasic phase-transfer conditions (giving product in over 70% yield) but with very little enantioenrichment only (entries 1 and 2). These low selectivities came as a surprise as we, as others, found these ammonium salt catalysts being well-suited for asymmetric α-functionalizations of compounds in the past. We started our investigations by focusing on the addition of the parent isoxazolidin-5-one to ethyl allenoate, in the presence of known and new chiral ammonium salt catalysts (Fig. 1) (Table 1 gives an overview of the most significant results obtained in a detailed screening of different catalysts and conditions).

![Figure 1 Chiral ammonium salt catalysts used herein.](image)

Table 1 Identification of the best-suited catalyst and conditions for the enantioselective addition of 1a to 3a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Base</th>
<th>Solv.</th>
<th>T [°C]</th>
<th>Yield [%]</th>
<th>e.r.</th>
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<td>1</td>
<td>A1</td>
<td>Cs2CO3</td>
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<tr>
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<td>toluene</td>
<td>25</td>
<td>71</td>
<td>46:54</td>
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<tr>
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<td>B1</td>
<td>Cs2CO3</td>
<td>toluene</td>
<td>25</td>
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<td>54:46</td>
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<tr>
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<td>toluene</td>
<td>25</td>
<td>53</td>
<td>55:45</td>
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<tr>
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<td>25</td>
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<td>6</td>
<td>D</td>
<td>Cs2CO3</td>
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<td>25</td>
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<td>7</td>
<td>D</td>
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<td>-20</td>
<td>87</td>
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<tr>
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<td>25</td>
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<tr>
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<td>toluene</td>
<td>20-90</td>
<td>91:9</td>
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</table>

* All reactions were run for 20-24 h using 0.1 mmol 1a, 0.11 mmol 3a, 0.05 M 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.

* Isolated yields.

* Measured by HPLC using a chiral stationary phase, given as the ratio of (−)- to (+)-enantiomer.

* 0.05 M with respect to 1a.

* using 3 equiv. base and 5 equiv. allenoate 3a.

During the initial period of these investigations, we also started a project aiming on the design of spirobinindane-based ammonium salts in our group. Relying on recent reports describing the straightforward synthesis of enantioenriched dialdehyde starting from bisphenol, 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 for asymmetric α-allylations already, 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 (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 bimetallic-spirobiindane hybrid system E4 (using the RR as well as the RS 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 CsCO3 (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 h 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 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-aryl-isoxazolidin-5-ones 1 were generally well-tolerated, albeit t-butyl allenoates were found to be less suited then sterically less demanding esters (compare products 2a-2d). 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-documented15 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.

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After investigating the asymmetric application scope, we also tested if compound 2a can be transferred into the corresponding acyclic β22-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. 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 a KAHA-type ligation9a,9b,27 with the α-ketoacid 10, thus providing aces 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).
As stated in the introductory part, the acceptor behavior of allenoates 3 can be influenced by the nature of the used organocatalysts. As it has been well-established that the use of (chiral) tertiary phosphines leads to a preferred γ-attack of Cnucleophiles, 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 PBu3 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-attack product 2a). Attempts to render this reaction enantioselective next were unfortunately not very successful. A variety of easily available or commercially accessible chiral tert. phosphines were unfortunately not very successful. A variety of easily available or commercially accessible chiral tert. phosphines were tested but, as exemplified for derivatives 12-4, 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.

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 β1,2-AA derivatives 2 could be obtained with good enantioselectivities and in high yields by using the novel spirobihinane-based ammonium salt catalyst E under liquid-solid biphasic phase-transfer conditions. The cyclic products 2 can be transferred in a cyclic β1,2-AA derivatives 8 and 9 under reducing 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 tert. amino-catalysis, albeit with low enantioselectivities only.

The experimental section has no title; please leave this line here.

**General experimental details**

1H-, 13C- and 31P 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 cryprobe, which are both property of the Austro Czech NMR Research Center "IREI 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 12,3,4,5,6-hexakis(2,2,3,3-tetrafluoropropoxy)-1,1,2,4,6-triazatrophosphinane (exact mass for [M+H]+ = 121.050873) were used for internal mass calibration.

HPLC was performed using a Thermo Scientific Dionex Ultimate 3000 or a Shimadzu Prominance system with diode array detector with a CHIRALPAK AD-H, OD-H, CHIRAL ART Amyl-ose-5A, Cellulose-SR, or Cellulose-SZ (250 × 4.6 mm, 5 µm) chiral stationary phase. Optical rotations were recorded on a Schimdt + Haensch Polarisator Model UniPolL1000 at 589 nm.

All chemicals were purchased from commercial suppliers and used without further purification unless otherwise stated. Isolated isoxazolidin-5-ones 11 were all synthesized as described previously. Dry 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.

**Syntheses of dialdehydes 6:** A pressure Schlenk tube is charged with compound (β)-5, 3.5 eq. boronic acid, 2 eq KPO4 and 10 mol% KBr in dimethoxyethane/H2O = 3/1. The mixture is degassed by performing three freeze-pump thaw cycles. 10 mol% Pd(PPh3)4 are added and the mixture is stirred at 90 °C for 17 h. The mixture is cooled to r.t., 20 mL H2O are added and the aqueous phase is extracted four times with 15 mL EtOAc each. The combined organic phases are washed with brine, dried over Na2SO4, filtered over cotton and the solvent is evaporated.

**Analytical details for dialdehyde 6a (en route to catalyst E)14**

Obtained by starting from 0.25 mmol (162 mg) of compound (β)-5 as a light-yellow foam in 73% yield (142 mg).

\[ \alpha \parallel \mathrm{Cl} = -63.7^\circ \]

1H NMR (300 MHz, δ, CDCl3): 9.46 (s, 2H), 7.86 (s, 2H), 7.57 (d, J = 4.3 Hz, 4H), 7.34 (s, 2H), 2.56 (s, 4H), 2.03 (s, 6H), 1.51 (s, 6H), 1.48 (s, 6H).

13C NMR (75 MHz, δ, CDCl3): 191.1, 154.5, 149.3, 141.4, 140.3, 136.8, 1318 (dq, J = 33.4, 10.2 Hz), 129.8, 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, 292, 22.8, 20.7, 14.2.

31P NMR (202 MHz, δ, CDCl3): -62.7 (s), -62.9 (s).

Syntheses of dibromides 7: Cross coupling product [(2S,6S)-6a dissolved in THF/MeOH = 1/1 (0.025 M) and cooled to 0 °C. 4 eq NaH is slowly added and the reaction mixture is stirred for 1.5 h at 0 °C. The reaction is quenched by addition of H2O and the organic solvents are evaporated. The residue is extracted four times with EtOAc and the combined organic phases are once washed with brine. The organic phase is dried over Na2SO4, filtered over cotton and the solvent is evaporated.

Analytical details for dibromide 7a (en route to catalyst E1)²⁴

Obtained by starting from 0.1 mmol (71 mg) of compound [(2S,6S)-6a as a greenish brown oil in 93% yield (76 mg).

H NMR (300 MHz, δ, CDCl3) = +96.5°.

| C NMR (75 MHz, δ, CDCl3) | 133.1, 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, 23.2, 21.3.

Syntheses of catalysts E: A pressure Schlenk tube is charged with catalyst precursor [(2R)-7 and 2 eq Na2CO3 in ACN (0.025 M) 3 eq amine (morpholine or binalaphylin) are added and the reaction mixture is stirred at 70 °C for 66 h. The reaction mixture is cooled to rt, filtered and washed with DCM. The filtrate is evaporated to dryness. The crude product is purified by silica gel column chromatography (DCM, DCM/MeOH = 10/1).

Analytical details for catalyst E1²⁴

Obtained by starting from 0.18 mmol (161 mg) of compound [(2R)-7a as an off-white solid in 80% yield (159 mg).

H NMR (300 MHz, δ, CDCl3) = +117.8°.

| C NMR (75 MHz, δ, CDCl3) | 173.8, 170.6, 155.9, 138.5, 135.1, 129.1, 128.8, 127.5, 119.6, 94.2, 61.1, 58.0, 57.9, 38.4, 27.9, 14.2.


HPLC (YMC, Chiral ART Amyleose-A, eluent: n-hexane:i-PrOH = 20/1, 0.1 mL/min, 20 °C, λ = 210 nm) retention times: tmajor = 17.4 min, tminor = 15.1 min.

General procedure for the syntheses of products 12

A reaction vial equipped with a stirring bar is charged with photophase catalyst (10 mol%), N-Boc-4-phenylisoaxazolidin-5-one 1a (26.3 mg, 0.1 mmol) and toluene (1 mL, 0.1 M with respect to 1a). Ethyl 2,3-butanedioate 3a (14 µL, 1.2 eq.) is added and the resulting solution is stirred for 2 h at room temperature. After completion (determined by TLC analysis), the crude product is concentrated under reduced pressure and purified by preparative TLC (silica gel, heptanes/EtOAc = 2/1) to obtain γ-addition products 12.

Details for the major product 12a²⁴

Obtained in 84% yield (31.4 mg, 0.084 mmol) as a colorless oil which solidifies upon storage in a refrigerator when using 10 mol% of PPh3.

HR (heptanes/EtOAc = 2/1) = 0.17.

H NMR (300 MHz, δ, CDCl3) = 7.44-7.31 (m, 5H), 6.68 (dt, J = 15.6, 7.6 Hz, 1H), 5.86 (dt, J = 15.6, 1.3 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 4.06 (d, J = 11.9 Hz, 1H), 2.84 (2 ddd, J = 14.6, 7.6, 1.3 Hz, 2H), 1.31 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H).

C NMR (75 MHz, δ, CDCl3) = 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.


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 under argon atmosphere is added recrystallized naphthalene (320 mg, 2.5 mmol) and sodium naphthalide. The freshly prepared reductant solution is added dropwise, via syringe, to a second Schlenk tube containing compound 2a (58 µL, 5 equiv.) to afford product 8a (55 µL, 0.092 mmol) in 89% yield (60 mg, 0.2 mmol) as a colorless oil.

HRMS (ESI): calcd m/z for C11H5NO3: 164.0710; found: 164.0708.

Additional reactions of compounds 1 to alerones 3

General procedure for the asymmetric syntheses of products 2

A thermally controlled double-walled and oven dried Schlenk tube equipped with a stir-ring bar is charged with catalyst E1 (1.8 mg, 2 mol%) isoaxazolidin-5-one 1 (0.1 mmol) and dry toluene (2 mL, 0.05 M with respect to 1). The mixture is stirred until all components are completely dissolved to give a colorless solution, which is cooled to 20 °C. CsCO3 (97.7 mg, 3 equiv.) and alerones 3 (5 equiv.) are added and the reaction mixture is stirred for 24 h under an argon atmosphere. After completion, the crude product is concentrated under reduced pressure and subsequently subjected to column chromatography (silica gel, heptanes/EtOAc = 2/1) to obtain the β-addition products 2 in the given yields and enantiopurities.

Details for the parent product 2a²⁴

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 in 90% isolated yield (3.30 mg, 0.088 mmol) with e.e. = 91.9.

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with argon (3x) and a solution of 2a (38.4 mg, 0.102 mmol) in EtOH (2 mL, 0.05 M) is added under a hood. After addition of TFA (0.5 mL), the reaction mixture is stirred for 30 min at room temperature. After completion (determined by TLC analysis), the mixture is filtered through a pad of Celite, washed with DCM and concentrated under reduced pressure to yield 3a as a colorless oil (38.4 mg, 0.102 mmol, yield: 100%).

HRMS (ESI): calcd m/z for C20H18NO5: 410.1209; found: 410.1199.

KAHA-ligation (product 11)

Compound 2a (31.2 mg, 0.083 mmol, e.r. = 83:17) is dissolved in anhydrous DCM (1 mL, 0.1 M) and TFA (0.5 mL) is dropwise added at 0 °C. The reaction mixture is warmed to room temperature and stirred for 30 minutes, whereupon it is concentrated under reduced pressure, the crude product is purified via preparative TLC (silica gel, heptanes/EtOAc = 2:1) to obtain methyl ester 11 as a colorless oil in overall 95% yield (30.6 mg, 0.049 mmol).

HRMS (ESI): calcd m/z for C16H16NO5: 429.1105; found: 429.1106.

Synthesis

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Supporting Information

YES

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

References


SUPPORTING INFORMATION

Enantioselective β-selective addition of isoxazolidin-5-ones to allenoates catalyzed by quaternary ammonium salts

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1. General Information

1.1. General Methods

$^1$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 for 16 samples, on a Bruker Avance DRX 500 MHz spectrometer, and on a Bruker Avance III 700 MHz spectrometer with an Ascend magnet and TCI cryoprobe, which are both 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-triazatetriphosphinane (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 Prominance 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 and allenates 3 were synthesized as described previously. Dry solvents were obtained from an MBraun-SPS-800 solvent purification system. All reactions were carried out under argon atmosphere, unless stated otherwise.

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2. Preparation of novel spirobiindane-based quaternary ammonium salt catalysts E

Synthesis of catalyst precursor 5 was carried out following a slightly modified literature\(^3\) procedure.

**Step 1:** Bisphenol C (16.7 g, 65 mmol) is dissolved in 84 mL methanesulfonic acid and the resulting solution is stirred at r.t. for 24 h. Additional 33 mL of methanesulfonic acid is added and the solution is stirred for further 96 h. The reaction mixture is poured onto ice and the precipitate is filtered. The solid is washed with 50 mL sat. aq. NaHCO\(_3\) solution and with 50 mL H\(_2\)O. The dark red crude product is purified by means of column chromatography (silica gel, DCM) to afford 7.1 g of pure product appearing as off-white solid (96% yield, 21 mmol).

3,3',3',5,5'-hexamethyl-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-6,6'-dial (4,1): \(^1\)H NMR (300 MHz, \(\delta\), CDCl\(_3\), 298 K): 6.90 (s, 2H), 6.15-6.05 (m, 2H), 4.33-4.20 (s, 2H), 2.30 (d, \(J = 13.0 \text{ Hz}, 2\text{H} \)), 2.24 (s, 6H), 2.18 (d, \(J = 13.1 \text{ Hz}, 2\text{H} \)), 1.36 (s, 6H), 1.30 (s, 6H).

**Step 2:** Racemic spirocyclic compound 4,1 (5.1 g, 15.0 mmol) and (8S,9R)-(-)-N-Benzylcinchonidinium chloride (3.83 g, 9.1 mmol) are suspended in toluene (100 mL) and refluxed for 2 h. After slow cooling to r.t., the solid is filtered off and is washed with toluene. The filter cake is suspended in toluene (30 mL), refluxed for 1 h and slowly cooled to room temperature. The solid is collected by filtration and washed with toluene.

The solid is suspended in 50 mL EtOAc, 1N HCl (50 mL) is added and the mixture is stirred until the solid is dissolved completely (ca. 15 min). The phases are separated, the organic layer is washed with brine, dried over Na\(_2\)SO\(_4\), filtered over cotton and the solvent is evaporated. To enhance the enantiomeric

purity, the crude product is recrystallized 2-3 times using hexane/EtOAc = 5/1, yielding 2.3 g (44%) of (R)-4,1 with >98% ee (AD-H, hexane/i-PrOH = 10/1, 1.0 mL·min⁻¹, 220 nm, 10 °C; t_major = 7.2 min, t_minor = 8.7 min).

The combined filtrates are 5x washed with water, filtered and concentrated in vacuo. The residue is suspended in 50 mL EtOAc, 1N HCl (50 mL) is added and the mixture is stirred until the solid is dissolved completely (ca. 15 min). The phases are separated, the organic layer is washed with brine, dried over Na₂SO₄, filtered over cotton and the solvent is evaporated. To enhance the enantiomeric purity, the crude product is recrystallized 2-3 times using hexane/EtOAc = 5/1, yielding 1.8 g (35%) of (S)-4,1 with >98% ee (AD-H, hexane/i-PrOH = 10/1, 1.0 mL·min⁻¹, 220 nm, 10 °C; t_minor = 7.2 min, t_major = 8.7 min).

**Step 3:** Diol (R)-4,1 (2.0 mmol, 660 mg) is dissolved in 24 mL trifluoroacetic acid (TFA) and 8 eq of hexamethylene tetramine (HMTA) (16.0 mmol, 2.17 g) are added. The reaction mixture is heated to reflux and stirred for 24 h. 23 mL of acetic acid are added and stirring at reflux is continued for 72 h. After cooling to 95 °C, 23 mL of 4N HCl is added and the reaction mixture is stirred at 95 °C for 6 h. The reaction mixture is poured into 75 mL H₂O and the precipitate is collected by filtration obtaining dialdehyde (R)-4,2 as yellow solid (512 mg, 72%) without further purification.

(R)-6,6'-dihydroxy-3,3',3',5,5'-hexamethyl-2,2'-3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-dicarbaldehyde [(R)-4,2]: ¹H NMR (300 MHz, δ, CDCl₃, 298 K): 12.00 (s, 2H), 9.56 (s, 2H), 7.20 (s, 2H), 2.57 (d, J = 13.5 Hz, 2H), 2.38 (d, J = 13.5 Hz, 2H), 2.26 (s, 6H), 1.37 (s, 6H), 1.35 (s, 6H).

**Step 4:** Dialdehyde (R)-4,2 (0.41 mmol, 151 mg) is dissolved in 3 mL DCM and cooled to 0 °C. Subsequently, 8 eq pyridine (255 µL) and 4 eq triflic anhydride (262 µL) are added and the reaction mixture is stirred overnight during slow warming to room temperature. For work-up of the reaction, 20 mL DCM are added and the organic phase is washed with 10 mL of 1N HCl, with 20 mL brine, with 10 mL sat. aq. NaHCO₃ solution and with 20 mL brine. The organic phase is dried over Na₂SO₄, filtered
over cotton and the solvent is evaporated. The crude product is purified via silica gel column chromatography employing heptanes/ EtOAc = 50/1 as eluent yielding product 5 as light-yellow foam (206 mg, 76%).

(R)-7,7'-diformyl-3,3',5,5',6,6'-hexamethyl-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-6,6'-diyl bis(trifluoromethanesulfonate) [(R)-5]: 1H NMR (300 MHz, δ, CDCl3, 298 K): 9.79 (s, 2H), 7.35 (s, 2H), 2.51 (d, J = 12.8 Hz, 2H), 2.45 (s, 6H), 2.41 (d, J = 12.9 Hz, 2H), 1.50 (s, 6H), 1.40 (s, 6H).

Step 5 (General Procedure A): A pressure Schlenk tube is charged with compound (R)-5, 3.5 eq boronic acid, 2 eq K3PO4 and 10 mol% KBr in dimethoxyethane/H2O = 3/1. The mixture is degassed by performing three freeze-pump thaw cycles. 10 mol% Pd(PPh3)4 are added and the reaction mixture is stirred at 90 °C for 17 h. The reaction mixture is cooled to r.t., 20 mL H2O are added and the aqueous phase is extracted four times with 15 mL EtOAc each. The combined organic phases are washed with brine, dried over Na2SO4, filtered over cotton and the solvent is evaporated.

Cross coupling product (R)-6a: Synthesized according to the procedure A, using 0.25 mmol (162 mg) of compound (R)-5, obtained as light-yellow foam (142 mg, 73%). 1H NMR (300 MHz, δ, CDCl3, 298 K): 9.46 (s, 2H), 7.86 (s, 2H), 7.57 (d, J = 4.3 Hz, 4H), 7.34 (s, 2H), 2.56 (s, 4H), 2.03 (s, 6H), 1.51 (s, 6H), 1.48 (s, 6H). 13C NMR (75 MHz, δ, CDCl3, 298 K): 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. 19F NMR (282 MHz, δ, CDCl3, 298 K): -62.7 (s), -62.9 (s). HRMS (ESI): calcd m/z for C41H36F12NO2+: 802.2549 [M+NH4]⁺; found: 802.2546. [α]D23 (c = 1.00, CHCl3) = -63.7°.

Cross coupling product (R)-6b: Synthesized according to the procedure A, using 0.30 mmol (197 mg) of compound (R)-5, obtained as a white solid in 71% yield (150 mg). 1H NMR (300 MHz, δ, CDCl3, 298 K): 9.43 (s, 2H), 7.30 (s, 2H), 6.79-6.70 (m, 4H), 2.49 (dd, J = 20.9, 12.9 Hz, 4H), 2.07 (s, 6H), 1.50 (s, 6H), 1.45 (s, 6H). 13C NMR (75 MHz, δ, CDCl3, 298 K): 191.5, 154.3, 152.8, 149.4, 148.6, 140.8, 134.9, 137.5, 136.4, 135.2, 129.5, 129.3, 114.1 (dd, J = 29.3, 17.5, 3.1 Hz), 59.2, 58.2, 43.1, 32.6, 29.5, 20.5. 19F NMR (282 MHz, δ, CDCl3, 298 K): -133.8 – -134.0 (m), -134.3 – -134.4 (m), -161.9
Cross coupling product (R)-6c was synthesized according to procedure A, using 0.34 mmol (226 mg) of compound (R)-5, obtained as a white solid in 68% yield (190 mg). 1H NMR (300 MHz, δ, CDCl3, 298 K): 9.54 (s, 2H), 7.77 (t, J = 1.7 Hz, 2H), 7.63-7.57 (m, 8H), 7.43-7.31 (m, 18H), 2.70 (d, J = 12.6 Hz, 2H), 2.45 (d, J = 12.6 Hz, 2H), 2.19 (s, 6H), 1.57 (s, 6H), 1.50 (s, 6H). 13C NMR (75 MHz, δ, CDCl3, 298 K): 193.1, 153.9, 147.6, 144.1, 141.6, 141.6, 140.9, 140.7, 139.8, 136.0, 130.0, 129.0, 128.9, 128.7, 128.4, 127.7, 127.4, 127.3, 125.0, 59.7, 57.9, 43.1, 32.8, 29.8, 29.5, 20.8. HRMS (ESI): calcd m/z for C61H56N6O2+: 834.4306 [M+NH4]+; found: 834.4302. [α]D24 (c = 1.00, CHCl3) = -110.4°.

Step 6 (General Procedure B): Cross coupling product (R)-6 is dissolved in THF/MeOH = 1/1 (0.025 M) and cooled to 0 °C. 4 eq NaBH4 are slowly added and the reaction mixture is stirred for 1.5 h at 0 °C. The reaction is quenched by addition of H2O and organic solvents are evaporated. The residue is extracted four times with EtOAc and combined organic phases are once washed with brine. The organic phase is dried over Na2SO4, filtered over cotton and solvent is evaporated. The residue is taken up in HBr in AcOH (33%) (0.08 M) and refluxed for 1.5 h. After cooling to r.t., H2O is added and aqueous phase is extracted four times with EtOAc. Combined organic phases are washed 3x with H2O, 1x with sat. aq. NaHCO3 solution and 1x with brine. The organic phase is dried over Na2SO4, filtered over cotton and solvent is evaporated.

Compound (R)-7a: Synthesized according to the procedure B, using cross coupling product (R)-6a (0.1 mmol, 71 mg) obtaining product (R)-7a as greenish-brown oil in 93% yield (76 mg). 1H NMR (300 MHz, δ, CDCl3, 298 K): 7.90 (s, 2H), 7.81 (s, 2H), 7.66 (s, 2H), 7.13 (s, 2H), 3.86 (q, J = 10.2 Hz, 4H), 2.68 (d, J = 13.6 Hz, 2H), 2.45 (d, J = 13.6 Hz, 2H), 1.97 (s, 6H), 1.49 (s, 6H), 1.43 (s, 6H). 13C NMR (75 MHz, δ, CDCl3, 298 K): 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. 19F NMR (282 MHz, δ, CDCl3, 298 K): -62.8 (s), -63.0 (s). [α]D24 (c = 1.00, CHCl3) = +117.8°.
Compound (R)-7b: Synthesized according to the procedure B, using cross coupling product (R)-6b (0.2 mmol, 125 mg) obtaining product (R)-7b as white solid in 98% yield (150 mg).

\[ \text{H NMR (300 MHz, } \delta, \text{ CDCl}_3, 298 \text{ K): 6.97 (s, 1H), 6.80-6.7 (m, 3H), 4.14 (d, } J = 11.1 \text{ Hz, 1H), 4.03 (q, } J = 7.1 \text{ Hz, 2H), 3.85-3.81 (m, 1H), 2.39 (d, } J = 13.5 \text{ Hz, 2H), 2.15 (d, } J = 13.3 \text{ Hz, 2H), 1.92 (s, 6H), 1.33 (s, 6H), 1.30 (s, 6H).} \]

\[ \text{13C NMR (75 MHz, } \delta, \text{ CDCl}_3, 298 \text{ K): 152.8, 149.5 (q, } J = 4.7 \text{ Hz), 144.9, 140.8, 140.4, 137.5, 137.2, 135.1, 133.1, 132.1, 131.3, 125.3, 125.1, 124.2, 114.4 (t, } J = 17.2 \text{ Hz), 59.2, 56.8, 43.3, 32.7, 30.1, 29.2, 21.1.} \]

\[ \text{19F NMR (282 MHz, } \delta, \text{ CDCl}_3, 298 \text{ K): -134.5 – -134.6 (m), -135.5 – -135.6 (m), -163.0 – -163.1 (m).} \]

\[ \text{[} \alpha \text{]_D^{22} (c = 1.00, \text{ CHCl}_3) = -148.1^{\circ}.} \]

Compound (R)-7c: Synthesized according to the procedure B, using cross coupling product (R)-6c (0.06 mmol, 50 mg) obtaining product (R)-7c as a white solid in 97% yield (145 mg).

\[ \text{1H NMR (300 MHz, } \delta, \text{ CDCl}_3, 298 \text{ K): 7.83 (s, 2H), 7.73 (d, } J = 7.6 \text{ Hz, 4H), 7.63 (d, } J = 6.9 \text{ Hz, 4H), 7.56 (s, 2H), 7.49-7.32 (m, 14H), 7.13 (s, 2H), 4.13 (s, 4H), 2.81 (d, } J = 12.9 \text{ Hz, 2H), 2.45 (d, } J = 13.5 \text{ Hz, 2H), 2.07 (s, 6H), 1.52 (s, 6H), 1.46 (s, 6H).} \]

\[ \text{13C NMR (75 MHz, } \delta, \text{ CDCl}_3, 298 \text{ K): 152.1, 145.0, 143.3, 141.4, 141.3, 141.2, 141.0, 140.3, 137.2, 131.5, 128.9, 128.2, 127.9, 127.5, 127.4, 127.2, 125.1, 124.7, 59.4, 56.7, 43.2, 32.9, 30.5, 30.2, 21.5. [} \alpha \text{]_D^{22} (c = 1.00, \text{ CHCl}_3) = +129.8^{\circ}.} \]

**Step 7 (General Procedure C):** A pressure Schlenk tube is charged with catalyst precursor (R)-7 and 2 eq Na$_2$CO$_3$ in ACN (0.025 M). 3 eq Amine (morpholine or binaphthylamine) are added and the reaction mixture is stirred at 70 °C for 66 h. The reaction mixture is cooled to r.t., filtered and washed with DCM. The filtrate is evaporated to dryness. The crude product is purified by silica gel column chromatography (DCM, DCM/MeOH = 10/1).

Catalyst (R)-E1: Synthesized according to the procedure C, using catalyst precursor (R)-7a (0.18 mmol, 161 mg), obtained as an off-white solid in 80% yield (159 mg).

\[ \text{1H NMR (300 MHz, } \delta, \text{ CDCl}_3, 298 \text{ K): 7.96 (s, 2H), 7.84 (s, 2H), 7.80 (s, 2H), 7.32 (s, 2H), 4.89 (d, } J = 13.9 \text{ Hz, 2H), 4.19 (d, } J = 13.9 \text{ Hz, 2H), 3.38-3.32 (m, 2H), 3.11-3.09 (m, 2H), 2.70-2.68 (m, 2H), 2.64-2.50 (m, 4H), 2.22 (d, } J = 13.0 \text{ Hz, 2H), 2.10 (s, 6H), 1.58 (s, 6H), 1.49 (s, 6H).} \]

\[ \text{13C NMR (75 MHz, } \delta, \text{ CDCl}_3, 298 \text{ K): 153.6, 149.6, 140.7, 140.3, 138.1, 133.6, 133.2, 132.8, 132.3, 131.6, 131.3, 129.0, 125.2, 124.8, 122.4, 118.0, 61.3, 61.0, 57.5, 56.9,} \]
42.2, 32.6, 30.3, 21.8. $^{19}$F NMR (282 MHz, δ, CDCl$_3$, 298 K): -62.3 (s), -62.8 (s). HRMS (ESI): calcd m/z for C$_{58}$H$_{42}$F$_{12}$NO$: 840.3069 [M]$^+$; found: 840.3070. [α]$_D^{24}$ (c = 1.00, CHCl$_3$) = +96.5°.

Catalyst (R)-E2: Synthesized according to the procedure C, using catalyst precursor (R)-7b (0.08 mmol, 60 mg), obtained as off-white solid in 32% yield (19 mg). $^1$H NMR (300 MHz, δ, CDCl$_3$, 298 K): 7.24 (s, 2H), 7.22-7.20 (m, 2H), 6.92-6.89 (m, 2H), 4.55 (d, $J$ = 13.6 Hz, 2H), 4.35 (d, $J$ = 13.8 Hz, 2H), 4.04 (t, $J$ = 4.8 Hz, 2H), 3.50-3.47 (m, 2H), 3.15 (t, $J$ = 4.79 Hz, 2H), 3.05-2.98 (m, 4H), 2.81-2.78 (m, 2H), 2.47 (d, $J$ = 13.1 Hz, 2H), 2.15 (s, 6H), 2.07 (d, $J$ = 13.0 Hz, 2H), 1.54 (s, 6H), 1.41 (s, 6H). $^{13}$C NMR (75 MHz, δ, CDCl$_3$, 298 K): 152.2, 149.2, 143.5, 143.4, 142.7, 139.9, 139.8, 139.4, 138.1, 129.3, 129.2, 128.5, 128.4, 128.3, 127.7, 127.2, 126.0, 118.3, 63.5, 61.5, 61.0, 57.7, 57.1, 43.2, 42.2, 32.9, 30.3, 22.1. $^{19}$F NMR (282 MHz, δ, CDCl$_3$, 298 K): -131.1 -- -131.3 (m), -159.3 -- -159.4 (m). HRMS (ESI): calcd m/z for C$_{58}$H$_{42}$F$_{12}$NO$: 676.3014 [M]$^+$; found: 676.3020. [α]$_D^{22}$ (c = 1.00, CHCl$_3$) = -60.7°.

Catalyst (R)-E3: Synthesized according to the procedure C, using catalyst precursor (R)-7c (0.11 mmol, 100 mg), obtained as an off-white solid in 24% yield (24 mg). $^1$H NMR (300 MHz, δ, CDCl$_3$, 298 K): 7.85-7.84 (m, 2H), 7.78-7.75 (m, 4H), 7.60-7.57 (m, 4H), 7.50-7.44 (m, 10H), 7.42-7.32 (m, 6H), 4.83 (d, $J$ = 13.6 Hz, 2H), 4.50 (d, $J$ = 13.3 Hz, 2H), 4.03-4.00 (m, 2H), 3.39-3.33 (m, 2H), 3.14-3.11 (m, 2H), 2.92-2.87 (m, 2H), 2.77-2.74 (m, 2H), 2.55 (d, $J$ = 13.1 Hz, 2H), 2.27 (s, 6H), 1.60 (s, 6H), 1.49 (s, 6H). $^{13}$C NMR (75 MHz, δ, CDCl$_3$, 298 K): 152.2, 149.2, 143.5, 143.4, 142.6, 139.9, 139.8, 138.1, 129.3, 129.2, 128.5, 128.4, 128.3, 128.2, 127.7, 127.2, 126.0, 118.3, 63.3, 61.5, 61.0, 57.7, 57.1, 43.1, 42.2, 32.8, 30.3, 22.1. HRMS (ESI): calcd m/z for C$_{58}$H$_{42}$F$_{12}$NO$: 872.4831 [M]$^+$; found: 872.4834. [α]$_D^{22}$ (c = 1.00, CHCl$_3$) = -50.6°.

Catalyst (R,R)-E4: Synthesized according to the procedure C, using catalyst precursor (R)-7a (0.05 mmol, 47.3 mg), obtained as a white solid in 30% yield (17.3 mg). $^1$H NMR (300 MHz, δ, CDCl$_3$, 298 K): 7.90 (d, $J$ = 8.2 Hz, 2H), 7.84-7.78 (m, 4H), 7.59-7.53 (m, 4H), 7.39-7.26 (m, 8H), 7.14 (d, $J$ = 8.5 Hz, 2H), 6.88 (s, 2H), 5.03 (d, $J$ = 13.6 Hz, 2H), 3.93-3.86 (m, 4H), 2.55 (t, $J$ = 12.1 Hz, 4H), 2.37 (d, $J$ = 13.0 Hz, 2H), 2.03 (s, 6H), 1.61 (s, 12H). $^{13}$C NMR (75 MHz, δ, CDCl$_3$, 298 K): 153.6, 149.4, 140.7, 139.3, 137.5, 136.2, 133.8, 132.3, 131.9, 131.6, 131.2, 130.7, 130.4, 130.0, 128.7, 128.3, 127.7, 127.4, 127.3, 127.1, 125.3, 120.3, 118.6, 61.1, 56.5, 55.2, 42.3, 32.7, 30.4, 29.8, 21.4. $^{19}$F NMR (282 MHz, δ, CDCl$_3$, 298 K): -62.1 (s), -63.1 (s). HRMS (ESI): calcd m/z for C$_{58}$H$_{50}$F$_{12}$N$: 1048.3746 [M]$^+$; found: 1048.3741. [α]$_D^{23}$ (c = 1.00, CHCl$_3$) = -107.9°.
Catalyst (R,S)-E4: Synthesized according to the procedure C, using catalyst precursor (R)-7a (0.03 mmol, 28.2 mg), obtained as white solid in 16% yield (5.5 mg). 1H NMR (300 MHz, δ, CDCl3, 298 K): 7.96 (d, J = 8.3 Hz, 2H), 7.90 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 8.3 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 7.57 (t, J = 7.5 Hz, 2H), 7.53 (s, 1H), 7.42-7.40 (m, 2H), 7.33 (s, 2H), 7.29 (t, J = 7.6 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H), 6.88 (s, 2H), 5.00 (d, J = 13.4 Hz, 2H), 3.90 (d, J = 13.4 Hz, 2H), 3.84 (d, J = 12.3 Hz, 2H), 2.55 (q, J = 11.6 Hz, 4H), 2.36 (d, J = 13.1 Hz, 2H), 2.04 (s, 6H), 1.61 (s, 6H), 1.59 (s, 6H). 13C NMR (75 MHz, δ, CDCl3, 298 K): 153.6, 149.4, 140.7, 139.3, 137.5, 136.3, 133.8, 132.3, 132.0, 131.6, 131.4, 131.1, 130.9, 130.5, 130.4, 130.0, 129.8, 128.7, 128.6, 128.3, 127.9, 127.7, 127.5, 127.4, 127.3, 127.1, 126.5, 126.4, 125.3, 123.7, 122.9, 122.1, 121.3, 120.3, 118.6, 70.7, 61.1, 56.5, 55.2, 42.3, 32.7, 30.4, 29.8, 21.5. 19F NMR (282 MHz, δ, CDCl3, 298 K): -62.1 (s), -63.1 (s). HRMS (ESI): calcd m/z for C63H50F12N+: 1048.3746 [M]+; found: 1048.3749. [α]D23 (c = 0.50, CHCl3) = -39.5°.
3. Syntheses and Analytic Details of Targets 2 and 12

3.1. PTC-catalyzed β-addition of isoxazolidin-5-ones to allenoates

**General Procedure D (β-addition):** A thermostatically controlled double-walled and oven-dried Schlenk tube equipped with a stirring bar is charged with catalyst E1 (1.8 mg, 2 mol%), isoxazolidin-5-one 1 (0.1 mmol) and dry toluene (2 mL, 0.05 M with respect to 1). The mixture is stirred until all components are completely dissolved to give a colorless solution, which is cooled to -20 °C. Cs2CO3 (97.7 mg, 3 equiv) and allenolate 3 (5 equiv) are added successively and the reaction mixture is stirred for 24 h under argon atmosphere. After completion (determined by TLC-MS analysis), the crude product is concentrated under reduced pressure and subsequently subjected to column chromatography (silica gel, heptanes/Et2O = 2/1) to obtain β-addition products 2 in the given yields and enantiopurities.

**Compound 2a:** Following procedure D, the β-addition of N-Boc 4-phenylisoxazolidin-5-one 1a (25.8 mg, 0.098 mmol) to ethyl 2,3-buta dienoate 3a (58 µL, 5 equiv) gave 2a as a colorless oil in 90% isolated yield (33.0 mg, 0.088 mmol) with e.r. = 91:9. Rf (heptanes/Et2O = 2/1) = 0.27. [α]D24 (c = 0.96, CHCl3) = +120.2°. 1H NMR (300 MHz, δ, CDCl3, 298 K): 7.43-7.30 (m, 5H), 7.41 (s, 1H), 5.43 (s, 1H), 5.40 (s, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.01 (2 dq, J = 10.8, 7.2 Hz, ABX3 system, 2H), 3.06 (dd, J = 16.2, 0.9 Hz, 1H), 2.98 (dd, J = 16.2, 0.9 Hz, 1H), 1.37 (s, 9H), 1.18 (t, J = 7.2 Hz, 3H). 13C NMR (75 MHz, δ, CDCl3, 298 K): 173.8, 170.6, 155.9, 138.5, 135.1, 129.1, 128.7, 127.5, 119.6, 84.2, 61.1, 58.0, 57.9, 52.1, 38.2, 27.9. HRMS (ESI): calcd m/z for C30H29N2O6+: 579.1864 [M+NH4]+; found: 579.1866. HPLC (YMC Chiral ART Amylose-SA, eluent: n-hexane:i-PrOH = 20/1, 0.7 mL·min⁻¹, 20 °C, λ = 210 nm) retention times: t_major = 17.4 min, t_minor = 15.1 min.

**Compound 2b:** Synthesized according to procedure D, using methyl 2,3-buta dienoate 3b (54 µL, 5 equiv). Obtained as a colorless oil in 78% isolated yield (29.2 mg, 0.081 mmol) with e.r. = 86:14. Rf (heptanes/Et2O = 2/1) = 0.24. [α]D23 (c = 0.97, CHCl3) = +100.9°. 1H NMR (300 MHz, δ, CDCl3, 298 K): 7.41-7.30 (m, 5H), 5.42 (2 s, 2H), 4.62 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 3.55 (s, 3H), 3.07 (dd, J = 16.2, 0.8 Hz, 1H), 2.99 (dd, J = 16.2, 0.8 Hz, 1H), 1.37 (s, 9H). 13C NMR (75 MHz, δ, CDCl3, 298 K): 173.8, 171.1, 155.9, 138.4, 135.1, 129.1, 128.8, 127.5, 119.6, 84.2, 58.0, 57.9, 52.1, 38.2, 27.9. HRMS (ESI): calcd m/z for C30H27N2O6+: 379.1864 [M+NH4]+; found: 379.1866. HPLC (YMC Chiral ART Amylose-SA, eluent: n-hexane:i-PrOH = 20/1, 0.7 mL·min⁻¹, 20 °C, λ = 210 nm) retention times: t_major = 17.4 min, t_minor = 15.1 min.
ART Amylose-SA, eluent: n-hexane:i-PrOH = 20/1, 0.7 mL·min⁻¹, 20 °C, λ = 210 nm) retention times: 
t_major = 20.1 min, t_minor = 18.1 min.

Compound 2c: Synthesized according to procedure D, using benzyl 2,3-butadienoate 3e (82 µL, 5 equiv). Obtained as a colorless oil in 77% isolated yield (35.0 mg, 0.080 mmol) with e.r. = 82:18. Rf (heptanes/Et₂O = 2/1) = 0.30. [α]_D^23 (c = 0.97, CHCl₃) = +86.2°. ¹H NMR (300 MHz, δ, CDCl₃, 298 K): 7.40-7.27 (m, 10H), 5.42 (s, 1H), 5.41 (s, 1H), 4.98 (s, 2H), 4.60 (d, J = 12.0 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 3.11 (d, J = 16.3 Hz, 1H), 3.03 (d, J = 16.3 Hz, 1H), 1.36 (s, 9H). ¹³C NMR (75 MHz, δ, CDCl₃, 298 K): 173.8, 170.5, 138.3, 135.6, 135.1, 129.1, 128.8, 128.7, 127.5, 119.7, 84.2, 66.9, 58.0, 57.9, 38.3, 27.9. HRMS (ESI): calcd m/z for C₂₀H₁₄N₂O₅⁺: 455.2177 [M+NH₄]⁺; found: 455.2180. HPLC (Chiralpak AD-H, eluent: n-hexane:i-PrOH = 6/1, 0.5 mL·min⁻¹, 20 °C, λ = 210 nm) retention times: 
t_major = 23.0 min, t_minor = 30.6 min.

Compound 2d: Synthesized according to procedure D, using tert-butyl 2,3-butadienoate 3d (73 µL, 5 equiv). Obtained as a colorless oil in 38% isolated yield (15.0 mg, 0.037 mmol) with e.r. = 62:38. Rf (heptanes/Et₂O = 2/1) = 0.40. [α]_D^23 (c = 1.00, CHCl₃) = +13.3°. ¹H NMR (300 MHz, δ, CDCl₃, 298 K): 7.43-7.32 (m, 5H), 5.41 (s, 1H), 5.36 (s, 1H), 4.60 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 12.0 Hz, 1H), 2.97 (dd, J = 16.2, 0.9 Hz, 1H), 2.90 (dd, J = 16.2, 0.9 Hz, 1H), 1.37 (s, 1H). ¹³C NMR (75 MHz, δ, CDCl₃, 298 K): 173.8, 169.9, 155.9, 139.0, 135.4, 129.1, 128.7, 127.6, 119.3, 84.2, 81.3, 58.2, 58.0, 39.6, 28.0, 27.9. HRMS (ESI): calcd m/z for C₂₂H₂₁N₂O₅⁺: 421.2333 [M+NH₄]⁺; found: 421.2334. HPLC (YMC Chiral ART Amylose-SA, eluent: n-hexane:i-PrOH = 20/1, 0.7 mL·min⁻¹, 20 °C, λ = 210 nm) retention times: 
t_major = 12.9 min, t_minor = 10.4 min.

Compound 2f: Synthesized according to procedure D and obtained as a pale-yellow oil in 86% yield (33.6 mg, 0.088 mmol) with e.r. = 90:10. Rf (heptanes/Et₂O = 2/1) = 0.27. [α]_D^23 (c = 1.02, CHCl₃) = +15.3°. ¹H NMR (300 MHz, δ, CDCl₃, 298 K): 7.35 (dd, J = 5.0, 3.0 Hz, 1H), 7.32 (dd, J = 3.0, 1.5 Hz, 1H), 7.08 (dd, J = 5.0, 1.5 Hz, 1H), 5.38 (s, 1H), 5.36 (s, 1H), 4.60 (d, J = 12.0 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.05 (q, J = 7.2 Hz, 2H), 3.08 (dd, J = 16.2, 0.9 Hz, 1H), 3.01 (dd, J = 16.2, 0.9 Hz, 1H), 1.40 (s, 9H), 1.21 (s, 9H). ¹³C NMR (75 MHz, δ, CDCl₃, 298 K): 173.8, 170.7, 156.0, 138.3, 135.6, 127.2, 126.9, 124.2, 119.6, 84.3, 61.2, 58.3, 55.5, 38.5, 28.0, 14.2. HRMS (ESI): calcd m/z for C₁₉H₁₃N₂O₅S⁺: 399.1584 [M+NH₄]⁺; found: 399.1587. HPLC (Chiralpak AD-H, eluent: n-hexane:i-PrOH = 6/1, 0.5 mL·min⁻¹, 20 °C, λ = 210 nm) retention times: 
t_major = 20.5 min, t_minor = 18.6 min.
Compound 2g: Synthesized according to procedure D and obtained as a colorless oil in 93% yield (40.0 mg, 0.094 mmol) with e.r. = 89:11. Rf (heptanes/EtO = 2/1) = 0.21. \([\alpha]_D^{24}\) (c = 0.99, CHCl\(_3\)) = +206.5°. \(^1\)H NMR (300 MHz, \(\delta\), CDCl\(_3\), 298 K): 7.88-7.79 (m, 4H), 7.54-7.47 (m, 3H), 5.48 (s, 1H), 5.46 (s, 1H), 4.72 (d, \(J = 12.0\) Hz, 1H), 4.66 (d, \(J = 12.0\) Hz, 1H), 3.93 (2 dq, \(J = 10.8, 7.2\) Hz, ABX system, 2H), 3.11 (dd, \(J = 16.3, 0.8\) Hz, 1H), 3.02 (dd, \(J = 16.3, 0.8\) Hz, 1H), 1.26 (s, 9H), 1.08 (t, \(J = 7.2\) Hz, 3H). \(^13\)C NMR (75 MHz, \(\delta\), CDCl\(_3\), 298 K): 173.9, 170.7, 155.9, 138.4, 133.1, 133.0, 132.4, 129.2, 128.3, 127.7, 127.1, 127.0, 126.9, 124.8, 119.9, 84.2, 61.0, 58.2, 58.0, 38.4, 27.8, 14.0. HRMS (ESI): calcd m/z for C\(_{23}H_{31}N_2O_6^+\): 443.2177 [M+NH\(_4\)]\(^+\); found: 443.2179. HPLC (YMC Chiral ART Cellulose-SB, eluent: n-hexane:i-PrOH = 10/1, 0.5 mL·min\(^{-1}\), 20 °C, \(\lambda = 210\) nm) retention times: \(t_{\text{major}} = 24.8\) min, \(t_{\text{minor}} = 23.1\) min.

Compound 2h: Synthesized according to procedure D and obtained as a colorless oil in 84% yield (37.2 mg, 0.084 mmol) with e.r. = 91:9. Rf (heptanes/EtO = 2/1) = 0.27. \([\alpha]_D^{23}\) (c = 0.96, CHCl\(_3\)) = -206.0°. \(^1\)H NMR (300 MHz, \(\delta\), CDCl\(_3\), 298 K): 7.51 (d, \(J = 2.3\) Hz, 1H), 7.46 (d, \(J = 8.5\) Hz, 1H), 7.27 (dd, \(J = 8.5, 2.3\) Hz, 1H), 5.47 (s, 1H), 5.44 (s, 1H), 4.62 (d, \(J = 12.1\) Hz, 1H), 4.46 (d, \(J = 12.1\) Hz, 1H), 4.02 (q, \(J = 7.2\) Hz, 2H), 3.00 (s, 2H), 1.42 (s, 9H), 1.19 (t, \(J = 7.2\) Hz, 3H). \(^13\)C NMR (75 MHz, \(\delta\), CDCl\(_3\), 298 K): 173.0, 170.3, 155.7, 137.6, 135.4, 133.4, 131.0, 129.7, 127.1, 120.6, 84.7, 61.3, 57.5, 57.4, 38.4, 27.9, 14.1. HRMS (ESI): calcd m/z for C\(_{23}H_{22}Cl_2N_2O_6^+\): 461.1241 [M+NH\(_4\)]\(^+\); found: 461.1247. HPLC (Chiralpak AD-H, eluent: n-hexane:i-PrOH = 6/1, 0.5 mL·min\(^{-1}\), 20 °C, \(\lambda = 210\) nm) retention times: \(t_{\text{major}} = 16.5\) min, \(t_{\text{minor}} = 21.7\) min.

Compound 2i: Synthesized according to procedure D and obtained as a colorless oil in 91% yield (50.0 mg, 0.094 mmol) with e.r. = 90:10. Rf (heptanes/EtO = 2/1) = 0.45. \([\alpha]_D^{22}\) (c = 1.00, CHCl\(_3\)) = +89.2°. \(^1\)H NMR (300 MHz, \(\delta\), CDCl\(_3\), 298 K): 6.95 (s, 2H), 5.38 (s, 1H), 5.36 (s, 1H), 4.57 (d, \(J = 12.0\) Hz, 1H), 4.50 (d, \(J = 12.0\) Hz, 1H), 4.04 (2 dq, \(J = 10.9, 7.2\) Hz, ABX system, 2H), 3.05 (dd, \(J = 16.3, 0.8\) Hz, 1H), 2.94 (dd, \(J = 16.3, 0.8\) Hz, 1H), 2.19 (s, 6H), 1.38 (s, 9H), 1.20 (t, \(J = 7.2\) Hz, 3H), 1.02 (s, 9H), 0.17 (s, 6H). \(^13\)C NMR (75 MHz, \(\delta\), CDCl\(_3\), 298 K): 174.2, 170.8, 156.0, 152.5, 138.9, 129.3, 127.9, 127.2, 119.0, 83.9, 61.0, 58.1, 57.4, 38.4, 28.0, 26.2, 18.9, 18.1, 14.2, -2.8. HRMS (ESI): calcd m/z for C\(_{25}H_{34}O_7Si^+\): 551.3147 [M+NH\(_4\)]\(^+\); found: 551.3152. HPLC (YMC Chiral ART Cellulose-SZ, eluent: n-hexane:i-PrOH = 30/1, 0.5 mL·min\(^{-1}\), 20 °C, \(\lambda = 210\) nm) retention times: \(t_{\text{major}} = 17.0\) min, \(t_{\text{minor}} = 18.4\) min.
**Compound 2j**: Synthesized according to procedure D and obtained as a colorless oil in 85% yield (33.8 mg, 0.086 mmol) with e.r. = 88:12. Rf (heptanes/Et₂O = 2/1) = 0.27. [α]$_D^{22}$ (c = 0.97, CHCl₃) = -89.4°. $^1$H NMR (300 MHz, δ, CDCl₃, 298 K): 7.43-7.36 (m, 2H), 7.11-7.03 (m, 2H), 5.43 (s, 1H), 5.40 (s, 1H), 4.61 (d, $J = 12.1$ Hz, 1H), 4.51 (d, $J = 12.1$ Hz, 1H), 4.01 (2 dq, $J = 10.9, 7.2$ Hz, ABX₃ system, 2H), 3.02 (dd, $J = 16.2, 0.9$ Hz, 1H), 2.96 (dd, $J = 16.2, 0.9$ Hz, 1H), 1.39 (s, 9H), 1.18 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (75 MHz, δ, CDCl₃, 298 K): 173.7, 170.5, 162.8 (d, $J_CF = 216$ Hz), 119.9, 116.1 (d, $J_CF = 21.6$ Hz), 84.4, 61.1, 57.7, 57.5, 38.4, 27.9, 14.1. $^{19}$F NMR (282 MHz, δ, CDCl₃, 298 K): -112.8 (tt, $J = 8.2, 5.1$ Hz). HRMS (ESI): calcd $m/z$ for C$_{20}$H$_{25}$FN$_2$O$_5^+$: 411.1926 [M+NH$_4^+$]; found: 411.1930. HPLC (YMC Chiral ART Amylose-SA, eluent: n-hexane:i-PrOH = 20/1, 0.7 mL·min$^{-1}$, 20 °C, $\lambda = 210$ nm) retention times: $t_{major} = 21.2$ min, $t_{minor} = 18.7$ min.

**Compound 2k**: Synthesized according to procedure D and obtained as a colorless oil in 81% yield (33.4 mg, 0.081 mmol) with e.r. = 89:11. Rf (heptanes/Et₂O = 2/1) = 0.27. [α]$_D^{24}$ (c = 0.96, CHCl₃) = -127.2°. $^1$H NMR (300 MHz, δ, CDCl₃, 298 K): 7.35 (s, 4H), 5.44 (s, 1H), 5.41 (s, 1H), 4.61 (d, $J = 12.0$ Hz, 1H), 4.50 (d, $J = 12.0$ Hz, 1H), 4.01 (2 dq, $J = 10.9, 7.2$ Hz, ABX₃ system, 2H), 3.02 (dd, $J = 16.2, 0.9$ Hz, 1H), 2.96 (dd, $J = 16.2, 0.9$ Hz, 1H), 1.40 (s, 9H), 1.18 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (75 MHz, δ, CDCl₃, 298 K): 173.4, 170.4, 155.8, 138.1, 135.0, 133.7, 129.3, 129.1, 120.1, 84.5, 61.2, 57.6, 38.4, 27.9, 14.1. HRMS (ESI): calcd $m/z$ for C$_{20}$H$_{25}$ClN$_2$O$_6^+$: 427.1630 [M+NH$_4^+$]; found: 427.1629. HPLC (YMC Chiral ART Amylose-SA, eluent: n-hexane:i-PrOH = 20/1, 0.7 mL·min$^{-1}$, 20 °C, $\lambda = 210$ nm) retention times: $t_{major} = 22.1$ min, $t_{minor} = 20.9$ min.

**Compound 2l**: Synthesized according to procedure D and obtained as a colorless oil in 86% yield (39.0 mg, 0.086 mmol) with e.r. = 89:11. Rf (heptanes/Et₂O = 2/1) = 0.27. [α]$_D^{22}$ (c = 0.97, CHCl₃) = -139.0°. $^1$H NMR (300 MHz, δ, CDCl₃, 298 K): 7.53-7.48 (m, 2H), 7.31-7.27 (m, 2H), 5.44 (s, 1H), 5.41 (s, 1H), 4.61 (d, $J = 12.1$ Hz, 1H), 4.49 (d, $J = 12.1$ Hz, 1H), 4.01 (2 dq, $J = 10.9, 7.2$ Hz, ABX₃ system, 2H), 3.03 (dd, $J = 16.2, 0.9$ Hz, 1H), 2.96 (dd, $J = 16.2, 0.9$ Hz, 1H), 1.40 (s, 9H), 1.18 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (75 MHz, δ, CDCl₃, 298 K): 173.4, 170.4, 155.8, 138.0, 134.3, 132.2, 129.4, 123.2, 120.1, 84.5, 61.2, 57.7, 57.6, 38.4, 27.9, 14.1. HRMS (ESI): calcd $m/z$ for C$_{20}$H$_{25}$BrN$_2$O$_6^+$: 471.1125 [M+NH$_4^+$]; found: 471.1130. HPLC (YMC Chiral ART Amylose-SA, eluent: n-hexane:i-PrOH = 20/1, 0.7 mL·min$^{-1}$, 20 °C, $\lambda = 210$ nm) retention times: $t_{major} = 23.7$ min, $t_{minor} = 22.2$ min.
Compound 2m: Synthesized according to procedure D and obtained as a colorless oil in 83% yield (32.2 mg, 0.083 mmol) with e.r. = 96:4. Rf (heptanes/Et2O = 2/1) = 0.27. [α]D23 (c = 1.00, CHCl3) = +67.2°. 1H NMR (300 MHz, δ, CDCl3, 298 K): 7.27 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.2 Hz, 2H), 5.41 (s, 1H), 5.39 (s, 1H), 4.59 (d, J = 12.0 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.02 (2 dq, J = 10.9, 7.2 Hz, ABX system, 2H), 3.05 (dd, J = 16.2, 0.8 Hz, 1H), 2.97 (dd, J = 16.2, 0.8 Hz, 1H), 2.33 (s, 3H), 1.37 (s, 9H), 1.18 (t, J = 7.2 Hz, 3H). 13C NMR (75 MHz, δ, CDCl3, 298 K): 173.9, 170.7, 155.9, 138.7, 138.6, 132.1, 129.8, 127.4, 119.3, 84.1, 61.0, 57.9, 57.8, 38.4, 27.9, 21.1, 14.1. HRMS (ESI): calcd m/z for C21H31N2O5+: 407.2177 [M+NH4]+; found: 407.2180. HPLC (Chiralpak AD-H, eluent: n-hexane:i-PrOH = 6/1, 0.5 mL·min⁻¹, 20 °C, λ = 210 nm) retention times: t_major = 15.5 min, t_minor = 17.5 min.

Compound 2n: Synthesized according to procedure D and obtained as pale-yellow oil in 79% yield (32.0 mg, 0.079 mmol) with e.r. = 92:8. Rf (heptanes/Et2O = 2/1) = 0.18. [α]D22 (c = 0.98, CHCl3) = +12.2°. 1H NMR (300 MHz, δ, CDCl3, 298 K): 7.33-7.28 (m, 2H), 6.91-6.86 (m, 2H), 5.40 (s, 1H), 5.38 (s, 1H), 4.58 (d, J = 12.1 Hz, 1H), 4.53 (d, J = 12.1 Hz, 1H), 4.02 (2 dq, J = 10.9, 7.2 Hz, ABX3 system, 2H), 3.79 (s, 3H), 3.06 (dd, J = 16.2, 0.9 Hz, 1H), 2.97 (dd, J = 16.2, 0.9 Hz, 1H), 1.38 (s, 9H), 1.18 (t, J = 7.2 Hz, 3H). 13C NMR (75 MHz, δ, CDCl3, 298 K): 174.1, 170.7, 159.9, 156.0, 138.7, 126.8, 119.3, 114.5, 84.1, 61.1, 58.0, 57.5, 55.5, 38.4, 28.0, 14.2. HRMS (ESI): calcd m/z for C21H31N2O6+: 423.2126 [M+NH4]+; found: 423.2125. HPLC (Chiralpak AD-H, eluent: n-hexane:i-PrOH = 6/1, 0.5 mL·min⁻¹, 20 °C, λ = 210 nm) retention times: t_major = 20.0 min, t_minor = 21.7 min.
3.2. Phosphine-catalyzed γ-addition of isoxazolidin-5-ones to allenoates

**General Procedure E (γ-addition):** A reaction vial equipped with a stirring bar is 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) is added and the resulting solution is stirred for 24 h at room temperature. After completion (determined by TLC analysis), the crude product is concentrated under reduced pressure and purified by preparative TLC (silica gel, heptanes/Et₂O = 2/1) to obtain γ-addition products 12a and 12b.

**Compound 12a:** Synthesized according to procedure E, using triphenylphosphine (2.7 mg, 10 mol%). Obtained as a colorless oil which solidifies upon storage in a refrigerator (84% yield, 31.4 mg, 0.084 mmol). m.p. = 84 – 87 °C. Rf (heptanes/Et₂O = 2/1) = 0.17. ¹H NMR (300 MHz, δ, CDCl₃, 298 K): 7.44–7.31 (m, 5H), 6.68 (dt, J = 15.6, 7.6 Hz, 1H), 5.86 (dt, J = 15.6, 1.3 Hz, 1H), 4.69 (d, J = 11.9 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 4.06 (d, J = 11.9 Hz, 1H), 2.83 (2 ddd, J = 14.6, 7.6, 1.3 Hz, 2H), 1.31 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H). ¹³C NMR (75 MHz, δ, CDCl₃, 298 K): 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): calcd m/z for C₂₀H₂₉N₂O₆⁺: 393.2020 [M+NH₄⁺]; found: 393.2017.

HPLC (Chiralpak OD-H, eluent: n-hexane:i-PrOH = 20/1, 1.0 mL·min⁻¹, 20 °C, λ = 210 nm) retention times: t₁ = 24.1 min, t₂ = 28.1 min.

**Compound 12b:** Synthesized according to procedure E, using tributylphosphine (2.5 µL, 10 mol%). Obtained as a colorless oil in 13% yield (5.0 mg, 0.013 mmol). Rf (heptanes/Et₂O = 2/1) = 0.36. ¹H NMR (300 MHz, δ, CDCl₃, 298 K): 7.45–7.29 (m, 5H), 6.12 (dd, J = 11.5, 8.1, 7.1 Hz, 1H), 5.92 (dt, J = 11.5, 1.5 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 4.10 (d, J = 12.0 Hz, 1H), 3.52 (ddd, J = 15.2, 8.1, 1.5 Hz, 1H), 3.24 (ddd, J = 15.2, 7.1, 1.5 Hz, 1H), 1.29–1.27 (m, 12H). ¹³C NMR (75 MHz, δ, CDCl₃, 298 K): 175.5, 166.1, 156.0, 142.3, 136.6, 129.3, 128.6, 126.7, 123.9, 84.1, 60.4, 59.0, 52.4, 35.6, 27.8, 14.3. HRMS (ESI): calcd m/z for C₂₀H₂₅NNaO₇⁺: 398.1574 [M+Na⁺]; found: 398.1573. HPLC (Chiralpak OD-H, eluent: n-hexane:i-PrOH = 20/1, 1.0 mL·min⁻¹, 20 °C, λ = 210 nm) retention times: t₁ = 11.5 min, t₂ = 15.3 min.
3.2.1. Reactions employing chiral phosphines P2-P4

Chiral phosphine catalysts P2 and P3 were synthesized following established literature procedures\(^4\). Phosphine P4 was obtained from ABCR and used as received without any further purification.

Following procedure E, using phosphine catalysts P2-P4 (10 mol\%) gave 12a and 12b as mixtures of \(\gamma\)-addition products, which were purified by filtering through a short pad of silica gel (heptanes/Et\(_2\)O = 2/1) and analyzed by HPLC using a chiral stationary phase (Chiralpak OD-H, eluent: \(n\)-hexane/i-PrOH = 20/1, 1.0 mL·min\(^{-1}\), 20 °C, \(\lambda = 210\) nm).

**Table 1:** Conversions and HPLC results of the chiral phosphine-catalyzed \(\gamma\)-addition of \(N\)-Boc 4-phenylisoxazolidin-5-one 1a to ethyl 2,3-butenedioate 3a employing catalysts P2-P4.

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</tbody>
</table>

3.3. Further Transformations and Products

3.3.1. Reductive N-O cleavage of 2a with Na/Naphthalene

Following a known procedure\(^1(\text{a})\), to a flame-dried Schlenk tube equipped with a stirring bar under argon atmosphere is added recrystallized naphthalene\(^5\) (320 mg, 2.5 mmol) and anhydrous THF (5 mL). Sodium (63 mg, 2.7 mmol, 1.1 equiv) is added and the mixture is stirred for 30 min to provide a dark-green solution of sodium naphthalide. The freshly prepared reductant solution is added dropwise, \textit{via} syringe, to a second Schlenk tube containing 2a (34.6 mg, 0.092 mmol) in anhydrous THF (3.4 mL, 0.03 M) at -78 °C, until the dark-green color of the reaction mixture persists for at least 5 minutes. The reaction is quenched with deionized water and warmed to room temperature. The pH value is lowered to 2 with 1N HCl before it is extracted with DCM (3x). The collected organic phases are washed with brine, dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude product is purified by column chromatography with gradient elution (silica gel, DCM/MeOH = 1/0–10/1) to obtain 8a as a colorless oil in 75% yield (26.0 mg, 0.074 mmol).

2-(((\textit{tert}-butoxycarbonyl)amino)methyl)-5-ethoxy-3-methylene-5-oxo-2-phenylpentanoic acid (8a): Rf (DCM/MeOH = 10/1) = 0.20. \(^1\)H NMR (500 MHz, δ, MeOD-d4, 298 K): 7.34-7.21 (m, 6H), 5.35 (s, 1H), 5.30 (s, 1H), 4.05 (q, \(J = 7.2\) Hz, 2H), 3.87-3.76 (m, 2H), 3.07 (s, 2H), 1.31 (s, 9H), 1.20 (t, \(J = 7.2\) Hz, 3H). \(^13\)C NMR (125 MHz, δ, MeOD-d4, 298 K): 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): calcd m/z for C\(_{20}\)H\(_{27}\)NNaO\(_6\)^+: 400.1731 [M+Na]^+; found: 400.1732.

3.3.2. Reductive N-O cleavage/double bond hydrogenation of 2a with Pd/C

A flame-died Schlenk tube equipped with a magnetic stirrer is charged with 10% Pd/C (11.0 mg, 10 mol%). The flask is evacuated and backfilled with argon (3x) and a solution of 2a (38.4 mg, 0.102 mmol) in EtOH (2 mL, 0.05 M) is added under a counterflow of argon. The reaction mixture is

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degassed by means of three freeze-pump-thaw cycles, filled with hydrogen gas and vigorously stirred for 20 h at room temperature. After completion (determined by TLC analysis), the mixture is filtered through a pad of Celite, washed with DCM and concentrated under reduced pressure to give 9a as a colorless oil in 99% yield (38.4 mg, 0.101 mmol).

2-(((tert-butoxycarbonyl)amino)methyl)-5-ethoxy-3-methyl-5-oxo-2-phenylpentanoic acid (9a):
Obtained as a mixture of diastereomers (d.r. = 3:2). RF (DCM/MeOH = 10/1) = 0.53. $^1$H NMR (500 MHz, δ, MeOD-d4, 298 K): 7.33-7.22 (m, 5H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.82-3.58 (m, 2H), 2.89-2.78 (m, 1H), 2.58 and 2.46 (major: d, $J = 15.4$ Hz, minor: d, $J = 16.2$ Hz, 1H), 2.24 and 2.00 (minor: dd, $J = 16.2$, 10.9 Hz, major: dd, $J = 15.4$, 10.9 Hz, 1H), 1.36 and 1.29 (major: s, minor: s, 9H), 1.24-1.20 (m, 3H), 2.58 and 2.46 (major: d, $J = 15.4$, 10.9 Hz, minor: d, $J = 16.2$ Hz, 1H), 2.24 and 2.00 (minor: dd, $J = 16.2$, 10.9 Hz, major: dd, $J = 15.4$, 10.9 Hz, 1H), 1.36 and 1.29 (major: s, minor: s, 9H), 1.24-1.20 (m, 3H), 1.03 and 0.97 (minor: d, $J = 6.7$ Hz, major: d, $J = 6.8$ Hz, 3H). $^{13}$C NMR (125 MHz, δ, MeOD-d4, 298 K): 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): calcd m/z for C$_{20}$H$_{29}$NNaO$_6$+: 402.1887 [M+Na]$^+$; found: 402.1889.

3.3.3. KAHA-ligation of 2a with Fmoc-Leu-CO$_2$H 10

Following known procedures, 2a (31.2 mg, 0.083 mmol, e.r. = 83/17) is dissolved in anhydrous DCM (1 mL, 0.1 M) and TFA (0.5 mL) is dropwise added at 0 °C. The reaction mixture is warmed to room temperature and stirred for 30 minutes, whereupon it is concentrated under reduced pressure and dried in vacuo to give the deprotected isoxazolidin-5-one as a colorless oil. N-deprotected 2a is dissolved in rBuOH/THF/H$_2$O (1/1/1, 1.5 mL in total). Fmoc-Leu-CO$_2$H$^7$ (35.2 mg, 1.1 equiv) is added portion wise (gas evolution) and left to stir for 20 h at room temperature. H$_2$O and DCM are added and the phases are separated. The aqueous phase is extracted with DCM (3x) and the combined organic phases are dried over anhydrous Na$_2$SO$_4$, filtered through a short pad of silica, washed with DCM/MeOH (10/1, 25 mL in total) and concentrated under reduced pressure to give crude 11a as a white foam. The ligation product is dissolved in anhydrous DCM (2 mL, 0.05 M), MeOH is added (28 µL, 7 equiv) and cooled in an ice-bath. A solution of TMSCH$_2$N$_2$ in hexane (0.6 mol·L$^{-1}$, 0.8 mL, 5 equiv) is added and the reaction mixture is stirred for 30 min at room temperature. The reaction is quenched by dropwise addition of

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AcOH/Et₂O (9/1) until complete discoloration of the mixture. After removal of all volatiles under reduced pressure, the crude product is purified via preparative TLC (silica gel, heptanes/EtOAc = 2/1) to obtain methyl ester 11b as a colorless oil in overall 59% yield (30.6 mg, 0.049 mmol).

**5-ethyl 1-methyl 2-(((S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-methylpentanamido)methyl)-3-methylene-2-phenylpentanedioate (11b):** Obtained as a mixture of diastereomers (d.r. = >5:1). Rf (heptanes/EtOAc = 2/1) = 0.29. ¹H NMR (500 MHz, δ, MeOD-d4, 298 K): 7.78 (d, J = 7.5 Hz, 2H), 7.67-7.56 (m, 2H), 7.38 (t, J = 7.5 Hz, 3H), 7.32-7.25 (m, 4H), 7.24-7.19 (m, 3H), 5.39 (s, 1H), 5.30 (s, 1H), 4.41-4.29 (m, 2H), 4.18 (t, J = 6.7 Hz, 1H), 4.04-3.90 (m, 5H), 3.66 (s, 3H), 3.03 (d, J = 16.5 Hz, 1H), 2.96 (d, J = 16.5 Hz, 1H), 1.55-1.46 (m, 1H), 1.39-1.30 (m, 2H), 1.16 (t, J = 7.2 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 6.5 Hz, 3H). ¹³C NMR (125 MHz, δ, MeOD-d4, 298 K): 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): calcd m/z for C₃₇H₄₂N₂NaO₇⁺: 649.2884 [M+Na]⁺; found: 649.2887.
4. Copies of Product NMR Spectra

**NMR spectra of compound 2a**

$^1$H NMR (300 MHz, CDCl$_3$, 298 K)

$^{13}$C NMR (75 MHz, CDCl$_3$, 298 K)
NMR spectra of compound 2b

$^1$H NMR (300 MHz, CDCl$_3$, 298 K)

$^{13}$C NMR (75 MHz, CDCl$_3$, 298 K)
**NMR spectra of compound 2c**

**$^1$H NMR (300 MHz, CDCl$_3$, 298 K)**

![NMR spectrum of compound 2c](image)

**$^{13}$C NMR (75 MHz, CDCl$_3$, 298 K)**

![NMR spectrum of compound 2c](image)
**NMR spectra of compound 2d**

**¹H NMR** (300 MHz, CDCl₃, 298 K)

**¹³C NMR** (75 MHz, CDCl₃, 298 K)
NMR spectra of compound 2f

$^1$H NMR (300 MHz, CDCl$_3$, 298 K)

$^{13}$C NMR (75 MHz, CDCl$_3$, 298 K)
NMR spectra of compound 2g

$^1$H NMR (300 MHz, CDCl$_3$, 298 K)

$^{13}$C NMR (75 MHz, CDCl$_3$, 298 K)
NMR spectra of compound 2h

$^1$H NMR (300 MHz, CDCl$_3$, 298 K)

$^{13}$C NMR (75 MHz, CDCl$_3$, 298 K)
NMR spectra of compound 2i

$^1$H NMR (300 MHz, CDCl$_3$, 298 K)

$^{13}$C NMR (75 MHz, CDCl$_3$, 298 K)
NMR spectra of compound 2j

$^1$H NMR (300 MHz, CDCl$_3$, 298 K)

$^{13}$C NMR (75 MHz, CDCl$_3$, 298 K)
$^{19}$F NMR (282 MHz, CDCl₃, 298 K)

NMR spectra of compound 2k

$^1$H NMR (300 MHz, CDCl₃, 298 K)
$^{13}$C NMR (75 MHz, CDCl$_3$, 298 K)

NMR spectra of compound 2l

$^1$H NMR (300 MHz, CDCl$_3$, 298 K)
$^{13}$C NMR (75 MHz, CDCl$_3$, 298 K)

NMR spectra of compound 2m

$^1$H NMR (300 MHz, CDCl$_3$, 298 K)
\( ^{13}C\text{ NMR} \) (75 MHz, CDCl\(_3\), 298 K)

NMR spectra of compound 2n

\( ^1H\text{ NMR} \) (300 MHz, CDCl\(_3\), 298 K)
$^{13}$C NMR (75 MHz, CDCl$_3$, 298 K)

NMR spectra of compound 8a

$^1$H NMR (500 MHz, MeOD-d$_4$, 298 K)
$^{13}$C NMR (125 MHz, MeOD-d$_4$, 298 K)

NMR spectra of compound 9a

$^1$H NMR (500 MHz, MeOD-d$_4$, 298 K)
$^{13}$C NMR (125 MHz, MeOD-d4, 298 K)

NMR spectra of compound 11b

$^1$H NMR (500 MHz, MeOD-d4, 298 K)
$^{13}$C NMR (125 MHz, MeOD-d$_4$, 298 K)

NMR spectra of compound 12a

$^1$H NMR (300 MHz, CDCl$_3$, 298 K)
$^{13}$C NMR (75 MHz, CDCl$_3$, 298 K)

NMR spectra of compound 12b

$^1$H NMR (300 MHz, CDCl$_3$, 298 K)
**13C NMR** (75 MHz, CDCl₃, 298 K)

**NMR spectrum of compound 4.1**

**1H NMR** (300 MHz, CDCl₃, 298 K)
NMR spectrum of compound 4,2

$^1$H NMR (300 MHz, CDCl$_3$, 298 K)

NMR spectrum of compound (R)-5

$^1$H NMR (300 MHz, CDCl$_3$, 298 K)
NMR spectra of compound (R)-6a

$^1$H NMR (300 MHz, CDCl$_3$, 298 K)

$^{13}$C NMR (75 MHz, CDCl$_3$, 298 K)
**F NMR (282 MHz, CDCl₃, 298 K)**

**NMR spectra of compound (R)-6b**

**H NMR (300 MHz, CDCl₃, 298 K)**
$^{13}$C NMR (75 MHz, CDCl$_3$, 298 K)

$^{19}$F NMR (282 MHz, CDCl$_3$, 298 K)
NMR spectra of compound (R)-6c

$^1$H NMR (300 MHz, CDCl$_3$, 298 K)

$^{13}$C NMR (75 MHz, CDCl$_3$, 298 K)
**NMR spectra of compound (R)-7a**

**1H NMR (300 MHz, CDCl₃, 298 K)**

![1H NMR spectrum](image)

**13C NMR (75 MHz, CDCl₃, 298 K)**

![13C NMR spectrum](image)
**19F NMR (282 MHz, CDCl<sub>3</sub>, 298 K)**

**NMR spectra of compound (R)-7b**

**1H NMR (300 MHz, CDCl<sub>3</sub>, 298 K)**
$^{13}$C NMR (75 MHz, CDCl$_3$, 298 K)

$^{19}$F NMR (282 MHz, CDCl$_3$, 298 K)
NMR spectra of compound (R)-7c

$^1$H NMR (300 MHz, CDCl$_3$, 298 K)

$^{13}$C NMR (75 MHz, CDCl$_3$, 298 K)
NMR spectra of catalyst (R)-E1

**$^1$H NMR** (300 MHz, CDCl$_3$, 298 K)

**$^{13}$C NMR** (75 MHz, CDCl$_3$, 298 K)
Enantioselective β-selective addition of isoxazolidin-5-ones to allenoates catalyzed by quaternary ammonium salts

$^{19}$F NMR (282 MHz, CDCl$_3$, 298 K)

NMR spectra of catalyst (R)-E2

$^1$H NMR (300 MHz, CDCl$_3$, 298 K)
$^{13}$C NMR (75 MHz, CDCl$_3$, 298 K)

$^{19}$F NMR (282 MHz, CDCl$_3$, 298 K)
**NMR spectra of catalyst (R)-E3**

**1H NMR (300 MHz, CDCl₃, 298 K)**

**13C NMR (75 MHz, CDCl₃, 298 K)**
NMR spectra of catalyst \((R,R)-E4\)

**\(^1H\) NMR** (300 MHz, CDCl3, 298 K)

**\(^{13}C\) NMR** (75 MHz, CDCl3, 298 K)
$^{31}$F NMR (282 MHz, CDCl$_3$, 298 K)

NMR spectra of catalyst \( (R,S)-E4 \)

$^1$H NMR (300 MHz, CDCl$_3$, 298 K)
$^{13}$C NMR (75 MHz, CDCl$_3$, 298 K)

$^{19}$F NMR (282 MHz, CDCl$_3$, 298 K)
5. Copies of HPLC Chromatograms

HPLC traces of compound 2a

YMC Chiral ART Amylose-SA, eluent: n-hexane:i-PrOH = 20/1, 0.7 mL·min⁻¹, 20 °C, λ = 210 nm
**HPLC traces of compound 2b**

YMC Chiral ART Amylose-SA, eluent: *n*-hexane:*i*-PrOH = 20/1, 0.7 mL·min⁻¹, 20 °C, \( \lambda = 210 \) nm

**Integration Results**

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<td>2</td>
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<td>9872654</td>
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<td>Total</td>
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<td>19416423</td>
<td>100.00</td>
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</table>
**HPLC traces of compound 2c**

Chiralpak AD-H, eluent: *n*-hexane:*i*-PrOH = 6/1, 0.5 mL·min⁻¹, 20 °C, λ = 210 nm

<table>
<thead>
<tr>
<th>No.</th>
<th>Peak Name</th>
<th>Retention Time (min)</th>
<th>Area (mAU·min)</th>
<th>Height (mAU)</th>
<th>Relative Area (%)</th>
<th>Relative Height (%)</th>
<th>Amount (n.a.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>23.020</td>
<td>496,937</td>
<td>623,037</td>
<td>81.91</td>
<td>85.19</td>
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</tr>
<tr>
<td>2</td>
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<td>30.567</td>
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<td>103,336</td>
<td>18.09</td>
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<td>731,373</td>
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</table>

**Peak Table**

<table>
<thead>
<tr>
<th>Peak#</th>
<th>Ret. Time (min)</th>
<th>Area (mAU)</th>
<th>Area%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23.00</td>
<td>16914705</td>
<td>50.76</td>
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<tr>
<td>2</td>
<td>29.18</td>
<td>16409022</td>
<td>49.24</td>
</tr>
<tr>
<td>Total</td>
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<td>33323728</td>
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</tr>
</tbody>
</table>
HPLC traces of compound 2d

YMC Chiral ART Amylose-S-A, eluent: n-hexane:i-PrOH = 20/1, 0.7 mL·min⁻¹, 20 °C, λ = 210 nm
HPLC traces of compound 2f

Chiralpak AD-H, eluent: n-hexane:i-PrOH = 6/1, 0.5 mL·min⁻¹, 20 °C, λ = 210 nm
**HPLC traces of compound 2g**

YMC Chiral ART Cellulose-SB, eluent: *n*-hexane:*i*-PrOH = 10/1, 0.5 mL·min⁻¹, 20 °C, *λ* = 210 nm
HPLC traces of compound 2h

Chiralpak AD-H, eluent: n-hexane:i-PrOH = 6/1, 0.5 mL·min\(^{-1}\), 20 °C, \(\lambda = 210\) nm
HPLC traces of compound 2i

YMC Chiral ART Cellulose-SZ, eluent: n-hexane/i-PrOH = 30/1, 0.5 mL·min⁻¹, 20 °C, λ = 210 nm

Integration Results

<table>
<thead>
<tr>
<th>No</th>
<th>Peak Name</th>
<th>Retention Time (min)</th>
<th>Area (mAU)</th>
<th>Height (mAU)</th>
<th>Relative Area (%)</th>
<th>Relative Height (%)</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>n.a.</td>
<td>Peak 1</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
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<tr>
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<td>652,799</td>
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<td>99.9</td>
<td>99.9</td>
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</table>

Peak Table

<table>
<thead>
<tr>
<th>Peak#</th>
<th>Ret. Time</th>
<th>Area</th>
<th>Area%</th>
</tr>
</thead>
<tbody>
<tr>
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<td>18.97</td>
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<tr>
<td>Total</td>
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<td>27233084</td>
<td>100.00</td>
</tr>
</tbody>
</table>

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**HPLC traces** of compound 2j

YMC Chiral ART Amylose-SA, eluent: n-hexane:i-PrOH = 20/1, 0.7 mL·min⁻¹, 20 °C, λ = 210 nm

<table>
<thead>
<tr>
<th>Chromatogram</th>
<th>UV_VIS_1 WVL 210 nm</th>
</tr>
</thead>
</table>

### Integration Results

<table>
<thead>
<tr>
<th>No.</th>
<th>Peak Name</th>
<th>Retention Time (min)</th>
<th>Area (mAU·min)</th>
<th>Height (mAU)</th>
<th>Relative Area (%)</th>
<th>Relative Height (%)</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peak 1</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>21.247</td>
<td>213,723</td>
<td>308,093</td>
<td>97.73</td>
<td>82.79</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

**Total:** 243,627, 372,125, 100.00

---

<table>
<thead>
<tr>
<th>Chromatogram</th>
<th>UV_VIS_1 WVL 210 nm</th>
</tr>
</thead>
</table>

### Integration Results

<table>
<thead>
<tr>
<th>No.</th>
<th>Peak Name</th>
<th>Retention Time (min)</th>
<th>Area (mAU·min)</th>
<th>Height (mAU)</th>
<th>Relative Area (%)</th>
<th>Relative Height (%)</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>n.a.</td>
<td>Peak 1</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
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<tr>
<td>1</td>
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<td>18.717</td>
<td>123,346</td>
<td>188,538</td>
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<tr>
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<td>123,346</td>
<td>188,538</td>
<td>49.00</td>
<td>41.14</td>
<td>n.a.</td>
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</table>

**Total:** 247,073, 453,551, 100.00
HPLC traces of compound 2k

YMC Chiral ART Amylose-SA, eluent: n-hexane:i-PrOH = 20/1, 0.7 mL·min⁻¹, 20 °C, λ = 210 nm
**HPLC traces of compound 2l**

YMC Chiral ART Amylose-SA, eluent: *n*-hexane:*i*-PrOH = 20/1, 0.7 mL·min⁻¹, 20 °C, λ = 210 nm

---

**Integration Results**

<table>
<thead>
<tr>
<th>No</th>
<th>Peak Name</th>
<th>Retention Time</th>
<th>Area mAU*min</th>
<th>Height mAU</th>
<th>Relative Area %</th>
<th>Relative Height %</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>n.a.</td>
<td>Peak 1</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
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<td>27.651</td>
<td>11.11</td>
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<tr>
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<td></td>
<td>137,174</td>
<td>177,244</td>
<td>100.00</td>
</tr>
</tbody>
</table>
**HPLC traces** of compound 2m

Chiralpak AD-H, eluent: *n*-hexane:*i*-PrOH = 6/1, 0.5 mL·min⁻¹, 20 °C, *λ* = 210 nm

<table>
<thead>
<tr>
<th>No</th>
<th>Peak Name</th>
<th>Retention Time (min)</th>
<th>Area (mAU·min)</th>
<th>Height (mAU)</th>
<th>Relative Area (%)</th>
<th>Relative Height (%)</th>
<th>Amount (n.a.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>15.507</td>
<td>272,017</td>
<td>546,797</td>
<td>90.55</td>
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<tr>
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<td>123,890</td>
<td>24,422,229</td>
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<tr>
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<td>571,229</td>
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</table>

**Integration Results**

## mAU

### PDA Multi 1 210nm, 4nm

**Peak Table**

<table>
<thead>
<tr>
<th>Peak#</th>
<th>Ret. Time</th>
<th>Area</th>
<th>Area%</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>2</td>
<td>17.97</td>
<td>18111270</td>
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</tr>
<tr>
<td>Total</td>
<td></td>
<td>36151315</td>
<td>100.00</td>
</tr>
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</table>
HPLC traces of compound 2n

Chiralpak AD-H, eluent: n-hexane:i-PrOH = 6/1, 0.5 mL·min⁻¹, 20 °C, λ = 210 nm
HPLC traces of compounds 12a and 12b

Chiralpak OD-H, eluent: $n$-hexane:$i$-PrOH = 20/1, 1.0 mL·min$^{-1}$, 20 °C, $\lambda = 210$ nm
6. HRMS Data

**HRMS spectrum of compound 2a**

ESI-QTOF, MeOH, calcd m/z for C_{20}H_{29}N_{2}O_{6}: 393.2020 [M+NH_4]^+; found: 393.2021

**HRMS spectrum of compound 2b**

ESI-QTOF, MeOH, calcd m/z for C_{19}H_{27}N_{2}O_{6}: 379.1864 [M+NH_4]^+; found: 379.1866

**HRMS spectrum of compound 2c**

ESI-QTOF, MeOH, calcd m/z for C_{25}H_{31}N_{2}O_{6}: 455.2177 [M+NH_4]^+; found: 455.2180
**HRMS spectrum of compound 2d**

ESI-QTOF, MeOH, calcd \( m/z \) for C\(_{22}\)H\(_{33}\)N\(_2\)O\(_5\): 421.2333 \([\text{M+NH}_4]^+\); found: 421.2334

**HRMS spectrum of compound 2f**

ESI-QTOF, MeOH, calcd \( m/z \) for C\(_{18}\)H\(_{27}\)N\(_2\)O\(_5\)S: 399.1584 \([\text{M+NH}_4]^+\); found: 399.1587

**HRMS spectrum of compound 2g**

ESI-QTOF, MeOH, calcd \( m/z \) for C\(_{24}\)H\(_{31}\)N\(_2\)O\(_5\): 443.2177 \([\text{M+NH}_4]^+\); found: 443.2179
**HRMS spectrum of compound 2h**

ESI-QTOF, MeOH, calcd m/z for C_{20}H_{27}Cl_N_O^+: 461.1241 [M+NH_4]^+; found: 461.1247

**HRMS spectrum of compound 2i**

ESI-QTOF, MeOH, calcd m/z for C_{28}H_{47}N_O^+: 551.3147 [M+NH_4]^+; found: 551.3152

**HRMS spectrum of compound 2j**

ESI-QTOF, MeOH, calcd m/z for C_{20}H_{28}F_N_O^+: 411.1926 [M+NH_4]^+; found: 411.1930
**HRMS spectrum of compound 2k**

ESI-QTOF, MeOH, calcd m/z for C_{20}H_{28}ClN_{2}O_{6}^{+}: 427.1630 [M+NH_{4}]^{+}; found: 427.1629

**HRMS spectrum of compound 2l**

ESI-QTOF, MeOH, calcd m/z for C_{20}H_{28}BrN_{2}O_{6}^{+}: 471.1125 [M+NH_{4}]^{+}; found: 471.1130

**HRMS spectrum of compound 2m**

ESI-QTOF, MeOH, calcd m/z for C_{21}H_{31}N_{2}O_{6}^{+}: 407.2177 [M+NH_{4}]^{+}; found: 407.2180
**HRMS spectrum of compound 2n**

ESI-QTOF, MeOH, calcd m/z for C_{21}H_{31}N_{2}O_{7}: 423.2126 [M+NH₄]⁺; found: 423.2125

![HRMS spectrum of compound 2n](image)

**HRMS spectrum of compound 8a**

ESI-QTOF, MeOH, calcd m/z for C_{20}H_{26}N_{2}NaO_{6}: 400.1731 [M+Na]⁺; found: 400.1732

![HRMS spectrum of compound 8a](image)

**HRMS spectrum of compound 9a**

ESI-QTOF, MeOH, calcd m/z for C_{20}H_{26}N_{2}NaO_{6}: 402.1887 [M+Na]⁺; found: 402.1889

![HRMS spectrum of compound 9a](image)
HRMS spectrum of compound 11a

ESI-QTOF, MeOH, calcd m/z for C_{36}H_{41}N_{2}O_{7}^+: 613.2908 [M+H]^+; found: 613.2910

HRMS spectrum of compound 11b

ESI-QTOF, MeOH, calcd m/z for C_{37}H_{42}N_{2}NaO_{7}^+: 649.2884 [M+Na]^+; found: 649.2887
**HRMS spectrum of compound 12a**

ESI-QTOF, MeOH, calcd \( m/z \) for \( \text{C}_{20}\text{H}_{29}\text{N}_{2}\text{O}_{6} \): 393.2020 [M+NH\(_4\)]\(^+\); found: 393.2017

![Graph showing HRMS spectrum of compound 12a](image)

**HRMS spectrum of compound 12b**

ESI-QTOF, MeOH, calcd \( m/z \) for \( \text{C}_{20}\text{H}_{25}\text{NNaO}_{6} \): 398.1574 [M+N\(_{\text{Na}}\)]\(^+\); found: 398.1573.

![Graph showing HRMS spectrum of compound 12b](image)