Immobilization of *cis*-4-Hydroxydiphenylprolinol Silyl Ethers onto Polystyrene. Application in the Catalytic Enantioselective Synthesis of 5-Hydroxyisoxazolidines in Batch and Flow

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Abstract. A new family of polystyrene-supported *cis*-4-hydroxydiphenylprolinol has been prepared, and the resulting polymers have been evaluated as organocatalysts to promote the tandem reaction between *N*-protected hydroxylamines and α,β-unsaturated aldehydes in batch and flow. The new PS-supported catalysts compare favorably with well-established immobilized Jørgensen-Hayashi catalysts, affording 5-hydroxyisoxazolidines as single diastereoisomers with high enantioselectivities and good yields (up to 83% yield, up to 99% ee).

Keywords: supported catalysts; organic catalysis; flow chemistry; asymmetric catalysis; isoxazolidines

Introduction

The development of asymmetric catalysis has significantly expanded the toolkit of synthetic chemists when tackling the preparation of optically enriched compounds.[1] The advent of organocatalysis, that arrived to complement biocatalysis and transition metal-based approaches, has provided new opportunities to activate very reactive intermediates in generally mild conditions. α,α-Diarylprolinols, generally known as Jørgensen-Hayashi catalysts, are amongst the most successful aminocatalysts.[2] Their main drawback is the high catalyst loadings usually required as a consequence of unfavourable equilibria and the formation of off-cycle species.[3] To address this issue, our research group, as well as others, have studied their immobilization in an attempt to increase their lifespan.[4] In the cases where the anchoring strategy has proven successful, the resulting solid-supported Jørgensen-Hayashi catalysts display high catalytic activity and selectivity, while being recyclable and even amenable to application in continuous flow.[5]

Recently, we reported the preparation of a family of 37 modular *cis*-4-hydroxyprolinol derivatives starting from *trans*-4-hydroxyproline. The synthesis relied on the intermediacy of the bicyclic lactone depicted in Figure 1 (previously described by Joullié[6a]) to invert the stereochemistry at C4. With the help of high-throughput-experimentation (HTE) techniques and Design of Experiments (DoE) we were able identify the most promising catalysts for the *aza*-Michael addition and fine-tune the reaction conditions to optimize yield and enantioselectivity.[6c] Encouraged by the behavior of the *cis*-derivatives, which performed better than their *trans* analogues, we decided to study the immobilization of *cis*-4-hydroxyprolinol derivatives and establish a direct comparison with the *trans* series we have previously reported (Figure 1).

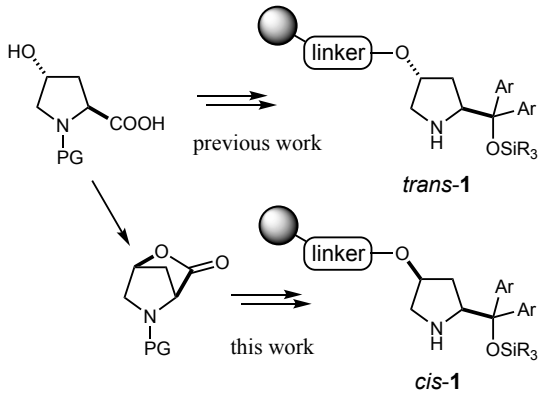
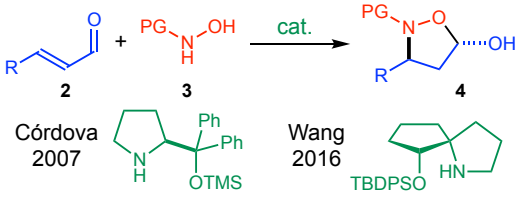


Figure 1. Immobilized *cis*- and *trans*-diarylprolinols.

Isoxazolidines[7] are valuable chiral building blocks that can be easily converted to γ-amino alcohols,[8] β-lactams[9] and β-amino acids,[10,7e,f] important scaffolds for chemical and biological applications. This has prompted several authors to develop novel asymmetric methods for their preparation. For instance, in 2000, MacMillan and co-workers were the first to report an imidazolidinone-catalyzed enantioselective synthesis of isoxazolidines that relied on 1,3-dipolar cycloaddition reactions of an iminium ion intermediate.[11] In 2007, Córdova reported the preparation of 5-hydroxyisoxazolidines mediated by α,α-diarylprolinol TMS ether via an asymmetric domino Michael reaction pathway between *N*-protected hydroxylamines and enals,[12] for which Wang later employed a spiranic catalyst[13] (Scheme 1). In 2010, Zlotin and co-workers used recoverable α,α-diarylprolinol-derived chiral ionic liquids which could be easily recycled and reused more than four times in this domino reaction.[14] However, to the best of our knowledge, the asymmetric organocatalytic synthesis of 5-hydroxyisoxazolidines in flow remains unexplored.

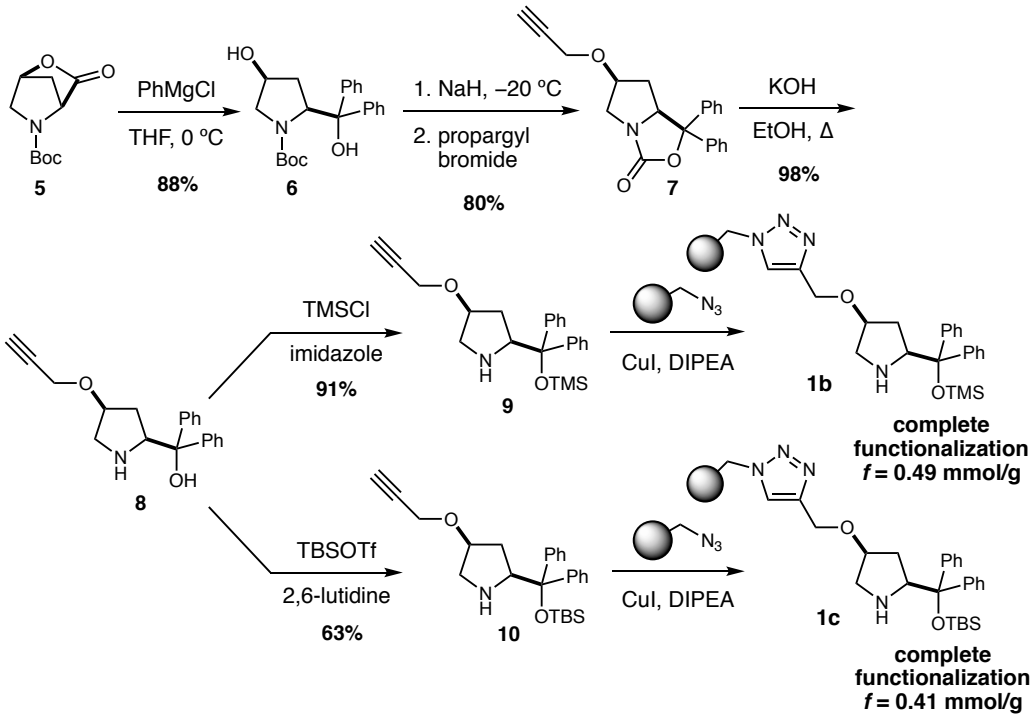


Scheme 1. Organocatalytic isoxazolidine formation.

When dealing with supported catalysts, besides the type of monomer and the immobilization strategy, the choice of solid phase is crucial because poor mechanical stability of non-properly selected supports can counterbalance the putative advantages of easy recycling and reuse.[15] In our experience, polystyrene resins have proven reliable in terms of thermal and mechanical stability. In this context, the implementation of flow processes entails a further advantage because, once the resin is packed, the beads are not shaken nor stirred. In light of the above-mentioned, we thought the addition of hydroxylamine derivatives to enals catalyzed by immobilized diarylprolinol derivatives would be a good benchmark to assess the relative merits of the *cis* and *trans* series both in batch and flow.

Results and Discussion

In order to establish the catalytic behavior of the supported *cis*-diarylprolinols, we prepared two members of this family, bearing TMS and TBDMS protecting groups, according to the sequence outlined in Scheme 2. First, lactone **5**[6] was treated with phenylmagnesium chloride to generate the 2,4-*cis* diphenylprolinol derivative **6**. Propargylation of the secondary alcohol took place with concomitant oxazolidinone formation and the product **7** was then hydrolyzed to the amino alcohol **8**. This intermediate was protected as a TMS (**9**) or TBS (**10**) ether which, after immobilization via azide-alkyne cycloaddition with azidomethyl-polystyrene, gave rise to resins **1b** and **1c**, respectively with full functionalization.

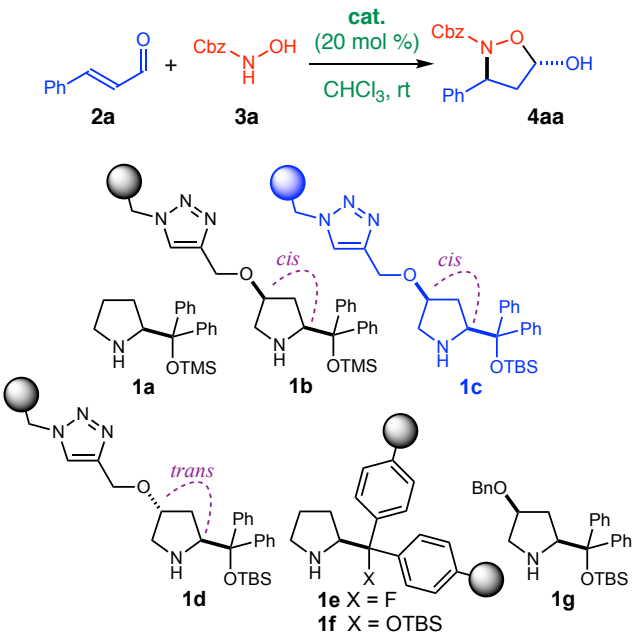


Scheme 2. Synthetic sequence for the preparation of resins **1b** and **1c**.

For the sake of comparison, we decided to evaluate as well the activity of supported diarylprolinol catalysts previously reported in our group, either having a 2,4-*trans* array[5c] (**1d**) or prepared by co-polymerization of a distyrylprolinol derivative[5e,16] (**1e,f**). Finally, homogeneous *cis*-**1g** would also tested in an attempt to assess the impact of the triazole linker.

Thus, the stage was set to run a comparative study of catalysts **1a**-**1g** (Table 1), placing special emphasis on the stereochemistry at C4. The model reaction selected was the addition of protected hydroxylamine **3a** to cinnamaldehyde **2a**, which afforded chiral 5-hydroxyisoxazolidine **4aa** via a tandem sequence consisting of aza-Michael addition followed by hemiacetalization. Preliminary tests run with **1b** established $CHCl_3$ and rt as a good starting point to optimize reaction conditions (see SI for details).

Table 1. Solid-supported catalyst screening for the enantioselective formation of isoxazolidines.

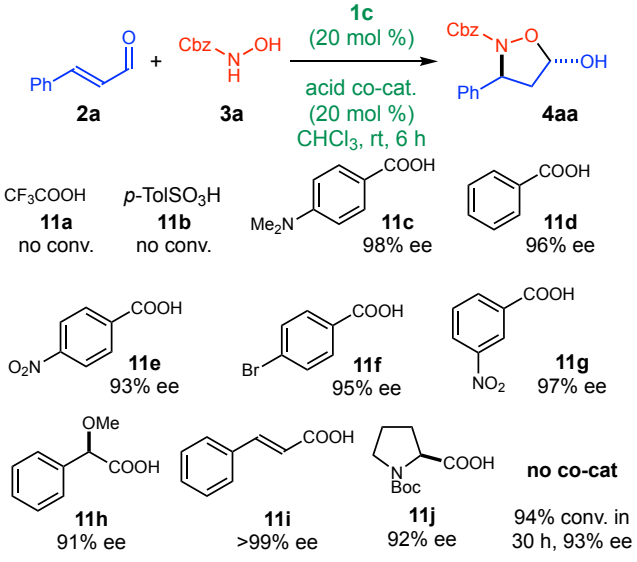


Entry[a)]	Cat.	time (h)	Conv. (%)	Yield (%)	ee (%)
1	**1a**	6	99	65	89
2	**1b**	6	99	80	90
3	**1c**	**7**	**100**	**76**	**95**
4	**1d**	7	98	71	92
5	**1e**	18	100	74	76
6	**1f**	18	97	68	95
7	**1g**	6	98	70	93

[a)] Conversion and yield determined by ^{1}H NMR using mesitylene as an internal standard; for the functionalization level of catalysts, see SI.

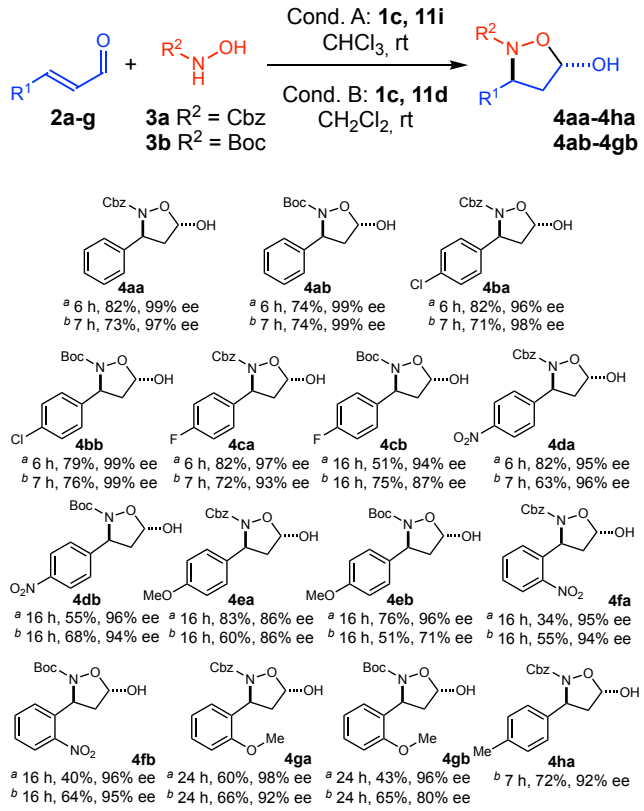
According to literature precedents,[12] diarylprolinol TMS ether **1a** proved competent in this reaction (entry 1). In comparison, the supported catalysts from the novel 2,4-*cis* series **1b** and **1c** (bearing a TMS and a TBS group, respectively; entries 2 and 3) displayed improved activity and enantioselectivity. Interestingly, the results were also better than those recorded for the *trans* analog **1d** (entry 4). A direct comparison between **1c** and **1d**, which differ only on the relative stereochemistry of the pyrrolidine 2,4 substituents allows to establish the superiority of the *cis*-derivatives over the *trans* ones in terms of yield and enantioselectivity, at least for this reaction. Although the catalytic activity of **1c** is only slightly better than that of **1d**, as indicated by the kinetics of comparative experiments (see SI), **1c** has the definitive advantage of its stereochemical integrity, secured by the fixed configurational arrangement of the pyrrolidine 2,4 substituents in **5**.[6c-d] In addition, two catalysts prepared by co-polymerization of a distyrylprolinol were submitted to the reaction conditions: **1e** (with a fluorine; entry 5) gave moderate enantioselectivity, whereas **1f**, bearing a silyl ether (entry 6), matched the ee's of **1c**, albeit with a slightly lower activity. Finally, an homogeneous analogue of **1c**, without the triazole (**1g**[6c] entry 7) was shown to behave similarly in terms of yield and selectivity, which points out to a steric rather than electronic effect of the linker. In summary, the catalyst of choice for this reaction is **1c**, with a *cis*-2,4 arrangement and a TBS group.

During the investigation of this tandem reaction, we found that the addition of acid had a significant impact on the reaction rate and selectivity, leading in most cases to full conversions in shorter times (Scheme 3).[17] While strong acids like TFA or TsOH completely shut down the catalytic activity, with less acidic co-catalysts the ee value increased (acids **11c-e**) and full conversion was reached in 6 h. Among all carboxylic acids tested, cinnamic acid turned out to give the best enantioselectivity in $CHCl_3$. Because of the toxicity of $CHCl_3$ which may limit the utilization of the immobilized diarylprolinol in flow, we carried out a similar screening in CH_2Cl_2 (see SI). In this solvent, benzoic and cinnamic acid behave similarly; given that the former is inexpensive, we established a second set of conditions involving CH_2Cl_2 and benzoic acid as an additive.



Scheme 3. Screening of the acidic co-catalyst. [a] Conv. determined by ^{1}H NMR using mesitylene as internal standard; full conversion recorded with acids **11c-11j** in 6 h.

Thus, we decided to investigate the scope of the catalytic asymmetric tandem reaction in batch using immobilized diarylprolinol **1c** with cinnamic acid as additive in $CHCl_3$ (Scheme 4, conditions A) or benzoic acid as additive in CH_2Cl_2 (Scheme 4, conditions B), in both cases at room temperature. Indeed, β-substituted enals provided the corresponding 5-hydroxyisoxazolidines **4** as single diastereoisomers with high enantioselectivities and moderate to good yields (34-83% yield, 71–99% ee). Moreover, the reactions with *N*-Boc-NHOH **3b** gave the corresponding products in 51–74% yield and in 71–99% ee. Cinnamaldehyde and its derivatives containing halogen atoms (F or Cl) or a nitro group at the *para*-position of the aromatic ring afforded the desired isoxazolidines in a short time. Introduction of a group in the *ortho*-position or the presence of a methoxy group at the *para*-position slowed down the reaction.

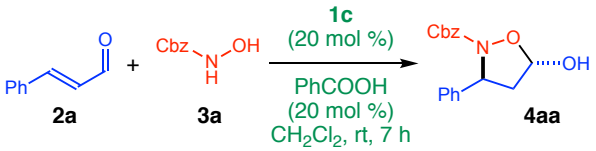


Scheme 4. Scope of the catalytic reaction in batch. [a] Reaction conditions: **2** (0.05 mmol, 1 eq.), **3** (10 mg, 0.06 mmol, 1.2 eq.), **1c** (23 mg, 20 mol %), **11i** (1.5 mg, 20 mol %), $CHCl_3$ (0.25 mL), rt. [b] Reactions run in CH_2Cl_2 (0.5 mmol of **2**) with **11d** (12 mg, 20 mol %) as co-catalyst.

The good results recorded prompted us to study the recyclability of the catalyst in batch. To our delight, the reaction between **2a** and **3a** catalyzed by **1c** could be run for 10 consecutive cycles after simply filtering and recovering the resin. As shown in Table 2, the results obtained in the tenth cycle match those recorded in the initial one, which bears witness of the catalyst robustness. Indeed, the accumulated TON in these ten runs was 36.5.

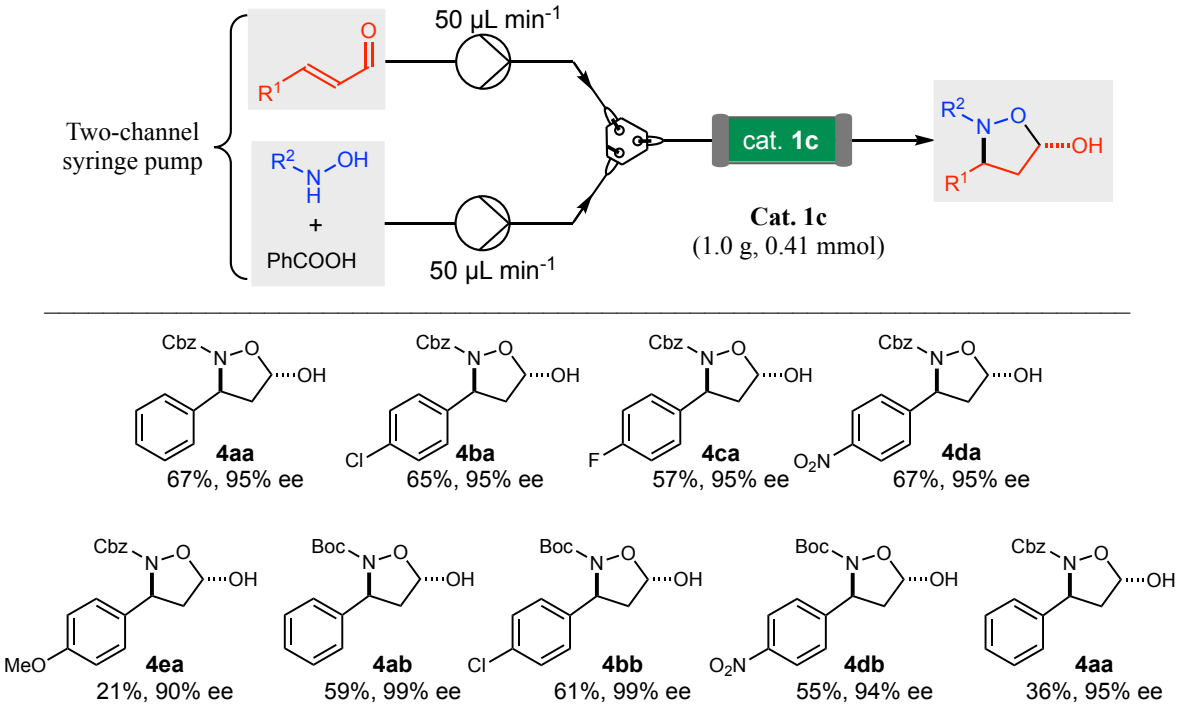
Encouraged by the robustness of the supported catalyst, a family of α,β-unsaturated aldehydes was submitted to the flow process with **3a** or **3b** as reaction partners (Scheme 5). To this end, a packed bed reactor was filled with catalyst **1c** (1.00 g, 0.41 mmol) and two channels were used to feed the reagents through the system. Due to compatibility issues, the first contained a solution of **2** while the second had a mixture of hydroxylamine **3** and benzoic acid (**11d**); the use of a single syringe pump equipped with two syringe slots ensured that both flow rates were equal. For each experiment, 9.84 mmol of **2** were passed through the packed bed reactor, at a combined flow rate of 100 µL min^{-1}. When the solutions of starting materials were consumed, the column was rinsed with CH_2Cl_2 to remove all organic products.

Table 2. Study of the catalyst recyclability.



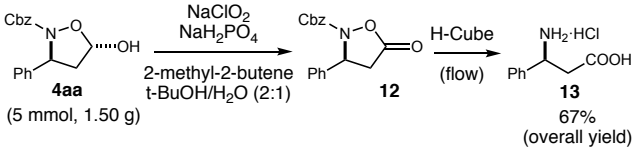
Run	Conv. (%)	Yield (%)	ee (%)
1	98	73	94
2	97	79	95
3	97	89	95
4	97	80	96
5	96	71	95
6	97	68	96
7	97	65	96
8	96	72	96
9	92	64	96
10	91	69	96

With this sequential approach, up to ten different 5-hydroxyisoxazolidines were prepared with excellent enantioselectivities and moderate to good yields. As shown in Scheme 5, cinnamaldehyde and its electron poor derivatives afforded the corresponding products in good yields and excellent ee's working at 100 µL min^{-1}. On the other hand, the slower kinetics observed for **2e** forced us to lower the flow rate to 50 µL min^{-1}; under these conditions, even if the yields were not fully satisfactory, the enantioselectivities remained excellent. Overall, the accumulated TON in these flow processes was of 134. Remarkably, the same packed bed reactor was used for all the flow experiments (preliminary runs and scope), carried out within a period of 2 months without apparent decrease in performance.



Scheme 5. Set-up and results of the continuous flow reaction promoted by **1c**.

The synthetic versatility of the products was demonstrated by taking the crude mixture from one of the reactions and submitting it to oxidation to furnish isoxazolidinone **12** (Scheme 6). Even more interestingly, this could be reduced to a β-amino acid in a continuous flow experiment carried out with a H-cube reactor (90 atm of H_2, 0.5 mL min^{-1}, 50 °C) that involved N-O bond reduction and hydrogenolysis of the Cbz protecting group. Remarkably, this allows the generation of enantioenriched β-amino acids in only three steps, two of which are carried out in a continuous flow manner. Moreover, the use of the H-cube enables to carry out the reduction without a bottle of gaseous hydrogen (it is generated in situ from water), which greatly improves the safety profile of the procedure.



Scheme 6. Derivatization of Product **4aa**.

Conclusion

In summary, a solid-supported organocatalyst has been applied to the enantioselective domino reaction between α,β-unsaturated aldehydes and *N*-protected hydroxylamines in batch and flow. Immobilized diarylprolinol **1c**, has afforded the best results while proving remarkably stable under the reaction conditions. This has allowed to run ten consecutive cycles of the same reaction, providing the same enantioselectivity and without significant loss of yield. In addition, eleven flow experiments involving nine different substrates have been carried out over a period of 2 months with the same packed column. Finally, a sequence consisting of oxidation and continuous flow hydrogenation allowed the preparation of β-amino acids, thus proving the synthetic potential of this methodology.

Experimental Section

Preparation of immobilized 2,4-*cis*-diarylprolinols 1b,1c

A solution of the lactone **5**[6] (1.377 g, 6.46 mmol) in dry THF (38 ml) under Ar was cooled to 0 °C and PhMgCl (2.0 M in THF, 6.5 ml, 12.92 mmol) was added dropwise. The mixture was stirred for 2 h (conversion was checked by TLC). Then, the reaction mixture was quenched with aq. sat. NH_4Cl (50 mL), the layers were separated, the aqueous phase was extracted with TBME (3 x 40 mL) and dried over Na_2SO_4. Purification by flash column chromatography (Cy/EtOAc 80:20 - 70:30 - 65:35 - 60:40) gave 2.11 g of product **6** (88% yield).

***tert*-Butyl (2*S*,4*S*)-4-hydroxy-2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate (6)**. White solid. **Melting point**: 197.3-199.5. R_f: 0.30 (Cy/EtOAc 60:40). $[\alpha]_D^{25}$ = +122.3 (*c* 1.00, DCM). **^{1}H NMR** (400, $CDCl_3$): δ = 7.52-7.48 (m, 2H), 7.41-7.35 (m, 4H), 7.33-7.28 (m, 1H), 7.26-7.17 (m, 3H), 4.92 (d, *J* = 9.1 Hz, 1H), 4.54 (br s, 1H), 4.35 (br s, 1H), 4.20-3.70 (br s, 2H), 3.33 (br s, 1H), 2.30 (ddd, *J* = 14.6, 9.3, 7.6 Hz, 1H), 1.82 (d, *J* = 14.6 Hz, 1H), 1.14 (br s, 9H). **^{13}C NMR** (100.4, $CDCl_3$): δ = 154.8, 145.0, 144.7, 128.2 (2C), 127.8 (2C), 127.2, 127.1 (3C), 126.9 (2C), 81.4, 79.7, 70.1, 64.7, 57.1, 38.2, 27.9 (3C). **HRMS** (ESI+): calcd for $C_{22}H_{27}NNaO_4$ $[M+Na]^+$: 392.1832, found: 392.1840.

A suspension of NaH (60% in mineral oil, 0.200 g, 5.0 mmol) in 9 mL of anhydrous DMF under N_2 was cooled to –25 °C (internal temperature) and a solution of alcohol **6** (0.924 g, 2.5 mmol) in 7 mL of DMF was added dropwise. The mixture was stirred at this temperature for 20 min and then propargyl bromide (80% in toluene, 0.28 mL, 2.5 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 1 h and then brought to RT. When TLC analysis showed complete conversion of the starting material, 35 mL of NH_4Cl were added and it was extracted with EtOAc (3 × 60 mL). the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (Cy/EtOAc 90:10 to 60:40) gave the propargylated derivative **7** in 80% yield (0.668 g, 2.00 mmol) as a white solid.

(6*S*,7a*S*)-1,1-Diphenyl-6-(prop-2-yn-1-yloxy)tetrahydro-1H,3H-pyrrolo[1,2-c]oxazol-3-one (7). White solid. **Melting point**: 140.0-141.8. R_f: 0.27 (Cy/EtOAc 70:30). $[\alpha]_D^{25}$ = −209.8 (*c* 1.00, DCM). **^{1}H NMR** (400, $CDCl_3$): δ = 7.53-7.48 (m, 2H), 7.38-7.25 (m, 8H), 4.64 (dd, *J* = 9.0, 7.1 Hz, 1H), 4.41 (qd, *J* = 5.9, 3.2 Hz, 1H), 4.04 (dd, *J* = 16.1, 2.4 Hz, 1H), 3.96 (dd, *J* = 16.1, 2.4 Hz, 1H), 3.89 (dd, *J* = 12.6, 3.2 Hz, 1H), 3.30 (dd, *J* = 12.6, 5.9 Hz, 1H), 2.39 (t, *J* = 2.4 Hz, 1H), 2.09 (ddd, *J* = 13.4, 7.1, 6.2 Hz, 1H), 1.42 (dddd, *J* = 13.5, 9.1, 5.4, 0.8 Hz, 1H). **^{13}C NMR** (125.0, $CDCl_3$): δ = 160.3, 143.2, 139.9, 128.6 (2C), 128.4 (2C), 128.3, 127.8, 126.0 (2C), 125.7 (2C), 86.2, 79.0, 78.0, 74.9, 67.4, 56.3, 52.0, 35.5. **HRMS** (ESI+): calcd. for $C_{21}H_{19}NNaO_3$ $[M+Na]^+$: 356.1257, found: 356.1251.

A solution of the oxazolidinone **7** (503 mg, 1.51 mmol) in EtOH (11 mL) was treated with a solution of KOH (423 mg, 7.54 mmol) in water (0.8 M). The mixture was heated at reflux overnight turning from a slurry to a clear yellowish solution. The next morning, TLC analysis (Cy/EA 50:50) shows that the starting material has disappeared, so the reaction mixture is concentrated in vacuo. The resulting slurry is diluted with water, extracted with EtOAc (3 × 25 mL), dried over Na_2SO_4 and evaporated. Purification by flash column chromatography gave 456 mg (1.51 mmol) of the amino alcohol **8** (98%).

Diphenyl((2*S*,4*S*)-4-(prop-2-yn-1-yloxy)pyrrolidin-2-yl)methanol (8). Colourless oil. $[\alpha]_D^{25}$ = −44.5 (*c* 1.00, DCM). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.62-7.56 (m, 2H), 7.53-7.47 (m, 2H), 7.32-7.25 (m, 4H), 7.20-7.14 (m, 2H), 4.32 (dd, *J* = 8.2, 7.1 Hz, 1H), 4.23 (dddd, *J* = 6.1, 5.1, 3.7, 2.3 Hz, 1H), 4.15 (dd, *J* = 15.9, 2.4 Hz, 1H), 4.08 (dd, *J* = 15.9, 2.4 Hz, 1H), 3.16 (ddd, *J* = 10.9, 2.3, 1.4 Hz, 1H), 3.04 (dd, *J* = 10.9, 5.1 Hz, 1H), 2.38 (t, *J* = 2.4 Hz, 1H), 1.90 (ddd, *J* = 14.4, 8.2, 6.3 Hz, 1H), 1.80 (dddd, *J* = 14.1, 7.1, 3.7, 1.4 Hz, 1H). **^{13}C NMR** (100.4 MHz, $CDCl_3$): δ = 147.2, 145.4, 128.2 (2C), 128.0 (2C), 126.5, 126.4, 125.9 (2C), 125.5 (2C), 79.7, 77.6, 76.9, 74.2, 63.8, 55.8, 51.9, 32.6. **HRMS** (ESI+): calcd for $C_{20}H_{22}NO_2$ $[M+H]^+$: 308.1645, found: 308.1641.

A solution of the amino alcohol **8** (250 mg, 0.813 mmol) in CH_2Cl_2 (8133 µl) was cooled to 0 °C. Then, imidazole (166 mg, 2.440 mmol) and chlorotrimethylsilane (258 µl, 2.033 mmol) were sequentially added. The solution was then allowed to reach 0 °C and stirred at this temperature for 3 h. Then, it was quenched with water and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography on silica gel with 2.5% Et_3N (Cy/EtOAc 50:50) afforded 282 mg of the silylated product **9** (91% yield, 0.813 mmol).

(2*S*,4*S*)-2-(Diphenyl((trimethylsilyl)oxy)methyl)-4-(prop-2-yn-1-yloxy)pyrrolidine (9). Colourless oil. R_f: 0.42 (Cy/EtOAc 80:20). $[\alpha]_D^{25}$ = −50.0 (*c* 1.00, DCM). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.51-7.47 (m, 2H), 7.35-7.31 (m, 2H), 7.29-7.18 (m, 6H), 4.14 (dtd, *J* = 6.7, 5.2, 3.0 Hz, 1H), 3.98 (dd, *J* = 15.8, 2.4 Hz, 1H), 3.92 (dd, *J* = 15.8, 2.4 Hz, 1H), 3.89 (dd, *J* = 9.3, 6.9 Hz, 1H), 3.01 (ddd, *J* = 12.0, 3.1, 1.0 Hz, 1H), 2.94 (dd, *J* = 12.0, 5.6 Hz, 1H), 2.34 (t, *J* = 2.4 Hz, 1H), 1.82 (br s, 1H), 1.74 (dt, *J* = 13.5, 6.9 Hz, 1H), 1.58 (dddd, *J* = 13.5, 9.4, 4.9, 1.0 Hz, 1H), −0.08 (s, 9H). **^{13}C NMR** (100.4 MHz, $CDCl_3$): δ = 146.8, 145.2, 128.7 (2C), 127.7 (2C), 127.6 (2C), 127.2 (2C), 127.1, 126.8, 82.4, 80.0, 78.6, 73.8, 65.8, 55.8, 53.2, 34.6, 2.1 (3C). **HRMS** (ESI+): calcd. for $C_{23}H_{30}NO_2Si$ $[M+H]^+$: 380.2040, found: 380.2050.

Azidomethylpolystyrene (*f* = 0.60, 5.90 g, 3.52 mmol) was suspended in DMF (53 ml) and THF (53 ml). Then, DIPEA (6.1 ml, 35.2 mmol) and copper(I) iodide (34 mg, 0.176 mmol) were added, followed by a solution of the alkyne **9** (1.61 g, 4.23 mmol) in the same solvent mixture (via cannula). The resulting mixture was shaken overnight at 40 ºC. The next morning, after checking a small aliquot by IR to confirm full conversion, the resin **1b** was filtered and washed with water, water/MeOH, MeOH, MeOH/CH_2Cl_2 and CH_2Cl_2. Then, it was dried overnight in the vacuum oven at 40 °C.

f_{max} = 0.49; *f* = 0.49 (based on N Elemental Analysis). Complete functionalization.

A solution of the diphenylprolinol derivative **8** (350 mg, 1.139 mmol) in DCE (5.5 mL) under Ar was cooled to 0 °C and treated with 2,6-lutidine (1.05 mL, 9.11 mmol) and TBSOTf (1.05 mL, 4.55 mmol). Then, it was heated at reflux overnight under vigorous stirring. The next morning, the reaction mixture was quenched with sat. aq. NH_4Cl (25 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography on silica gel with 2.5% Et_3N (Cy/EtOAc 90:10) gave silyl ether **10** in 63% yield (302 mg, 1.14 mmol).

(2*S*,4*S*)-2-(((*tert*-Butyldimethylsilyl)oxy)diphenylmethyl)-4-(prop-2-yn-1-yloxy)pyrrolidine (10). yellow oil. R_f: 0.28 (Cy/EtOAc 80:20). $[\alpha]_D^{25}$ = −33.3 (*c* 1.00, DCM). **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.61-7.55 (m, 2H), 7.38-7.32 (m, 2H), 7.32-7.22 (m, 6H), 4.13 (dtd, *J* = 6.8, 5.0, 3.2 Hz, 1H), 3.95 (dd, *J* = 15.8, 2.4 Hz, 1H), 3.89 (dd, *J* = 15.8, 2.4 Hz, 1H), 3.88 (dd, *J* = 9.5, 7.0 Hz, 1H), 2.99-2.89 (m, 2H), 2.34 (t, *J* = 2.4 Hz, 1H), 1.92 (br s, 1H), 1.77 (dt, *J* = 13.6, 6.9 Hz, 1H), 1.56 (ddd, *J* = 13.6, 9.7, 4.7 Hz, 1H), 0.99 (s, 9H), −0.12 (s, 3H), −0.51 (s, 3H). **^{13}C NMR** (100.4 MHz, $CDCl_3$): δ = 146.5, 144.8, 129.5, 127.7 (2C), 127.6 (2C), 127.4 (2C), 127.3 (2C), 126.9, 82.2, 80.0, 78.5, 73.7, 66.1, 55.7, 53.2, 35.0, 26.3 (3C), 19.1, −2.5, −3.6. **HRMS** (ESI+): calcd for $C_{26}H_{36}O_2$ $[M+H]^+$: 422.2510, found: 422.2513.

Azidomethylpolystyrene (*f* = 0.509, 6 g, 3.05 mmol) was suspended in DMF (46 ml) and THF (46 ml). Then, DIPEA (5.3 ml, 30.5 mmol) and copper(I) iodide (29 mg, 0.153 mmol) were added, followed by a solution of the alkyne (1.545 g, 3.66 mmol) in the same solvent mixture (via cannula). The resulting mixture was shaken overnight at 40 ºC. The next morning, after checking a small aliquot by IR to confirm full conversion, the resin **1c** was filtered and washed with water, water/MeOH, MeOH, MeOH/CH_2Cl_2 and CH_2Cl_2. Then, it was dried overnight in the vacuum oven at 40 °C.

f_{max} = 0.42; *f* = 0.41 (based on N Elemental Analysis). Complete functionalization.

General Procedures for the Batch Experiments

Conditions A

To a 2 mL glass vial were sequentially added PS-catalyst **1c** (*f* = 0.41 mmol/g, 0.01mmol, 23 mg, 20 mol % loading), 0.25 mL $CHCl_3$ and **11i** (1.5 mg, 20 mol %), followed by **2** (1 eq., 0.05 mmol) and **3** (1.2 eq., 0.06 mmol) at room temperature. The reaction mixture was shaken until TLC analysis showed consumption of the enal (for reaction times, see Scheme 4). Then, it was filtered and the resin beads were washed with DCM (5 x 0.25 mL). The solvent was concentrated under reduced pressure and the product was isolated after purification by column chromatography on silica gel with cyclohexane/ethyl acetate (EtOAc/*c*-Hex = 1:5) to yield **4**.

Conditions B

To a 5 mL glass vial were sequentially added PS-catalyst **1c** (*f* = 0.41 mmol/g, 0.1 mmol, 232 mg, 20 mol % loading), 2.5 mL CH_2Cl_2 and **11d** (12 mg, 0.1mmol, 20 mol %), followed by **2** (1 eq., 0.5 mmol) and **3** (1.2 eq., 0.6 mmol) at room temperature. The reaction mixture was shaken until TLC analysis showed consumption of the enal (for reaction times, see Scheme 4). Then, it was filtered and the resin beads were washed with DCM (8 x 1.5 mL). The solvent was concentrated under reduced pressure and the product was isolated after purification by column chromatography on silica gel with cyclohexane/ethyl acetate (EtOAc/*c*-Hex = 1:5) to yield **4**.

General Procedure for the Flow Experiments

Using the set-up depicted in Scheme 5, the packed bed reactor (Omnifit glass column, 10 mm Ø) was filled with 1.0 g of catalyst **1c**, which was swollen by pumping CH_2Cl_2 at 0.1 mL min^{-1} for one hour. The reagents were then introduced in the system in two separate streams (50 µL min^{-1} each unless otherwise stated) using a dual syringe pump: (a) containing **2** (0.4 M, 1.0 eq) in 21.5 mL of CH_2Cl_2 and (b) containing a mixture of **3** (0.48 M, 1.2 eq.) and PhCOOH in 21.5 mL of CH_2Cl_2. When the solutions of reagents were consumed, the packed bed reactor was rinsed with CH_2Cl_2 at 0.1 mL min^{-1} for 2 h. The collected outstream was concentrated under reduced pressure and purified by column chromatography on silica gel with cyclohexane/ethyl acetate (EtOAc/*c*-Hex 1:5) to yield the corresponding product **4**.

Preparation of β-Amino Acid Hydrochloride 13

To a 25 mL round-bottom flask were sequentially added **4aa** (1.50 g, 5 mmol), *tert*-butanol (8 mL), H_2O (4 mL), 2-methylbut-2-ene (2 mL), KH_2PO_4 (1088 mg, 8 mmol), $NaClO_2$ (720 mg, 8 mmol). The reaction mixture was stirred at room temperature for 16 h and then it was washed with saturated Na_2SO_3 and concentrated under reduced pressure. The residue obtained was dissolved in MeOH (200 mL), filtered to remove insoluble material and circulated through the H-Cube at 0.5 mL min^{-1} flow rate (90 atm, 50 °C). The outstream collected was concentrated in vacuo and the residue was washed with 2 M HCl in diethyl ether (10 mL), then with diethyl ether (5 x 10 mL), to give hydrochloride **13** in 67% yield (673 mg, 3.35 mmol).

Compound Characterization Data

Benzyl (3*S*,5*S*)-5-hydroxy-3-phenylisoxazolidine-2-carboxylate (4aa).[12] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.17 (m, 10H), 5.91 (d, *J* = 4.4 Hz, 1H), 5.38 (t, *J* = 8.2 Hz, 1H), 5.17 (s, 2H), 2.79 (dd, *J* = 12.6, 8.4 Hz, 1H), 2.30 (ddd, *J* = 12.6, 8.2, 4.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 141.4, 135.6, 128.6 (x2), 128.4 (x2), 128.1, 127.7 (x2), 127.4, 126.0 (x2), 98.8, 68.1, 61.3, 45.3. IR (neat): 3362, 3063, 3032, 2860,1707, 1496, 1453, 1390, 1301, 1238, 1027, 902, 754, 696 cm^{-1}. $[\alpha]_D^{25}$ = –29.5 (*c* = 1.0, $CHCl_3$). HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 210 nm): major isomer: t_R = 13.2 min; minor isomer: t_R = 15.3 min.

***tert*-Butyl (3*S*,5*S*)-5-hydroxy-3-phenylisoxazolidine-2-carboxylate (4ab).**[12] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 4.4 Hz, 4H), 7.26 (dd, *J* = 8.2, 4.5 Hz, 1H), 5.92 (d, *J* = 4.0 Hz, 1H), 5.29 (dd, *J* = 8.9, 7.7 Hz, 1H), 2.76 (dd, *J* = 12.5, 8.3 Hz, 1H), 2.33-2.21 (m, 1H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 142.1, 128.5 (x2), 127.2, 126.1 (x2), 98.6, 82.5, 61.4, 45.3, 28.1 (x3). IR (neat): 3347, 2977, 2933, 1703, 1456, 1367, 1346, 1316, 1247, 1162, 1070, 911, 848, 758, 697 cm^{-1}. $[\alpha]_D^{25}$ = –15.2 (*c* = 1.0, $CHCl_3$). HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 210 nm): major isomer: t_R = 6.3 min; minor isomer: t_R = 7.5 min.

Benzyl (3*S*,5*S*)-3-(4-chlorophenyl)-5-hydroxyisoxazolidine-2-carboxylate (4ba). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.21 (m, 9H), 5.94-5.83 (m, 1H), 5.38 (t, *J* = 8.2 Hz, 1H), 5.21 (s, 2H), 2.80 (dd, *J* = 12.6, 8.4 Hz, 1H), 2.33-2.21 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 139.9, 135.5, 133.2, 128.8 (x3), 128.4 (x2), 128.2, 127.8, 127.4 (x2), 98.7, 68.2, 60.8, 45.2. IR (neat): 3356, 3033, 2961, 1707, 1492, 1391, 1296, 1237, 1087, 1014, 903, 825, 736, 696 cm^{-1}. HRMS (ESI): m/z: $[M+Na]^+$ ($C_{17}H_{16}ClNNaO_4$), calcd.: 356.0660; found: 356.0660. $[\alpha]_D^{25}$ = –33.2 (c = 1.0, $CHCl_3$). HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 210 nm): major isomer: t_R = 14.911 min; minor isomer: t_R = 17.611 min.

***tert*-Butyl (3*S*,5*S*)-3-(4-chlorophenyl)-5-hydroxyisoxazolidine-2-carboxylate (4bb).**[12] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.22 (m, 4H), 5.91 (d, *J* = 4.4 Hz, 1H), 5.27 (t, *J* = 8.3 Hz, 1H), 2.76 (dd, *J* = 12.4, 8.3 Hz, 1H), 2.22 (ddd, *J* = 12.6, 8.5, 4.4 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7, 140.6, 133.1, 128.7 (x2), 127.5 (x2), 98.6, 82.8, 60.9, 45.3, 28.1 (x3). IR (neat): 3378, 2979, 2931, 2854, 1702, 1491, 1351, 1325, 1249, 1163, 1089, 1014, 956, 907, 847, 821, 769 cm^{-1}. $[\alpha]_D^{25}$ = –14.6 (*c* = 1.0, $CHCl_3$). HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98:2, flow rate 1.0 mL/min, λ = 210 nm): minor isomer: t_R = 22.3 min; major isomer: t_R = 24.7 min.

Benzyl (3*S*,5*S*)-3-(4-fluorophenyl)-5-hydroxyisoxazolidine-2-carboxylate (4ca). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.15 (m, 7H), 7.00 (t, *J* = 8.7 Hz, 2H), 5.84 (d, *J* = 4.2 Hz, 1H), 5.34 (t, *J* = 8.2 Hz, 1H), 5.17 (s, 2H), 2.76 (dd, *J* = 12.6, 8.4 Hz, 1H), 2.24 (ddd, *J* = 12.6, 8.1, 4.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1 (d, *J* = 245.8 Hz), 159.2, 137.1 (d, *J* = 3.1 Hz), 135.5, 128.4 (x2), 128.2, 127.8 (x2), 127.7 (x2, d, *J* = 8.0 Hz), 115.5 (x2, d, *J* = 21.6 Hz), 98.7, 68.2, 60.8, 45.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.1. IR (neat): 3367 (s), 3035, 2962, 1709, 1605, 1509, 1454, 1390, 1297, 1224, 1070, 905, 835, 736, 697 cm^{-1}. HRMS (ESI): m/z: $[M+Na]^+$ ($C_{17}H_{16}FNNaO_4$), calcd.: 340.0956; found: 340.0961. $[\alpha]_D^{25}$ = –33.2 (c = 1.0, $CHCl_3$). HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 210 nm): major isomer: t_R = 13.3 min; minor isomer: t_R = 15.8 min.

***tert*-Butyl (3*S*,5*S*)-3-(4-fluorophenyl)-5-hydroxyisoxazolidine-2-carboxylate (4cb).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.26 (m, 2H), 7.10-6.99 (m, 2H), 5.93-5.82 (m, 1H), 5.29 (t, *J* = 8.3 Hz, 1H), 2.77 (dd, *J* = 12.5, 8.3 Hz, 1H), 2.26 (dddd, *J* = 12.6, 8.3, 4.4, 1.7 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1 (d, *J* = 245.41), 158.6, 137.8 (d, *J* = 3.2), 127.7 (x2, d, *J* = 8.1), 115.4 (x2, d, *J* = 21.5), 98.5, 82.6, 60.8, 45.4, 28.1 (x3). ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.52. IR (neat): 3395, 2979, 2935, 1714, 1604, 1367, 1321, 1248, 1221, 1155, 1069, 910, 833, 766, 551 cm^{-1}. HRMS (ESI): m/z: $[M+Na]^+$ ($C_{14}H_{18}FNO_4Na$), calcd.: 306.1112; found: 306.1112. $[\alpha]_D^{25}$ = –10.7 (c = 1.0, $CHCl_3$). HPLC (Daicel Chiralpak AD-H, hexane/i-PrOH = 90:10, flow rate 1.0 mL/min, λ = 210 nm): major isomer: t_R = 9.3 min; minor isomer: t_R = 11.3 min.

Benzyl (3*S*,5*S*)-5-hydroxy-3-(4-nitrophenyl)isoxazolidine-2-carboxylate (4da).[12] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.37-7.16 (m, 5H), 5.94 (d, *J* = 4.2 Hz, 1H), 5.48 (t, *J* = 8.3 Hz, 1H), 5.18 (s, 2H), 2.87 (dd, *J* = 12.5, 8.5 Hz, 1H), 2.25 (ddd, *J* = 12.5, 8.2, 4.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 148.6, 147.2, 135.1, 128.4 (x2), 128.3, 127.8 (x2), 126.8 (x2), 123.9 (x2), 98.7, 68.5, 60.8, 45.0. IR (neat): 3363, 2958, 2837, 1706, 1612, 1513, 1455, 1392, 1319, 1290, 1243, 1113, 1029, 903, 849, 747, 695 cm^{-1}. HRMS (ESI): m/z: $[M+Na]^+$ ($C_{17}H_{16}N_2NaO_6$), calcd.: 367.0901; found: 367.0903. $[\alpha]_D^{25}$ = –40.5 (*c* = 1.0, $CHCl_3$). HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 210 nm): minor isomer: t_R = 19.7 min; major isomer: t_R = 22.1 min.

***tert*-Butyl (3*S*,5*S*)-5-hydroxy-3-(4-nitrophenyl)isoxazolidine-2-carboxylate (4db).**[12] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 5.94 (d, *J* = 4.3 Hz, 1H), 5.40 (t, *J* = 8.4 Hz, 1H), 2.85 (dd, *J* = 12.4, 8.4 Hz, 1H), 2.23 (ddd, *J* = 12.6, 8.5, 4.4 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 149.4, 147.25, 126.9 (x2), 123.9 (x2), 98.5, 83.3, 61.0, 45.1, 28.0 (x3). IR (neat): 3329, 2960, 2931, 2840, 1702, 1614, 1514, 1455, 1368, 1336, 1299, 1246, 1159, 1088, 1064, 1032, 965, 913, 868, 835, 807 cm^{-1}. $[\alpha]_D^{25}$ = –26.9 (*c* = 1.0, $CHCl_3$). HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 210 nm): minor isomer: t_R = 12.1 min; major isomer: t_R = 14.1 min.

Benzyl (3*S*,5*S*)-5-hydroxy-3-(4-methoxyphenyl)isoxazolidine-2-carboxylate (4ea). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.17 (m, 7H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.90 (d, *J* = 4.2 Hz, 1H), 5.33 (t, *J* = 8.2 Hz, 1H), 5.17 (s, 2H), 3.79 (s, 3H), 2.75 (dd, *J* = 12.6, 8.3 Hz, 1H), 2.29 (ddd, *J* = 12.6, 8.3, 4.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 159.0, 135.7, 133.4, 128.4 (x2), 128.1, 127.7 (x2), 127.3 (x2), 114.0 (x2), 98.7, 68.0, 60.9, 55.3, 45.2. IR (neat): 3475, 3120, 2960, 2850, 1707, 1610, 1513, 1396, 1346, 1324, 1261, 1124, 1012, 962, 833, 758, 694, 518 cm^{-1}. HRMS (ESI): m/z: $[M+Na]^+$ ($C_{18}H_{19}NNaO_5$), calcd.: 352.1155; found: 352.1152. $[\alpha]_D^{25}$ = –51.7 (*c* = 1.0, $CHCl_3$). HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 85:15, flow rate 1.0 mL/min, λ = 210 nm): major isomer: t_R = 16.1 min; minor isomer: t_R = 19.8 min.

***tert*-Butyl (3*S*,5*S*)-5-hydroxy-3-(4-methoxyphenyl)-isoxazolidine-2-carboxylate (4eb).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.93-5.82 (m, 1H), 5.23 (t, *J* = 8.2 Hz, 1H), 3.79 (s, 3H), 2.71 (dd, *J* = 12.5, 8.3 Hz, 1H), 2.26 (dddd, *J* = 12.6, 8.3, 4.5, 2.0 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 158.7, 134.1, 127.4 (x2), 113.9 (x2), 98.6, 82.3, 60.9, 55.3, 45.3, 28.1 (x3). IR (neat): 3329, 2960, 2931, 1702, 1613, 1514, 1455, 1336, 1299, 1246, 1159, 1088, 1064, 1032, 965, 91, 807 cm^{-1}. HRMS (ESI): m/z: $[M+Na]^+$ ($C_{15}H_{21}NNaO_5$), calcd.: 318.1312; found: 318.1311. $[\alpha]_D^{25}$ = –33.8 (*c* = 1.0, $CHCl_3$). HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 210 nm): major isomer: t_R = 9.1 min; minor isomer: t_R = 10.0 min.

Benzyl (3*S*,5*S*)-5-hydroxy-3-(2-nitrophenyl)isoxazolidine-2-carboxylate (4fa). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.79 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.65 (td, *J* = 7.8, 1.2 Hz, 1H), 7.49 – 7.41 (m, 1H), 7.35-7.20 (m, 5H), 6.09 (t, *J* = 7.8 Hz, 1H), 5.91 (d, *J* = 4.3 Hz, 1H), 5.24-5.15 (m, 2H), 3.17 (dd, *J* = 12.9, 8.6 Hz, 1H), 2.28-2.16 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 147.3, 137.7, 135.3, 134.1 (x2), 128.5 (x2), 128.3 (x2), 127.9, 127.8, 124.8, 98.9, 68.4, 58.7, 45.2. IR (neat): 3366, 3067, 3035, 2961, 1710, 1609, 1578, 1523, 1446, 1391, 1339, 1292, 1067, 907, 738, 676 cm^{-1}. HRMS (ESI): m/z: $[M+Na]^+$ ($C_{17}H_{16}N_2NaO_6$), Calcd.: 367.0901. Found: 367.0910. $[\alpha]_D^{25}$ = +67.7 (*c* = 1.0, $CHCl_3$). HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 210 nm): major isomer: t_R = 11.3 min; minor isomer: t_R = 14.7 min.

***tert*-Butyl (3*S*,5*S*)-5-hydroxy-3-(2-nitrophenyl)isoxazolidine-2-carboxylate (4fb).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.60-7.50 (m, 1H), 7.42-7.28 (m, 1H), 5.92-5.76 (m, 2H), 3.01 (dd, *J* = 12.7, 8.4 Hz, 1H), 2.10 (ddd, *J* = 7.9, 4.6, 2.1 Hz, 1H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 147.6, 138.2, 133.9, 128.1(x2), 124.4, 98.8, 83.1, 58.4, 45.3, 28.0 (x3). IR (neat): 3348, 2977, 2927, 2854, 1707, 1345, 1244, 1138, 1066, 958, 913, 848, 788, 744 cm^{-1}. HRMS (ESI): m/z: $[M+Na]^+$ ($C_{14}H_{18}N_2NaO_6$), calcd.: 333.1057; found: 333.1059. $[\alpha]_D^{25}$ = +83.4 (*c* = 1.0, $CHCl_3$). HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 210 nm): minor isomer: t_R = 19.0 min; major isomer: t_R = 20.2 min.

Benzyl (3*S*,5*S*)-5-hydroxy-3-(2-methoxyphenyl)isoxazolidine-2-carboxylate (4ga). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.6 Hz, 1H), 7.32-7.18 (m, 6H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 5.81 (s, 1H), 5.72 (t, *J* = 7.8 Hz, 1H), 5.19 (s, 2H), 3.80 (s, 3H), 2.89 (dd, *J* = 12.7, 8.4 Hz, 1H), 2.13 (ddd, *J* = 12.4, 7.2, 4.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 156.1, 135.9, 129.9, 128.3 (x2), 128.2, 128.1, 127.7 (x2), 125.8, 120.6, 110.3, 98.8, 67.9, 56.8, 55.3, 44.2. IR (neat): 3360, 2960, 2838, 1707, 1601, 1491, 1460, 1389, 1339, 1285, 1239, 1068, 1025, 908, 751, 696 cm^{-1}. HRMS (ESI): m/z: $[M+Na]^+$ ($C_{18}H_{19}NNaO_5$), calcd.: 352.1155; found: 352.1154. $[\alpha]_D^{25}$ = –42.0 (*c* = 1.0, $CHCl_3$). HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 210 nm): major isomer: t_R = 7.8 min; minor isomer: t_R = 13.2 min.

***tert*-Butyl (3*S*,5*S*)-5-hydroxy-3-(2-methoxyphenyl)isoxazolidine-2-carboxylate (4gb).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.29-7.16 (m, 1H), 6.94 (td, *J* = 7.5, 0.9 Hz, 1H), 6.86 (dd, *J* = 8.2, 0.7 Hz, 1H), 5.84 (dd, *J* = 4.2, 2.8 Hz, 1H), 5.64 (t, *J* = 7.9 Hz, 1H), 3.84 (s, 3H), 2.85 (dd, *J* = 12.7, 8.4 Hz, 1H), 2.14-2.03 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 156.1, 130.6, 128.0, 126.0, 120.6, 110.2, 98.7, 82.1, 56.7, 55.3, 44.2, 28.1 (x3). IR (neat): 3356, 2976, 2930, 2850, 1703, 1602, 1491, 1461, 1348, 1315, 1239, 1160, 1066, 1027, 916, 848, 806, 751 cm^{-1}. HRMS (ESI): m/z: $[M+Na]^+$ ($C_{15}H_{21}NNaO_5$), calcd.: 318.1312; found: 318.1312. $[\alpha]_D^{25}$ = –22.0 (*c* = 1.0, $CHCl_3$). HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 210 nm): major isomer: t_R = 7.9 min; minor isomer: t_R = 11.1 min.

(*S*)-3-Amino-3-phenylpropanoic acid hydrochloride (13).[18] ^{1}H NMR (400 MHz, Deuterium Oxide) δ 7.38 (s, 5H), 4.69 (m, 5 H), 3.10 (dd, *J* = 17.2, 7.7 Hz, 1H), 2.98 (dd, *J* = 17.2, 6.6 Hz, 1H). ^{13}C NMR (101 MHz, D_2O) δ 173.4, 135.1, 129.7, 129.4 (x2), 127.1 (x2), 51.5, 37.7. $[\alpha]_D^{25}$ = +2.8 (*c* = 0.28, H_2O).

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