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Note

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Chiral Brønsted Acid-Catalyzed Stereoselective Mannich-type Reaction of Azlactones with Aldimines‡

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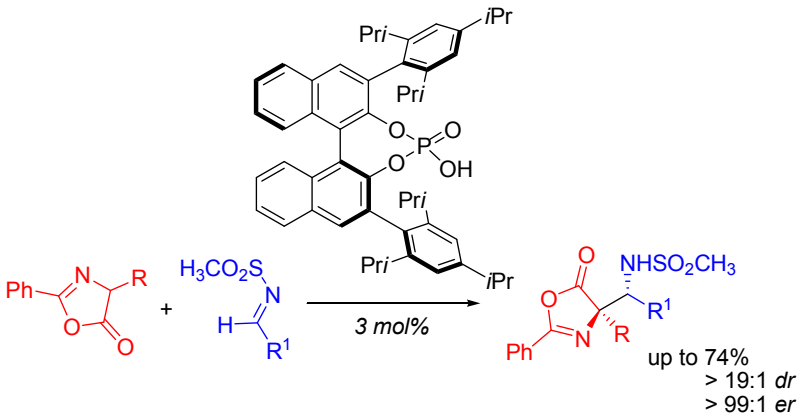
‡Dedicated to Professor Fernando Coelho in recognition of his outstanding contributions to Brazilian chemistry.

TOC graphic



Abstract

A highly diastereo- and enantioselective Mannich-type reaction of azlactones with aldimines catalyzed by a chiral phosphoric acid is described. Only 3 mol% of the catalyst was required to prepare the Mannich adducts in good yields with high stereochemical control (up to > 19:1 dr, > 99:1 er). Moreover, the final

product contains two consecutive stereogenic centers, one of which is quaternary.

Keywords: azlactones; aldimines; Mannich-type reaction; asymmetric organocatalysis; chiral phosphoric acid.

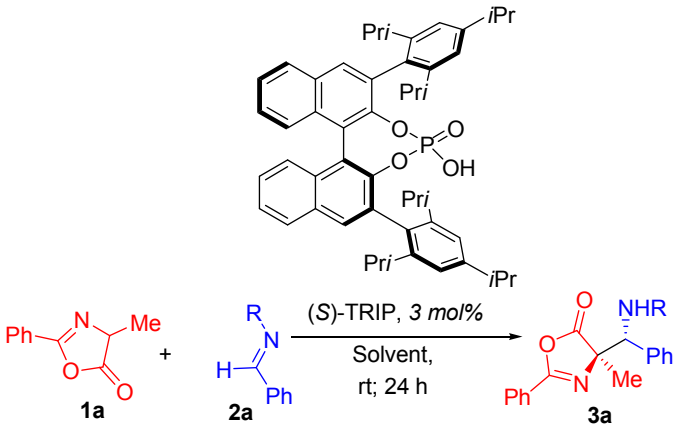
Chiral α,β-diaminoacid derivatives are very important building blocks in organic chemistry as they possess remarkable pharmacological properties. Viso and co-workers have showed the importance of these motifs in treatment of neurodegenerative diseases and various cancers. [1] A variety of methods for the synthesis chiral α,β-diaminoacid derivatives have been reported. [1] One attractive route utilizes azlactones; as these rings are essentially protected aminoacids that are readily unmasked under acidic conditions. Additionally, azlactones can be easily prepared on preparative scale following literature protocols and derivatized through [2] Mannich-type reaction [3] mediated by transition metals or organocatalysts [4], [5].

In particular, chiral gold(I) complexes have been used to catalyze the enantioselective Mannich reaction of azlactones. Reaction of aliphatic mesitylsulfonimines with azlactones in the presence of a spirocyclic bisphosphine gold(I) benzoate complex (xylyl-SDP$(AuOBz)_2$), provided the desired 1,2-*anti*-Mannich adducts in high yields and selectivities. [4] In contrast, organocatalytic approaches tolerate both aromatic and aliphatic imines for synthesis of chiral α,β-diaminoacid derivatives in high yields and selectivities. [5a], [5b]. Interestingly, the major product observed in these reactions were the 1,2-*syn* diastereomers.

Since the pioneering work of Terada [6] and Akiyama [7] which demonstrated the potential of chiral phosphoric acids as organocatalysts, new applications exploiting the H-donor capacity of these catalysts have appeared in the literature. [8] In our research program [9], we envisioned that chiral phosphoric acids could be an alternative, metal-free catalyst for the reaction between azlactones and aldimines. Moreover, we envisioned that this approach may be complementary to existing organocatalytic methods and provide access to the 1,2-*anti*-diaminoacid derivatives from aromatic imines.

The azlactone and imine skeletons are both readily accessed following literature protocols. [4] To our delight, the reaction between azlactone **1a** and aldimine **2a** catalyzed by only 3 mol% of the comercial available (*S*)-3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate, (*S*)-TRIP [10], in toluene gave the desired Mannich adduct **3a** in good yield (70 %; isolated yield) and excellent enantio- and diastereoselectivity (Table 1, entry 3). However, increasing the size of the sulfonamide led to a decrease in yield. Only traces of product was detected when dichloromethane (Table 1, entry 2) was used as solvent. While performing the reaction in THF provided the desired product in moderate yield, the diastereoselectivity of the transformation was low. Significant background of reaction was observed when either acetone or chloroform was used. The catalyst loading could be drop to 2 mol% without any loss of stereoselectivity, albeit at a lower isolated yield (50 %). Having optimized reaction conditions, experiments to evaluate the substrate scope of this transformation were conducted (Table 2).

Table 1. Optimization of reaction conditions for the stereoselective Mannich-type reaction [a].



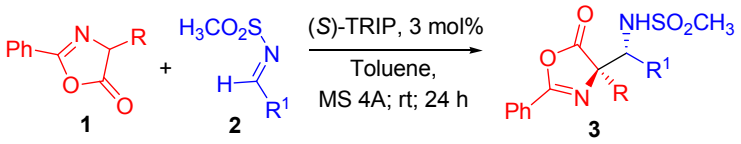
entry	R	solvent	d.r.[b] (*anti/syn*)	e.r.[c]	yield[d]
1	mesyl	THF	1:1	99:1/99:1	40
2	mesyl	CH_2Cl_2	1:1	Nd[e]	traces
3	**mesyl**	**PhMe**	**> 19:1**	**> 99:1**	**70**
4	tosyl	PhMe	5:1	Nd[e]	20
5	mesityl	PhMe	2:1	Nd[e]	15
6[f]	mesyl	PhMe	> 19:1	> 99:1	55
7[g]	mesyl	PhMe	-	-	-

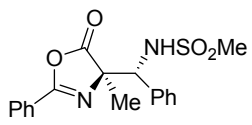
[a] Reactions were carried out using 0.2 mmol of **1**, 0.006 mmol of (*S*)-TRIP (3 mol%), and 0.21 mmol of **2** in PhMe (0.2 M in azlactone). [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by enantiodiscriminating HPLC. [d] Isolated yield. [e] Not determined. [f] Without molecular sieves. [g] No catalyst, 48 h.

Various aromatic imines, containing either electron-withdrawing or electron donating groups, could be used in the reaction. For example, a benzaldehyde derivative containing fluorine at *p*-position works quite well, providing the Mannich adduct **3g** in good yield with both diastereo- and enantioselectivity (> 19:1 dr and 98:2 er). Phenylalanine derivative azlactone could also be used under optimized reaction conditions, yielding product **3i** in >98% ee. The relative and absolute stereochemistry (1,2-*anti*) of the Mannich adduct **3b** was determined by X-ray crystallographic structure (Figure 1). The other products

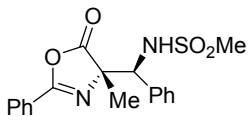
were assigned on the analogy. To the best of our knowledge this work comprises the first highly enantio- and diastereoselective Mannich-type reaction between azlactone and aldimines catalyzed by a chiral phosphoric acid. A variety of aliphatic imines were evaluated; however, all led to complex product mixtures which could not be deciphered [12].

Table 2. Diastereo- and Enantioselective Mannich-type addition of azlactones to aldimines [a].

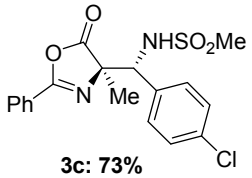




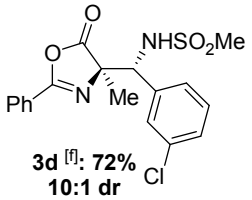
3a: 70%
> 19:1 dr [b]
> 99:1 er [c]



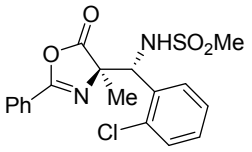
3b [d,e]: 72%
> 19:1 dr
> 99:1 er



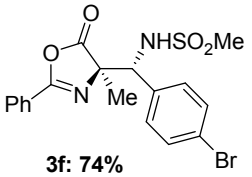
3c: 73%
> 19:1 dr
99:1 er



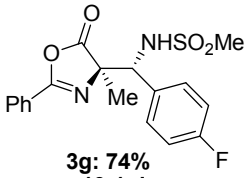
3d [f]: 72%
10:1 dr
96:4 er



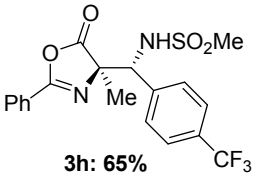
3e: 51%
> 19:1 dr
91:9 er



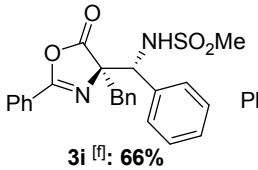
3f: 74%
> 19:1 dr
98:2 er



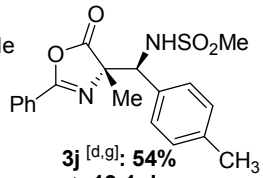
3g: 74%
> 19:1 dr
98:2 er



3h: 65%
> 19:1 dr
88:12 er



3i [f]: 66%
11:1 dr
>99:1 er



3j [d,g]: 54%
> 19:1 dr
> 99:1 er

[a] Reactions were carried out using 0.2 mmol of **1**, 0.006 mmol of (*S*)-TRIP (3 mol%), and 0.21 mmol of **2** in PhMe (0.2 M in azlactone). [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Determined by chiral HPLC. [d] (*R*)-TRIP used as catalyst. [e] Relative and absolute stereochemistry of **3b** was determined by X-ray crystallography and the other products were assigned in analogy. [f] Only the major diastereomer was isolated. [g] 5 mol% of catalyst.

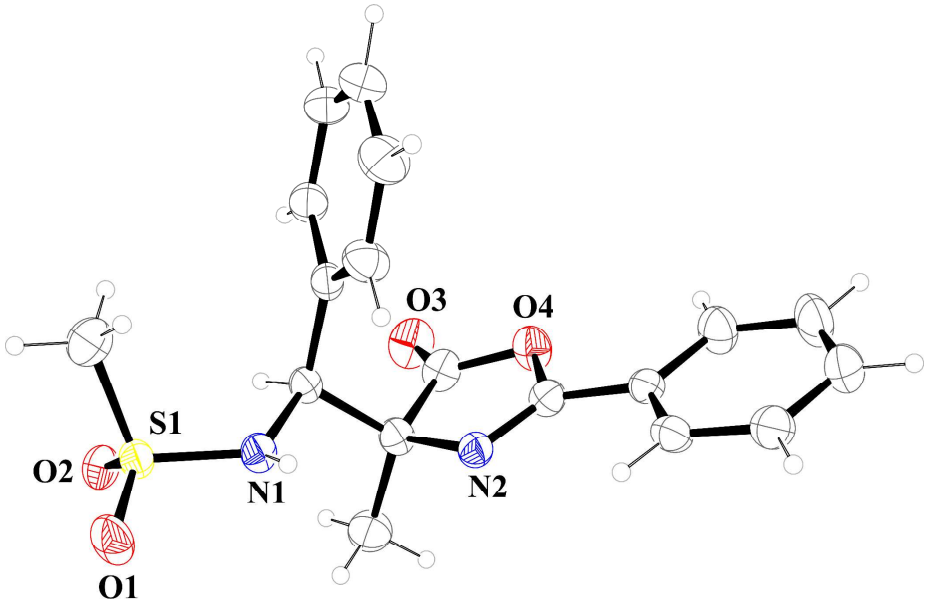


Figure 1. X-ray crystallographic structure of **3b**.

Yamanaka and Akiyama have proposed that the Mannich-type reaction of a special hydroxyaldimine catalyzed by a chiral phosphoric acid proceeds through coordination of both oxygen atoms of the chiral phosphoric acid to the aldimine. [13] Terada and co-workers have showed a chiral phosphoric acid catalyzed enantioselective addition of azlactones to 3-vinylindoles; in this case, the chiral phosphoric acid activates both the enol intermediate of azlactone and the vinyl double bond system. [14] Thus, a plausible transition state for the reaction of imine and azlactone in the presence of TRIP is proposed. [15] We hypothesize that the phosphoric acid could stabilize the enol intermediate of azlactone and also activated the imine through protonation of the nitrogen lone pair, providing the Mannich adducts in high selectivities (Figure 2).

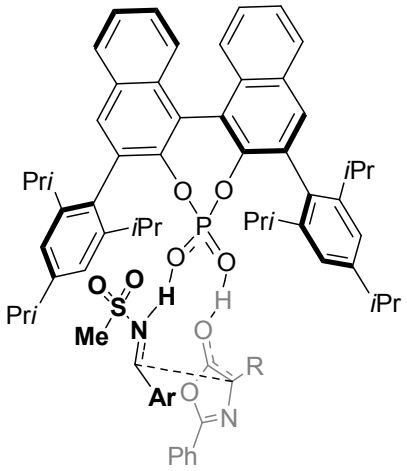
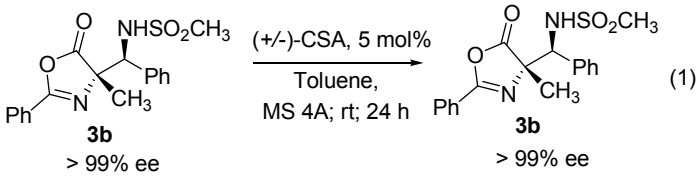


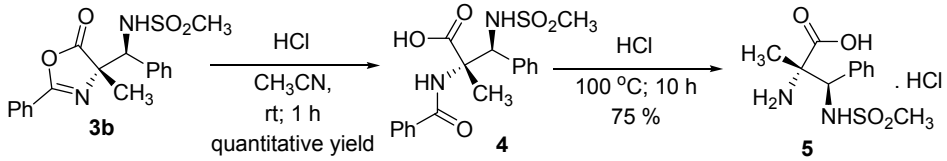
Figure 2. Plausible activation mode for the stereoselective reaction between azlactones and aldimines catalyzed by a phosphoric acid.

To probe the reversibility of the reaction the enantioenriched Mannich addition product **3b** was resubjected to catalytic reaction condition in the presence of a racemic acid, (+/-)-CSA (camphorsulfonic acid), following the general procedure for Mannich reaction. After 24 h at room temperature, the product was re-isolated in > 99% ee, suggesting that the σ C-C bond step formation is irreversible (eq 1).



(1)

The ring opening, followed by amide deprotection of the enantioenriched Mannich addition product **3b** under the presence of a mineral acid provided the amino acid **5** in two steps and with 75 % overall yield (Scheme 1).



Scheme 1. Preparation of amino acid **5**.

Conclusion

In summary, a Brønsted acid catalyzed highly diastereo- and enatioselective Mannich-type addition of azlactones with aldimines is presented. Only 3 mol% of the commercial available phosphoric acid (TRIP) was used to provide protected 1,2-*anti* diamino acid derivatives in moderate to good yields and with near perfect control of both diastereo- and enantioselectivity (up to > 19:1 dr and > 99:1 er). Besides the new σ C-C bond formation, two stereogenic centers are created, one of them a quaternary.

Experimental Section

Representative experimental for the enantio- and diastereoselective Mannich-type addition of azlactones to aldimines: In a flammed screw cap vial and under nitrogen atmosphere and with molecular sieves (50 mg), 0.2 mmol of azlactone was added. After, toluene was canulated at the concentration of 0.2 mol.L^{-1} in azlactone. To this solution, 0.006 mmol (3 mol%) of phosphoric acid was added followed by 0.21 mmol of imine. The reaction was kept at room temperature and under nitrogen atmosphere for 24 h. The reaction was then diluted in CH_2Cl_2 (10 mL) and washed with saturated solution of sodium bicarbonate (5 mL). The organic phase was dried over anidrous Na_2SO_4 and concentrated under reduced pression. An aliquot was taken to the NMR and the diastereoisomeric ratio was measured by ^{1}H NMR analysis. After, the crude reaction mixture was

purified through silica gel chromatography by using ethyl acetate: hexanes as solvents (up to 2:1 ethyl acetate/hexanes). The major diastereomers were submitted to chiral HPLC analysis and then fully characterized by the conventional elemental analysis.

Characterization data for the Mannich adducts **3a**-**j**

(**3a**): Diastereoisomeric ratio (dr) from ^{1}H NMR analysis of crude reaction mixture (> 19:1) (*anti/syn*). The product was purified by column chromatography on silica gel (Hexanes/AcOEt 3:1 to 2:1) to afford product **3a** (50.1 mg, 70%); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.86 (d, 2H, *J* = 7.1 Hz), 7.58-7.55 (m, 1H), 7.49-7.43 (m, 2H), 7.22-7.19 (m, 5H), 5.71 (d, 1H, *J* = 10 Hz), 4.87 (d, 1H, *J* = 10 Hz), 2.56 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (63 MHz) δ: 177.5, 161.5, 135.5, 133.1, 129.1, 128.8, 128.7, 128.0, 127.6, 125.1, 73.7, 61.9, 41.9, 22.1; HRMS: calcd for $[C_{18}H_{18}N_2O_4S]$+ ([M+H]+): *m/z* 359.1066, found 359.1079; HPLC Chiralpak IA column (Hex/iPrOH 95/05, 0.7 mL/min) tR 26.6 min (major), 28.7 min (minor): > 99:1 er. See reference 4.

(**3b**): Diastereoisomeric ratio (dr) from ^{1}H NMR analysis of crude reaction mixture (> 19:1) (*anti/syn*). The product was purified by column chromatography on silica gel (Hexanes/AcOEt 3:1 to 2:1) to afford product **3b** (51.6 mg, 72%); ^{1}H NMR (250 MHz, $CDCl_3$) and ^{13}C NMR (63 MHz): identical **3a**; HPLC Chiralpak IA column (Hex/iPrOH 95/05, 0.7 mL/min) tR 26.8 min (minor), 29.3 min (major): > 99:1 er. See reference 4.

(**3c**): Diastereoisomeric ratio (dr) from ^{1}H NMR analysis of crude reaction mixture (> 19:1) (*anti/syn*). The product was purified by column chromatography on silica gel (Hexanes/AcOEt 3:1 to 2:1) to afford product **3c** (57.2 mg, 73%); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.88-7.85 (m, 2H), 7.60-7.45 (m, 3H), 7.26-7.14 (m, 4H), 5.75 (d, 1H *J* = 9.8 Hz), 4.86 (d, 1H, *J* = 9.8 Hz), 2.61 (s, 3H), 1.63 (s, 3H). ^{13}C NMR (75 MHz) δ: 177.5, 162.0, 135.4, 134.6, 133.6, 129.4, 129.3, 128.3, 125.1, 78.8, 61.5, 42.4, 22.4.; HRMS: calcd for $[C_{18}H_{17}N_2O_4SCl]$+ ([M+H]+): *m/z* 393.0676, found 393.0707; HPLC Chiralpak IA column (Hex/iPrOH 90/10, 0.5 mL/min) tR 26.0 min (major), 30.4 min (minor): 99:1 er.

(**3d**): Diastereoisomeric ratio (dr) from ^{1}H NMR analysis of crude reaction mixture (10:1) (*anti/syn*). The product was purified by column chromatography on silica gel (Hexanes/AcOEt 3:1 to 2:1) to afford product **3d** (56.5 mg, 72%); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.85-7.57 (m, 2H), 7.56-7.26 (m, 3H), 7.22-7.12 (m, 5H), 5.70 (d, 1H, *J* = 9.8 Hz), 4,85 (d, 1H, *J* = 9.9 Hz), 2.64 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (75 MHz) δ: 177.4, 162.0, 138.0, 135.0, 133.6, 130.3, 129.6, 129.2, 128.2, 128.1, 126.0, 125.1, 73.7, 61.6, 42.4, 22.3; HRMS: calcd for $[C_{18}H_{17}N_2O_4SCl]$+ ([M+H]+): *m/z* 393.0676, found 393.0677; HPLC Chiralpak IA column (Hex/iPrOH 90/10, 0.5 mL/min) tR 19.6 min (major), 22.4 min (minor): 96:4 er.

(**3e**): Diastereoisomeric ratio (dr) from ^{1}H NMR analysis of crude reaction mixture (> 19:1) (*anti/syn*). The product was purified by column chromatography on silica gel (Hexanes/AcOEt 3:1 to 2:1) to afford product **3e** (39.9 mg, 51%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.05 (d, 1H, *J* = 7.8 Hz), 7.67-7.62 (m, 2H), 7.56-7.32 (m, 5H), 5.60 (d, 1H, *J* = 11.1 Hz), 5.27 (d, 1H, *J* = 11.1 Hz), 2.66 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz) δ: 179.4, 162.4, 135.1, 134.5, 133.7, 130.3, 130.1, 129.2, 129.0, 128.5, 128.0, 125.5, 73.7, 57.3, 41.5, 21.0; HRMS: calcd for $[C_{18}H_{17}N_2O_4SCl]$+ ([M+H]+): *m/z* 393.0676, found 393.0681; HPLC Chiralpak IA column (Hex/iPrOH 96/04, 0.45 mL/min) tR 59.4 min (major), 67.9 min (minor): 91:9 er.

(**3f**): Diastereoisomeric ratio (dr) from ^{1}H NMR analysis of crude reaction mixture (> 19:1) (*anti/syn*). The product was purified by column chromatography on silica gel (Hexanes/AcOEt 3:1 to 2:1) to afford product **3f** (64.5 mg, 74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.90-7.87 (m, 2H) , 7.66-7.60 (m, 1H), 7.53-7.48 (m, 2H), 7.41-7.37 (m, 2H), 7.12-7.10 (m, 2H), 5.67 (d, 1H, *J* = 9.9 Hz), 4.86 (d, 1H, *J* = 9.9 Hz), 2.63 (s, 3H), 1.82 (s, 3H); ^{13}C NMR (75 MHz) δ: 177.5, 162.0, 135.1, 133.6, 132.2, 129.5, 129.2, 128.3, 125.1, 123.7, 73.7, 61.5, 42.5, 22.5; HRMS: calcd for $[C_{18}H_{17}N_2O_4SBr]$+ ([M+H]+): *m/z* 437.0171, found 437.0181; HPLC Chiralpak IB column (Hex/iPrOH 97/03, 0.8 mL/min) tR 44.9 min (major), 54.3 min (minor): 98:2 er.

(**3g**): Diastereoisomeric ratio (dr) from ^{1}H NMR analysis of crude reaction mixture (> 19:1) (*anti/syn*). The product was purified by column chromatography on silica gel (Hexanes/AcOEt 3:1 to 2:1) to afford product **3g** (55.6 mg, 74%); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.90-7.88 (m, 2H), 7.65-7.60 (m, 1H), 7.52-7.47 (m, 2H), 7.28-7.22 (m, 2H), 6.98-6.92 (m, 2H), 5.93 (d, 1H, *J* = 9.9 Hz), 4.90 (d, 1H, *J* = 9.9 Hz), 2.63 (s, 3H), 1.83 (s, 3H); ^{13}C NMR (75 MHz) δ: 177.6, 163.4

(d, *J* = 207 Hz), 162.0, 161.5, 133.6, 131.9, 131.8, 129.8, 129.7, 129.2, 128.3, 125.1, 116.1 (d, *J* = 22 Hz), 74.0, 61.5, 42.3, 22.3; HRMS: calcd for $[C_{18}H_{17}N_2O_4SF]+$ ([M+H]+): *m/z* 377.0971, found 377.0991; HPLC Chiralpak IB column (Hex/iPrOH 97/03, 0.8 mL/min) tR 38.4 min (major), 47.4 min (minor): 98:2 er.

(**3h**): Diastereoisomeric ratio (dr) from ^{1}H NMR analysis of crude reaction mixture (> 19:1) (*anti/syn*). The product was purified by column chromatography on silica gel (Hexanes/AcOEt 3:1 to 2:1) to afford product **3h** (55.4 mg, 65%): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89-7.87 (m, 2H), 7.64-7.61 (m, 1H), 7.54-7.49 (m, 4H), 7.39-7.37 (m, 2H), 5.86 (d, 1H, *J* = 9.8 Hz), 4.98 (d, 1H, *J* = 9.8 Hz), 2.67 (s, 3H), 1.85 (s, 3H). ^{13}C NMR (125 MHz): 177.2, 161.8, 133.5, 131.3 (q, *J* = 32.7 Hz), 129.0, 128.1, 128.0 125.7 (q, *J* = 3.8 Hz), 123.6 (q, *J* = 270.6 Hz), 73.5, 61.4, 42.3, 22.3. HRMS: calcd for $[C_{19}H_{17}N_2O_4SF_3]+$ ([M+H]+): *m/z* 427.0939, found 427.0951; HPLC Chiralpak IB column (Hex/iPrOH 97/03, 0.8 mL/min) tR 41.8 min (major), 52.2 min (minor): 88:12 er.

(**3i**): Diastereoisomeric ratio (dr) from ^{1}H NMR analysis of crude reaction mixture (11:1) (*anti/syn*). The product was purified by column chromatography on silica gel (Hexanes/AcOEt 3:1) to afford product **3i** (57.3 mg, 66 %); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70-7.68 (m, 2H), 7.56-7.53 (m, 1H), 7.44-7.40 (m, 2H), 7.29-7.26 (m, 5H), 7.17-7.12 (m, 5H), 5.82 (d, 1H, *J* = 10.0 Hz), 5.06 (d, 1H, *J* = 10.0 Hz), 3.85 (d, 1H, *J* = 13.2 Hz), 3.43 (d, 1H, *J* = 13.2 Hz), 2.58 (s, 3H). ^{13}C NMR (125 MHz) δ: 176.1, 161.7, 133.5, 133.0, 130.3, 129.2, 128.9, 128.7, 128.2, 127.80, 127.75, 127.3, 124.9, 78.8, 61.7, 42.0, 41.7.; HRMS: calcd for $[C_{24}H_{22}N_2O_4S]+$ ([M+H]+): *m/z* 435.1379, found 435.1385; HPLC Chiralpak IA column (Hex/iPrOH 95/05, 0.5 mL/min) tR 38.8 min (major), 45.8 min (minor): > 99:1 er.

(**3j**): Diastereoisomeric ratio (dr) from ^{1}H NMR analysis of crude reaction mixture (> 19:1) (*anti/syn*). The product was purified by column chromatography on silica gel (Hexanes/AcOEt 3:1) to afford product **3i** (47.5 mg, 54 %); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91-7.87 (m, 2H), 7.64-7.58 (m, 1H), 7.51-7.46 (m, 2H), 7.11-7.02 (m, 4H), 5.74 (d, 1H, *J* = 10.0 Hz), 4.84 (d, 1H, *J* = 10.0 Hz), 2.56 (s, 3H), 2,25 (s, 3H), 1.83 (s, 3H). ^{13}C NMR (75 MHz) δ: 177.8, 161.7, 139.2, 133.3, 132.8, 129.7, 129.1, 128.2, 127.7, 125.4, 74.0, 61.9, 42.2, 22.4, 21.3.; HRMS: calcd for

$[C_{19}H_{20}N_2O_4S]+$ ([M+H]+): *m/z* 373.1222, found 373.1240; HPLC Chiralpak IA column (Hex/iPrOH 95/05, 0.5 mL/min) tR 41.1 min (minor), 53.4 min (major): > 99:1 er.

Procedure for azlactone opening/amide deprotection of Mannich adduct **3b**

To a solution of **3b** (35.0 mg, 0.098 mmol) in 2 mL of CH_3CN was added HCl (12 mol L^{-1}, 0.04 mL, 0.56 mmol). The mixture was stirred for 1h at rt, then the volatile materials were removed under reduced pressure to give the intermediate **4**. To the crude, 2 mL of *conc.* HCl was added and the reaction was stirred at 100 ^oC for 10 h. The resulting mixture was concentrated under reduced pressure, diluted with water (5 mL) and washed three times with ethyl acetate (3 mL each one). The amino acid **5** (22.5 mg, 0.072 mmol) was obtained by purification through Amberlite IR 120 resin (HCl) in 75 % yield.

(**4**): ^1H NMR (500 MHz, CD_3OD): δ 8.06 (d, 1H, *J* = 10.0 Hz), 7.94 (br, 1H), 7.68-7.66 (m, 2H), 7.56-7.53 (m, 1H), 7.49-7.45 (m, 4H), 7.35-7.32 (m, 2H), 7.30-7.27 (m, 1H), 5.06 (d, 1H, *J* = 9.5 Hz), 2.60 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (125 MHz, CD_3OD): 172.8, 166.6, 138.0, 134.1, 131.6, 128.4, 128.2, 128.0, 127.8, 127.1, 62.5, 61.2, 41.3, 19.5. HRMS: calcd for $[C_{18}H_{20}N_2O_5S]+$ ([M+Na]+): *m/z* 399.0991, found 399.0982.

(**5**): ^1H NMR (500 MHz, D_2O): δ 7.50-7.46 (m, 5H), 2.68 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (125 MHz, D_2O + Dioxane): 173.4, 135.7, 131.8, 131.3, 130.4, 74.2, 64.1, 42.6, 20.8. HRMS: calcd for $[C_{11}H_{17}ClN_2O_4S]+$ ([M-Cl]+): *m/z* 273.0909, found 273.0897.

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Supporting Information Copies of NMR spectra, HPLCs as well as X-ray crystallographic details (CCDC 1005467 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.) This material is available free of charge via the Internet at http://pubs.acs.org.

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