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Pd-Catalyzed Directed *ortho*-C−H Alkenylation of Phenylalanine Derivatives

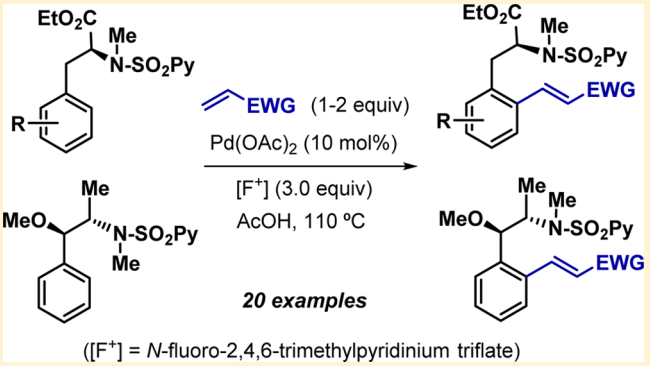
Alfonso García-Rubia,[†] Eduardo Laga,[†,‡] Carlos Cativiela,[‡] Esteban P. Urriolabeitia,[‡] Ramón Gómez-Arrayás,*[,†] and Juan C. Carretero*[,†]

[†]Departamento de Química Orgánica, Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

[‡]Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), CSIC-Universidad de Zaragoza, Pedro Cerbuna 12, E-50009 Zaragoza, Spain

Supporting Information

ABSTRACT: A practical Pd-catalyzed *ortho*-olefination of enantioenriched *N*-(SO_2Py)-protected aryl-alanine and norephedrine derivatives with electron-deficient alkenes has been developed using *N*-fluoro-2,4,6-trimethylpyridinium triflate as the terminal oxidant. The reaction occurs efficiently with excellent monosubstitution selectivity and without loss of enantiopurity. This cross-coupling proved to be broad in scope, tolerating a variety of steric and electronic changes to both coupling partners. Removal of the directing group under mild conditions provides access to optically active tetrahydroisoquinoline-3-carboxylic acid derivatives (Tics) with good diastereocontrol and with very small erosion of enantiomeric purity.



The direct functionalization of C−H bonds is an area of great interest because of its potential to streamline synthetic routes.[1] The use of directing groups has become a common strategy to address the challenge of achieving predictable selectivity in substrates that lack strong steric or electronic biases or to override the inherent substrate biasing elements.[1−3]

Coordination-directed C−H bond functionalization of nitrogen-containing compounds, such as α-amino acids, is particularly attractive given their prevalence in natural products and therapeutic agents.[4−8] Moreover, the incorporation of flexible functional handles into the amino acid skeleton provides products that offer high versatility as building blocks for their diversification into valuable heterocyclic frameworks.[9] Despite their significance, catalytic metal-controlled direct functionalization of α-amino acids remains underdeveloped.[5,7,8] An important challenge is to find a suitable directing function capable of preventing interference by the potentially coordinating proximal α-ester group and overcoming the increased steric restriction caused by the already installed α-stereocenter. An added requirement of such methods is mild functionalization/deprotection conditions tolerant of sensitive functional groups and the easily racemizable α-stereocenter. Most of the reported procedures are suited for *N*-protected *NH*-amino acid derivatives,[5−8] due to the participation of active metal amide intermediate complexes, whereas catalytic direct functionalization of *N*-substituted substrates (instead of *NH*-amino acid derivatives) remains an important ongoing challenge. Additionally, controlling mono- vs. disubstitution selectivity is often problematic in this type of processes.[10]

Within this field, the Pd^{II}-catalyzed oxidative coupling between arenes and olefins (Fujiwara−Moritani reaction) is arguably one of the most important reactions in this field.[11,12] Recently, our group introduced the use of the *N*-(2-pyridyl)sulfonyl (SO_2Py) moiety as an easily installable and removable protecting/directing group in a variety of Pd-catalyzed C−H functionalization reactions.[13] In particular, it showed a high directing ability, as well as structural flexibility, in the Pd^{II}-catalyzed aryl C−H *ortho* alkenylation of anilines, benzylamines, and phenethylamines with electron-defficient alkenes.[13c] Subsequently, Yu and co-workers demonstrated the suitability of this *N*-SO_2Py-strategy for Pd^{II}-catalyzed intramolecular C−H amination of phenethylamine derivatives, including optically active phenylalanine derivatives.[7h] Herein, we report a practical and efficient Pd^{II}-catalyzed mono-*ortho*-olefination of enantioenriched phenylalanine derivatives. The use of the *N*-SO_2Py-protecting group allows for facile deprotection and subsequent cyclization via aza-Michael addition of the free amino group to the acrylate moiety to form disubstituted tetrahydroisoquinolines with good diastereocontrol.

On the basis of the knowledge acquired in our previous contribution,[13c] the enantiomerically pure *N*-methyl-*N*-(SO_2Py)-protected phenylalanine ethyl ester derivative (*S*)-**1**

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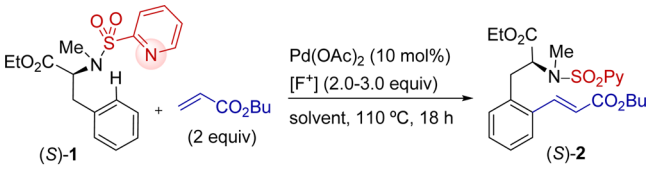
was probed for its potential in the olefination reaction with butyl acrylate (2.0 equiv) using $Pd(OAc)_2$ as catalyst (10 mol %) and *N*-fluoro-2,4,6-trimethylpyridium triflate [F^+] as stoichiometric oxidant,[14] at 110 °C for 18 h. The results of this optimization study are shown in Table 1. The reaction in

Table 1. Optimization of Reaction Conditions[a]



[F^+] = *N*-fluoro-2,4,6-trimethylpyridinium triflate

entry	solvent	[F^+] (equiv)	conversion (%)[b]	ee (%)[c]
1	DCE	2.0	40	
2	AcOH	2.0	53 (45)[d]	97
3	HFIP	2.0	94 (83)[d]	88
4	AcOH	2.5	72	
5	AcOH	3.0	>98	
6[e]	AcOH	3.0	>98 (84)[d]	97

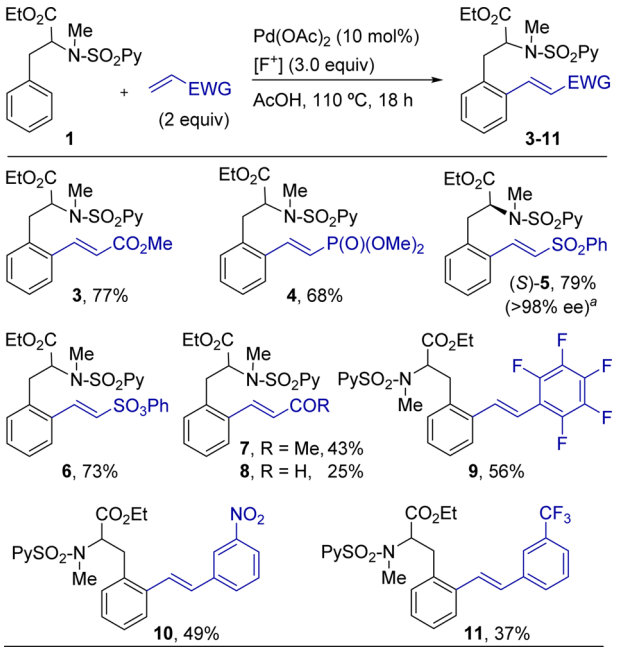
[a]Conditions: (*S*)-**1** (0.15 mmol), $Pd(OAc)_2$ (0.015 mmol), [F^+] (0.45 mmol), AcOH (1 mL) at 110 °C, butyl acrylate (0.30 mmol). [b]By ^1H NMR from the crude mixture, measuring the relative ratio of **2** to starting **1** by integration of characteristic, baseline separated signals. [c]Enantiomeric excess of (*S*)-**2**, determined by chiral stationary phase HPLC. [d]In parentheses, isolated yield after chromatography. [e]Reaction time: 6 h.

DCE showed poor conversion (40%, entry 1), while changing the solvent to AcOH resulted in a slightly higher conversion (entry 2). Despite the low conversions, the reactions were very clean, and in the latter case, the desired *ortho*-olefination product (*S*)-**2** was isolated in 45% yield. It is important to note that the stereochemical information present in the starting phenylalanine derivative (*S*)-**1** was preserved in the olefin-bearing product (*S*)-**2** with minimal erosion in the enantiomeric purity (97% ee, entry 2; the starting (*S*)-**1** was prepared from commercially available L-phenylalanine of ≥98% ee). The use of hexafluoroisopropanol (HFIP), a solvent that proved to be highly effective in C–H functionalization of α-amino acid derivatives,[8i] resulted in a boost in conversion up to 94%. However, this increase in reactivity (83% yield of the desired product **2**) came at the cost of a loss of enantiomeric purity (88% ee, entry 3).

To our satisfaction, the solution to the problem of low reactivity without compromising the stereochemical integrity was found by increasing the amount of the oxidant. Thus, the model reaction of **1a** with butyl acrylate in AcOH in the presence of 2.5 equiv of [F^+] led to 72% conversion of **2** (entry 4), while a further increase of [F^+] to 3.0 equiv allowed for complete conversion (entry 5). Furthermore, under these latter conditions, complete conversion was observed after only 6 h, affording the acrylate **2** in good yield (84%) without appreciable loss of enantiopurity (97% ee, entry 6). It should be noted that, in contrast to literature precedents,[11] in which mono-olefination selectivity is often difficult to control, complete monosubstitution selectivity was observed under our reaction conditions.

After the optimal reaction parameters had been established, the effect of electronic and structural variations on the alkene was studied. For that purpose, a variety of monosubstituted electrophilic alkenes were surveyed in the reaction with the parent substrate **1** (Scheme 1). For this study, racemic (±)-**1**

Scheme 1. Scope with Regard to the Olefin Coupling Partner



[a]The starting (*S*)-**1** was prepared from commercially available L-phenylalanine of ≥98% ee. [F^+] = *N*-fluoro-2,4,6-trimethylpyridinium triflate. EWG = electron-withdrawing functional group.

was used in most cases. Not only acrylates (products **2** and **3**) but also dimethyl vinyl phosphonate (**4**), phenyl vinyl sulfone (**5**), and phenyl vinyl sulfonate (**6**) coupled efficiently with **1** to give the corresponding *ortho*-alkenylated products with excellent regioselectivity, monosubstitution selectivity, and *E*-stereoselectivity in synthetically useful yields (68–84%). Other carbonyl derivatives such as methyl vinyl ketone (**7**) or acrolein (**8**) were found to be less efficient coupling partners (43% and 25% yield, respectively). Interestingly, styrene derivatives bearing electron-withdrawing substituents (pentafluoro, NO_2, or CF_3) at the phenyl ring were found to be also capable reactants for the alkenylation reaction, affording the corresponding products in acceptable yields (products **9**–**11**, 37–56% yield). Unfortunately, styrene itself provided poor reactivity (<10% conversion, not shown). We confirmed again that the alkenylation reaction takes place with no appreciable racemization, as demonstrated in the reaction with phenyl vinyl sulfone (product (*S*)-**5**, 79% yield, >98% ee).

Encouraged by the good tolerance of our catalyst system toward different functional groups, structurally diverse phenylalanine derivatives were subjected to the catalytic olefination with butyl acrylate in order to evaluate the scope and limitations with regard to the aromatic substitution of the amino acid counterpart. This scope study was limited by the number of commercially available aryl-alanines. The results are presented in Scheme 2. Both electron-rich groups (OMe and Me) and electron-deficient groups (F, Cl, Br) were tolerated, although substrates with electron-releasing groups are generally more reactive. Thus, the *p*-OMe product **12** (a derivative of tyrosine) was obtained with 71% yield, whereas no reactivity was observed in the substrate holding a *p*-NO_2 group (<10% conversion; result not shown in Scheme 2). Nevertheless, a

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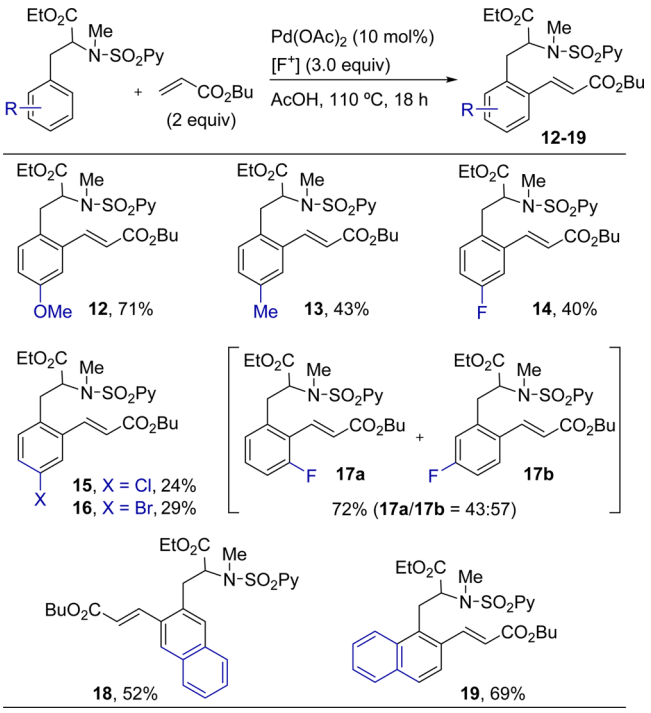
Scheme 2. Scope with Regard to the Substitution at the Aromatic Ring



[a][F+] = *N*-fluoro-2,4,6-trimethylpyridinium triflate.

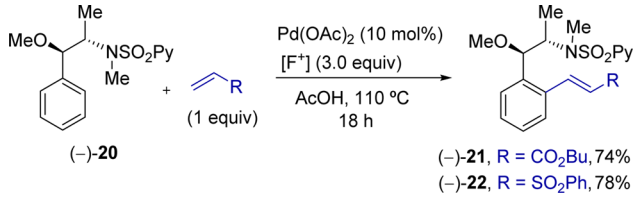
number of mono-*ortho*-olefinated phenylalanine derivatives were isolated in acceptable yields (24−72%). It should be noted that, in the case of *p*-Cl or *p*-Br substituted substrates, the incomplete conversions and the difficulty in the complete chromatographic separation of the products from the starting material and a trace amount of unidentified byproducts resulted in low yields upon isolation (products **15** and **16**, 24% and 29% yield, respectively).[15] Despite these shortcomings, the partial tolerance to halogen-containing substrates is useful for subsequent product derivatization since it provides orthogonal reactivity relative to the Pd^0-catalyzed cross-coupling chemistry.

When a substrate having blocked the *meta* position was employed, as in the case of the 2-naphthyl derivative, the reaction occurred at a sterically more accessible site (C-3′) to avoid the steric congestion (product **18**, 52% yield). However, *meta*-fluoro-substitution caused the formation of a mixture of the two *ortho*-olefination regioisomers (**17a** and **17b** were isolated with 72% yield in a 43:57 relative ratio), probably arising from the low steric discrimination of the two *ortho* positions by the small fluoro substituent. The 1-naphthyl derivative underwent clean olefination at the available C-2′ position (**19**, 69% yield).

Notably, this method can be further extended to chiral enantiomerically pure α,β-disubstituted phenethylamines, such as the norephedrine derivative **20** (Scheme 3). Compound **20** was smoothly alkenylated under the standard reaction conditions with butyl acrylate or phenyl vinyl sulfone (1.0 equiv) to give the corresponding products in good yields (74%−78%) without epimerization, according to ^{1}H NMR.

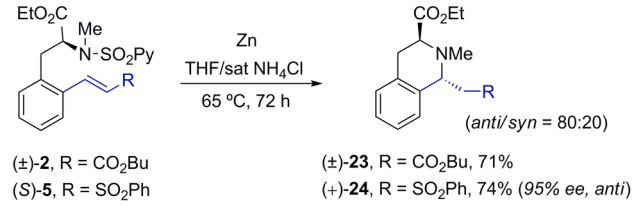
The easy reductive removal of the *N*-(2-pyridyl)sulfonyl protecting/directing group under smooth conditions (Zn powder, 1:1 THF/sat. aq NH_4Cl, 65 °C) without affecting the sensitive acrylate moiety enabled the direct access to valuable 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

Scheme 3. Extension to Norephedrine Derivatives



(Tic)[16] skeletons in synthetically useful yields (Scheme 4). For example, *N*-deprotection of product (±)-**2** simultaneously

Scheme 4. *N*-Deprotection/Cyclization To Afford Tetrahydroisoquinolines



triggers the cyclization of the free amine under the reaction conditions to afford **23** in 71% yield and good diastereoselectivity (*anti*/*syn* = 80:20).[17] When the enantiomerically pure product (*S*)-**5** (>98% ee) was submitted to identical conditions, the same *N*-deprotection/intramolecular aza-Michael sequence was produced, affording the corresponding enantioenriched bicyclic product (+)-**24** in similar yield (74%) and diastereocontrol (*anti*/*syn* = 80:20), albeit with a small degree of racemization (95% ee in the major *anti* diastereomer).

In conclusion, we have demonstrated that the directing ability of the easily removable *N*-(2-pyridyl)sulfonyl group can be extended to the Pd^{II}-catalyzed direct *ortho*-olefination of *N*-substituted phenylalanine and norephedrine derivatives in acceptable yields and with preservation of enantiopurity of the starting substrate. This protocol features good structural versatility in both alkene and nitrogen arene components. The smooth *N*-deprotection without affecting the acrylate moiety enables rapid access to enantioenriched tetrahydroisoquinoline derivatives.

EXPERIMENTAL SECTION

General Methods. Solvents were used as received from commercial sources. They were not distilled nor subjected to additional purification. All reactions were carried out without special protections against air and moisture unless otherwise specified. Flash column chromatography was performed on silica gel (70−230 mesh). The ^{1}H, ^{13}C{^{1}H}, ^{19}F, and ^{31}P{^{1}H} NMR spectra were recorded in $CDCl_3$ solutions at 25 °C on 300, 400, or 500 MHz spectrometers (δ, ppm; *J*, Hz); ^{1}H and ^{13}C{^{1}H} spectra were referenced using the solvent signal as internal standard, while ^{19}F and ^{31}P NMR spectra were referenced to $CFCl_3$ and H_3PO_4 (85%), respectively. HRMS and ESI (ESI+) mass spectra were recorded using a MicroToF Q, API-Q-ToF ESI with a mass range from 20 to 3000 *m*/*z* and mass resolution of 15000 (fwhm). HPLC experiments were conducted using Daicel Chiralpak IA, AD, AS-H and Chiralcel OJ-H columns as chiral stationary phase. Optical rotations were measured on a polarimeter, and they are reported as follows: $[\alpha]^{\text{temperature}}_{\text{wavelength}}$ (*c*, solvent). Melting points were determined in open-end capillary tubes.

Synthesis of the Starting *N*-(2-Pyridyl)sulfonyl Phenylalanine Ethyl Ester Derivatives from Aryl-alanines. *Step 1: Protection of the Carboxylic Acid Group As Ethyl Ester. Typical Procedure: Synthesis of (S)-Ethyl 2-Amino-3-phenylpropanoate (S)-*

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I. To an ice-cooled solution (−5 °C) of (*S*)-phenylalanine (2.00 g, 12.11 mmol; ≥98% ee) in ethanol (10 mL) was added thionyl chloride (1.32 mL, 18.16 mmol). The resulting mixture was heated to reflux for 3 h. It was allowed to reach room temperature, and the solvent was evaporated. The solid residue was treated with a sat. aq solution of sodium hydrogen carbonate (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated to give (*S*)-**I** as a clear yellow oil; yield: 1.82 g (78%)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29−7.10 (m, 5H), 4.09 (q, J = 7.1 Hz, 2H), 3.63 (t, br, J = 5.3 Hz, 1H), 3.01 (dd, J = 13.5, 5.3 Hz, 1H), 2.81 (dd, J = 13.5, 7.6 Hz, 1H), 1.58 (s, br, 2H), 1.17 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 174.7, 137.1, 129.0, 128.2, 126.4, 60.5, 55.5, 40.9, 13.9. ESI-HRMS: Calcd for $C_{11}H_{16}NO_2$ [M + H]$^+$: 194.1176. Found: 194.1185. $[\alpha]_D^{298}$ = −7.04 (*c* 1.09, $CHCl_3$).

*(±)-Ethyl 2-Amino-3-(4-methoxyphenyl)propanoate [(±)-**II**].* Following the typical procedure, thionyl chloride (445.9 μL, 6.15 mmol) reacted with *O*-methyltyrosine (800.0 mg, 4.10 mmol) in ethanol (5 mL) to give, after workup, (±)-**II** as a pale yellow oil; yield: 694.4 mg (76%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (d, J = 8.6 Hz, 2H), 6.68 (d, J = 8.6 Hz, 2H), 4.00 (q, J = 7.2 Hz, 2H), 3.60 (d, J = 1.0 Hz, 3H), 3.50 (dd, J = 7.5, 5.5 Hz, 1H), 2.85 (dd, J = 13.6, 5.4 Hz, 1H), 2.67 (dd, J = 13.6, 7.5 Hz, 1H), 1.74 (s, br, 2H), 1.09 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 174.6, 158.0, 129.8, 128.8, 113.4, 60.3, 55.4, 54.6, 39.7, 13.7. ESI-HRMS: Calcd for $C_{12}H_{18}NO_3$ [M + H]$^+$: 224.1281. Found: 224.1276.

*(±)-Ethyl 2-Amino-3-(p-tolyl)propanoate [(±)-**III**].* Following the typical procedure, thionyl chloride (242.9 μL, 3.35 mmol) reacted with *p*-methylphenylalanine (400.0 mg, 2.23 mmol) in ethanol (10 mL) to give, after workup, (±)-**III** as a pale yellow oil; yield: 461.0 mg (99%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14−7.01 (m, 4H), 4.15 (q, J = 7.2 Hz, 2H), 3.66 (dd, J = 7.8, 5.2 Hz, 1H), 3.02 (dd, J = 13.5, 5.2 Hz, 1H), 2.80 (dd, J = 13.5, 7.8 Hz, 1H), 2.30 (s, 3H), 1.49 (s, 2H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 175.0, 136.2, 134.1, 129.1, 129.1, 60.8, 55.8, 40.6, 21.0, 14.1. ESI-HRMS: Calcd for $C_{12}H_{18}NO_2$ [M + H]$^+$: 208.1332. Found: 208.1327.

*(±)-Ethyl 2-Amino-3-(4-fluorophenyl)propanoate [(±)-**IV**].* Following the typical procedure, thionyl chloride (475.2 μL, 6.55 mmol) reacted with *p*-fluorophenylalanine (800.0 mg, 4.37 mmol) in ethanol (5 mL) to give, after workup, (±)-**IV** as a pale yellow oil; yield: 851.0 mg (92%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11−6.99 (m, 2H), 6.92−6.81 (m, 2H), 4.03 (q, J = 7.1 Hz, 2H), 3.56 (s, br, 1H), 2.91 (dd, J = 13.5, 5.3 Hz, 1H), 2.74 (dd, J = 13.6, 7.4 Hz, 1H), 1.51 (s, br, 2H), 1.11 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 174.6, 161.5 (d, $J_{C\text{-}F}$ = 244.6 Hz), 132.9 (d, $J_{C\text{-}F}$ = 3.2 Hz), 130.5 (d, $J_{C\text{-}F}$ = 7.9 Hz), 115.0 (d, $J_{C\text{-}F}$ = 21.2 Hz), 60.6, 55.5, 40.0, 13.9. ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$): δ −115.88. ESI-HRMS Calcd for $C_{11}H_{15}FNO_2$ [M + H]$^+$: 212.1081. Found: 212.1080.

*(±)-Ethyl 2-Amino-3-(4-chlorophenyl)propanoate [(±)-**V**].* Following the typical procedure, thionyl chloride (545.1 μL, 7.51 mmol) reacted with *p*-chlorophenylalanine (1.00 g, 5.01 mmol) in ethanol (10 mL) to give, after workup, (±)-**V** as a pale yellow oil; yield: 1.12 g (99%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (d, J = 7.9 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 4.10 (q, J = 7.2 Hz, 2H), 3.62 (t, J = 6.9 Hz, 1H), 2.97 (dd, J = 13.4, 5.4 Hz, 1H), 2.78 (dd, J = 13.6, 7.7 Hz, 1H), 1.43 (s, br, 2H), 1.19 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 174.7, 135.8, 132.5, 130.6, 128.5, 60.9, 55.6, 40.3, 14.1. ESI-HRMS: Calcd for $C_{11}H_{15}ClNO_2$ [M + H]$^+$: 228.0786. Found: 228.0772.

*(±)-Ethyl 2-Amino-3-(4-bromophenyl)propanoate [(±)-**VI**].* Following the typical procedure, thionyl chloride (445.8 μL, 6.14 mmol) reacted with *p*-bromophenylalanine (1.00 g, 4.10 mmol) in ethanol (10 mL) to give, after workup, (±)-**VI** as a pale yellow oil; yield: 1.04 g (93%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45−7.34 (m, 2H), 7.13−7.02 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.65 (dd, J = 7.8, 5.4 Hz), 3.00 (dd, J = 13.6, 5.4 Hz, 1H), 2.80 (dd, J = 13.6, 7.7 Hz, 1H), 1.43 (s, 2H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 174.87, 136.46, 131.62, 131.10, 120.77, 61.07, 55.73, 40.53, 14.27. ESI-HRMS: Calcd for $C_{11}H_{15}BrNO_2$ [M + H]$^+$: 272.0286. Found: 272.0269.

*(±)-Ethyl 2-Amino-3-(3-fluorophenyl)propanoate [(±)-**VII**].* Following the typical procedure, thionyl chloride (207.1 μL, 2.85 mmol) reacted with *m*-fluorophenylalanine (366.4 mg, 2.00 mmol) in ethanol (5 mL) to give, after workup, (±)-**VII** as a pale yellow oil; yield: 333.5 mg (79%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.82 (s, br, 2H), 7.29 (m, 1H), 7.12 (t, J = 8.1 Hz, 2H), 6.95 (t, J = 7.8 Hz, 1H), 4.44 (m, 1H), 4.13 (m, 2H), 3.51 (m, 1H), 3.36 (m, 1H), 1.15 (t, J = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 168.8, 162.0 (d, $J_{C\text{-}F}$ = 46.5 Hz), 136.9 (d, $J_{C\text{-}F}$ = 7.8 Hz), 130.3 (d, $J_{C\text{-}F}$ = 8.2 Hz), 125.4 (d, $J_{C\text{-}F}$ = 2.9 Hz), 116.7 (d, $J_{C\text{-}F}$ = 21.4 Hz), 114.5 (d, $J_{C\text{-}F}$ = 20.9 Hz), 62.5, 54.2, 36.0, 13.8. ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$): δ −112.7. ESI-HRMS: Calcd for $C_{11}H_{15}FNO_2$ [M + H]$^+$: 212.1081. Found: 212.1088.

*(±)-Ethyl 2-Amino-3-(naphthalen-1-yl)propanoate [(±)-**VIII**].* Following the typical procedure, thionyl chloride (207.1 μL, 2.85 mmol) reacted with 1-naphthylalanine (430.3 mg, 2.00 mmol) in ethanol (5 mL) to give, after workup, (±)-**VIII** as a pale yellow oil; yield: 340.6 mg (70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.40−7.18 (m, 6H), 4.43 (m, 1H), 3.97 (m, 1H), 3.64 (m, 3H), 0.63 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.5, 133.8, 131.9, 131.0, 128.7, 128.5, 128.1, 126.5, 125.7, 125.5, 123.6, 62.1, 53.9, 34.0, 13.3. ESI-HRMS: Calcd for $C_{15}H_{18}NO_2$ [M + H]$^+$: 244.1332. Found: 244.1335.

*(±)-Ethyl 2-Amino-3-(naphthalen-2-yl)propanoate [(±)-**IX**].* Following the typical procedure, thionyl chloride (207.1 μL, 2.85 mmol) reacted with 2-naphthylalanine (430.3 mg, 2.00 mmol) in ethanol (5 mL) to give, after workup, (±)-**IX** as a pale yellow oil; yield: 384.4 mg (79%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.88 (s, br, 2H), 7.80−7.74 (m, 4H), 7.44−7.39 (m, 3H), 4.52 (t, J = 7.1 Hz, 1H), 3.97 (m, 2H), 3.67 (dd, J = 5.4, 14.1 Hz, 1H), 3.50 (dd, J = 7.9, 13.9 Hz, 1H), 0.96 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.0, 133.4, 132.6, 131.9, 128.7, 128.3, 127.8, 127.6, 127.4, 126.1, 125.8, 62.3, 54.3, 36.6, 13.7. ESI-HRMS: Calcd for $C_{15}H_{18}NO_2$ [M + H]$^+$: 244.1332. Found: 244.1338.

*Step 2: N-Sulfonylation Reaction. Typical Procedure: Synthesis of (S)-Ethyl 3-Phenyl-2-(pyridine-2-sulfonamido)propanoate [(S)-**X**].* To a solution of (*S*)-**I** (1.82 g, 9.43 mmol) and pyridine (2.7 mL, 33.96 mmol) in dry THF (20 mL), cooled to −5 °C and under Ar atmosphere, was added dropwise a solution of 2-pyridylsulfonyl chloride (2.01 g, 11.32 mmol) in dry THF (5 mL). The resulting mixture was allowed to reach room temperature and stirred for a further 18 h before it was filtered and concentrated to dryness. The resulting solid residue was triturated in a 1:1 mixture of hexane:water (20 mL) and then filtered to give compound (*S*)-**X** as a white solid; yield: 2.69 g (85%); mp: 131−133 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 7.90 (dt, J = 7.8, 1.1 Hz, 1H), 7.84 (td, J = 7.7, 1.7 Hz, 1H), 7.43 (ddd, J = 7.5, 4.7, 1.4 Hz, 1H), 7.26−7.16 (m, 3H), 7.15−7.09 (m, 2H), 5.57 (d, J = 8.9 Hz, 1H), 4.58 (dt, J = 8.8, 6.0 Hz, 1H), 3.98 (qq, J = 7.1, 3.6 Hz, 2H), 3.10 (d, J = 6.1 Hz, 2H), 1.10 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.9, 157.8, 149.8, 138.0, 135.2, 129.6, 128.5, 127.2, 126.7, 121.7, 61.7, 57.6, 39.8, 14.0. ESI-HRMS: Calcd for $C_{16}H_{19}N_2O_4S$ [M + H]$^+$: 335.1060. Found: 335.1052. $[\alpha]_D^{298}$ = −9.75 (*c* = 1.11, $CHCl_3$).

*(±)-Ethyl 3-(4-Methoxyphenyl)-2-(pyridine-2-sulfonamido)-propanoate [(±)-**XI**].* Following the typical procedure, (±)-**II** (694.4 mg, 3.11 mmol) and pyridine (905.6 μL, 11.20 mmol) in THF (20 mL) reacted with a soln of 2-pyridylsulfonyl chloride (662.9 mg, 3.73 mmol) in THF (5 mL) to give (±)-**XI** as a white solid; yield: 829.4 g (73%); mp: 125−128 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (d, J = 4.6 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.84 (td, J = 7.7, 1.7 Hz, 1H), 7.43 (ddd, J = 7.4, 4.7, 1.3 Hz, 1H), 7.03 (d, J = 8.6 Hz, 2H), 6.75 (d, J = 8.6 Hz, 2H), 5.53 (d, J = 8.8 Hz, 1H), 4.53 (dt, J = 8.8, 5.9 Hz, 1H), 3.98 (m, 2H), 3.75 (s, 3H), 3.04 (d, J = 5.9 Hz, 2H), 1.12 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.9, 158.8, 157.9, 149.8, 138.0, 130.6,

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127.1, 126.7, 121.7, 113.9, 61.6, 57.7, 55.3, 38.9, 14.1. ESI-HRMS: Calcd for $C_{17}H_{20}N_2O_5S$ $[M + H]^+$: 365.1166. Found: 365.1143.

*(±)-Ethyl 2-(Pyridine-2-sulfonamido)-3-(p-tolyl)propanoate [(±)-**XII**].* Following the typical procedure, (±)-**III** (461.0 mg, 2.22 mmol) and pyridine (647.6 μL, 8.00 mmol) in THF (20 mL) reacted with a soln of 2-pyridylsulfonyl chloride (474.0 mg, 2.67 mmol) in THF (5 mL) to give (±)-**XII** as a yellow solid. Further purification by column chromatography (hexane−EtOAc, 2:3) provided (±)-**XII** as a white powder; yield: 389.3 mg (50%); mp: 129−131 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (dq, *J* = 4.7, 1.3 Hz, 1H), 7.89 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.84 (td, *J* = 7.6, 1.7 Hz, 1H), 7.43 (ddd, *J* = 7.3, 4.7, 1.5 Hz, 1H), 7.05−6.98 (m, 4H), 5.46 (d, *J* = 8.9 Hz, 1H), 4.56 (dt, *J* = 8.8, 5.9 Hz, 1H), 3.99 (qd, *J* = 7.1, 2.2 Hz, 2H), 3.06 (d, *J* = 5.9 Hz, 2H), 2.28 (s, 3H), 1.12 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.9, 157.8, 149.8, 138.0, 136.7, 131.9, 129.4, 129.2, 126.6, 121.7, 61.6, 57.6, 39.3, 21.1, 14.0. ESI-HRMS: Calcd for $C_{17}H_{21}N_2O_4S$ $[M + H]^+$: 349.1217. Found: 349.1212.

*(±)-Ethyl 3-(4-Fluorophenyl)-2-(pyridine-2-sulfonamido)-propanoate [(±)-**XIII**].* Following the typical procedure, (±)-**IV** (851.0 mg, 4.03 mmol) and pyridine (1170 μL, 14.50 mmol) in THF (20 mL) reacted with a soln of 2-pyridylsulfonyl chloride (858.7 mg, 4.835 mmol) in THF (5 mL) to give (±)-**XIII** as a white solid. Yield: 1.24 g (87%); mp: 132−134 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H), 7.90 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.85 (td, *J* = 7.6, 1.7 Hz, 1H), 7.45 (ddd, *J* = 7.4, 4.7, 1.4 Hz, 1H), 7.11 (m, 2H), 6.91 (m, 2H), 5.60 (d, *J* = 8.7 Hz, 1H), 4.55 (dt, *J* = 8.7, 6.0 Hz, 1H), 4.00 (qd, *J* = 7.1, 3.1 Hz, 2H), 3.10 (dd, *J* = 13.8, 6.0 Hz, 1H), 3.05 (dd, *J* = 13.6, 6.1 Hz, 1H), 1.12 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.84, 162.13 (d, *J* = 245.5 Hz), 157.88, 149.91, 138.14, 131.20 (d, $J_{C\text{-}F}$ = 8.1 Hz), 131.05 (d, $J_{C\text{-}F}$ = 3.3 Hz), 126.81, 121.76, 115.43 (d, $J_{C\text{-}F}$ = 21.3 Hz), 61.86, 57.71 (d, $J_{C\text{-}F}$ = 1.4 Hz), 39.05, 14.12. ^{19}F{^{1}H} NMR: δ −115.55 (s). ESI-HRMS: Calcd for $C_{16}H_{18}FN_2O_4S$ $[M + H]^+$: 353.0966. Found: 353.0991.

*(±)-Ethyl 3-(4-Chlorophenyl)-2-(pyridine-2-sulfonamido)-propanoate [(±)-**XIV**].* Following the typical procedure, (±)-**V** (1.12 g, 4.93 mmol) and pyridine (718.2 μL, 8.88 mmol) in THF (20 mL) reacted with a soln of 2-pyridylsulfonyl chloride (1.05 g, 5.92 mmol) in THF (5 mL) to give (±)-**XIV** as a white solid; yield: 1.42 g (78%); mp: 129−131 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.59 (dt, *J* = 4.8, 1.3 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.85 (td, *J* = 8.0, 1.5 Hz, 1H), 7.45 (ddd, *J* = 6.9, 4.8, 1.8 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 5.47 (d, *J* = 8.6 Hz, 1H), 4.58 (dt, *J* = 8.6, 6.0 Hz, 1H), 4.03 (qd, *J* = 7.1, 1.7 Hz, 2H), 3.12 (dd, *J* = 13.9, 5.9 Hz, 1H), 3.04 (dd, *J* = 13.9, 6.2 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.7, 149.9, 138.1, 133.8, 133.2, 131.0, 128.7, 126.8, 121.7, 61.9, 57.6, 39.2, 14.1 [The quaternary C atom of the π fragment was not observed, in spite of the use of long accumulation periods]. ESI-HRMS: Calcd for $C_{16}H_{18}ClN_2O_4S$ $[M + H]^+$: 369.0670. Found: 369.0663.

*(±)-Ethyl 3-(4-Bromophenyl)-2-(pyridine-2-sulfonamido)-propanoate [(±)-**XV**].* Following the typical procedure, (±)-**VI** (1.04 g, 3.82 mmol) and pyridine (556.4 μL, 6.88 mmol) in THF (5 mL) reacted with a soln of 2-pyridylsulfonyl chloride (814.5 mg, 4.59 mmol) in THF (20 mL) to give (±)-**XV** as a white solid; yield: 1.217 g (77%); mp: 126−128 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (dt, *J* = 4.6, 1.3 Hz, 1H), 7.88 (d, *J* = 7.0 Hz, 1H) 7.84 (td, *J* = 7.9, 1.4 Hz, 1H), 7.45 (ddd, *J* = 6.8, 4.8, 2.1 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.01 (d, *J* = 8.3 Hz, 2H), 5.59 (d, *J* = 8.7 Hz, 1H), 4.56 (dt, *J* = 8.7, 6.1 Hz, 1H), 4.03 (qd, *J* = 7.1, 1.5 Hz, 2H), 3.09 (dd, *J* = 13.9, 5.8 Hz, 1H), 3.01 (dd, *J* = 13.8, 6.4 Hz, 1H), 1.14 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.7, 157.8, 149.9, 138.1, 134.4, 131.6, 131.3, 126.7, 121.7, 121.3, 61.9, 57.5, 39.2, 14.1. ESI-HRMS: Calcd for $C_{16}H_{18}BrN_2O_4S$ $[M + H]^+$: 413.0165. Found: 413.0159.

*(±)-Ethyl 3-(3-Fluorophenyl)-2-(pyridine-2-sulfonamido)-propanoate [(±)-**XVI**].* Following the typical procedure, (±)-**VII** (316.8 mg, 1.50 mmol) and pyridine (548.8 μL, 6.78 mmol) in THF (20 mL) reacted with a soln of 2-pyridylsulfonyl chloride (401.7 mg, 2.26 mmol) in THF (5 mL) to give (±)-**XVI** as a white solid; yield: 422.8 mg (80%); mp: 144−146 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53 (dt, *J* = 0.7, 4.7 Hz, 1H), 7.85 (dd, *J* = 0.7, 7.5 Hz, 1H), 7.80 (dt, *J* = 1.6, 8.9 Hz, 1H), 7.39 (m, 1H), 7.16 (m, 1H), 6.88−6.74 (m, 3H), 5.27 (d, *J* = 8.5 Hz, 1H), 4.52 (m, 1H), 3.95 (dc, *J* = 5.5, 7.0 Hz, 2H), 3.04 (d, *J* = 5.8 Hz, 2H), 1.07 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.6, 164.2 (d, $J_{C\text{-}F}$ = 245.9 Hz), 157.8, 149.8, 138.0, 137.7 (d, $J_{C\text{-}F}$ = 7.1 Hz), 130.0 (d, $J_{C\text{-}F}$ = 8.2 Hz), 126.7, 125.3 (d, $J_{C\text{-}F}$ = 2.7 Hz), 121.6, 116.4 (d, $J_{C\text{-}F}$ = 20.0 Hz), 114.1 (d, $J_{C\text{-}F}$ = 20.9 Hz), 61.8, 57.4, 39.5, 14.0. ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$): δ −113.0. ESI-HRMS: Calcd for $C_{16}H_{18}FN_2O_4S$ $[M + H]^+$: 353.0966. Found: 353.0961.

*(±)-Ethyl 3-(Naphthalen-1-yl)-2-(pyridine-2-sulfonamido)-propanoate [(±)-**XVII**].* Following the typical procedure, (±)-**VIII** (364.9 mg, 1.50 mmol) and pyridine (548.8 μL, 6.78 mmol) in THF (20 mL) reacted with a soln of 2-pyridylsulfonyl chloride (401.7 mg, 2.26 mmol) in THF (5 mL) to give (±)-**XVII** as a colorless oil; yield: 409.5 mg (71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53 (m, 1H), 7.85−7.72 (m, 5H), 7.59 (s, 1H), 7.48−7.49 (m, 2H), 7.34−7.25 (m, 3H), 4.70 (m, 1H), 4.05 (c, *J* = 7.0 Hz, 2H), 3.31−3.27 (m, 2H), 1.13 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 171.0, 157.6, 149.7, 137.8, 133.3, 133.0, 132.5, 128.4, 128.1, 127.7, 127.6, 127.5, 126.4, 126.0, 125.8, 121.5, 61.7, 57.8, 39.8, 14.0. ESI-HRMS: Calcd for $C_{20}H_{21}N_2O_4S$ $[M + H]^+$: 385.1217. Found: 385.1211.

*(±)-Ethyl 3-(Naphthalen-2-yl)-2-(pyridine-2-sulfonamido)-propanoate [(±)-**XVIII**].* Following the typical procedure, (±)-**IX** (364.9 mg, 1.50 mmol) and pyridine (548.8 μL, 6.78 mmol) in THF (20 mL) reacted with a soln of 2-pyridylsulfonyl chloride (401.7 mg, 2.26 mmol) in THF (5 mL) to give (±)-**XVIII** as a white solid; yield: 440.0 mg (77%); mp: 53−55 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (d, *J* = 4.6 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.75−7.64 (m, 5H), 7.44−7.39 (m, 2H), 7.28−7.20 (m, 2H), 5.42 (d, *J* = 8.8 Hz, 1H), 4.61 (c, *J* = 7.0 Hz, 1H), 3.83 (m, 2H), 3.46 (d, *J* = 7.1 Hz, 2H), 0.90 (t, *J* = 7.0 Hz, 3H) ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 171.3, 157.7, 149.6, 137.7, 133.8, 131.8, 131.6, 128.8, 128.1, 128.0, 126.4, 126.3, 125.7, 125.3, 123.5, 121.4, 61.6, 57.2, 37.2, 13.8. ESI-HRMS: Calcd for $C_{20}H_{21}N_2O_4S$ $[M + H]^+$, 385.1217. Found: 385.1215.

*Step 3: N-Methylation. Typical Procedure: Synthesis of (S)-Ethyl 2-(N-Methylpyridine-2-sulfonamido)-3-phenylpropanoate [(S)-**1**].* To a solution of (*S*)-**X** (2.69 g, 8.05 mmol) and K_2CO_3 (2.23 g, 16.11 mmol) in MeCN (20 mL), was added methyl iodide (1.5 mL, 24.16 mmol). The reaction mixture was refluxed for 16 h before it was cooled to room temperature and concentrated to dryness. The residue was purified by flash chromatography (*n*-hexane−EtOAc 9:1) to give compound (*S*)-**1**. Further purification by trituration in a 1:2 mixture of *n*-hexane−Et_2O gave (*S*)-**1** as a white solid; yield: 2.21 g (79%); mp: 119−121 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61 (dt, *J* = 4.7, 1.6 Hz, 1H), 7.85−7.75 (m, 2H), 7.42 (ddd, *J* = 6.1, 4.7, 2.6 Hz, 1H), 7.25−7.15 (m, 5H), 4.96 (dd, *J* = 8.3, 7.3 Hz, 1H), 3.95 (q, *J* = 7.1 Hz, 2H), 3.24 (dd, *J* = 14.0, 7.3 Hz, 1H), 3.07 (s, 3H), 2.96 (dd, *J* = 14.0, 8.3 Hz, 1H), 1.05 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.1, 157.5, 149.8, 137.7, 136.3, 129.1, 128.6, 126.9, 126.4, 122.1, 61.2, 61.0, 35.9, 31.3, 14.0. ESI-HRMS: Calcd for $C_{17}H_{21}N_2O_4S$ $[M + H]^+$: 349.1217. Found: 349.1190. $[\alpha]_D^{298}$ = −19.12 (*c* 1.00, $CHCl_3$).

*(±)-Ethyl 3-(4-Methoxyphenyl)-2-(N-methylpyridine-2-sulfonamido)propanoate [(±)-**XIX**].* Following the typical procedure, (±)-**XI** (829.4 mg, 2.28 mmol) reacted with MeI (425.1 μL, 6.828 mmol) in the presence of K_2CO_3 (629.1 mg, 4.55 mmol) in MeCN (10 mL) to give, after column chromatography (*n*-hexane−EtOAc 8:2), (±)-**XIX** as a white solid; yield: 669.9 mg (78%); mp: 115−117 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (d, *J* = 4.7 Hz, 1H), 7.84−7.67 (m, 2H), 7.39 (t, *J* = 5.7 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 2H), 6.71 (d, *J* = 8.2 Hz, 2H), 4.87 (t, *J* = 7.8 Hz, 1H), 3.92 (q, *J* = 7.1 Hz, 2H), 3.71 (s, 3H), 3.14 (dd, *J* = 14.2, 7.1 Hz, 1H), 3.03 (s, 3H), 2.85 (dd, *J* = 14.1, 8.5 Hz, 1H), 1.02 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.0, 158.3, 157.3, 149.7, 137.6, 129.9, 128.1, 126.3, 121.9,

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113.8, 61.0, 60.9, 55.0, 34.8, 31.1, 13.9. ESI-HRMS: Calcd for $C_{18}H_{23}N_2O_5S$ $[M + H]^+$: 379.1328. Found: 379.1322.

*(±)-Ethyl 2-(N-Methylpyridine-2-sulfonamido)-3-(p-tolyl)-propanoate [(±)-**XX**].* Following the typical procedure, (±)-**XII** (389.3 mg, 1.12 mmol) reacted with MeI (208.6 μL, 3.35 mmol) in the presence of K_2CO_3 (308.8 mg, 2.23 mmol) in MeCN (10 mL) to give, after column chromatography (*n*-hexane−EtOAc 8:2), (±)-**XX** as a white solid; yield: 387.3 mg (96%); mp: 121−123 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60 (dt, *J* = 4.7, 1.5 Hz, 1H), 7.87−7.73 (m, 2H), 7.42 (ddd, *J* = 6.7, 4.7, 2.3 Hz, 1H), 7.09−7.00 (m, 4H), 4.93 (dd, *J* = 8.6, 7.0 Hz, 1H), 3.96 (q, *J* = 7.1 Hz, 2H), 3.20 (dd, *J* = 14.1, 7.0 Hz, 1H), 3.07 (s, 3H), 2.90 (dd, *J* = 14.0, 8.5 Hz, 1H), 2.29 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.2, 157.6, 149.8, 137.7, 136.4, 133.2, 129.3, 129.0, 126.3, 122.1, 61.2, 61.0, 35.5, 31.3, 21.2, 14.0. ESI-HRMS: Calcd for $C_{18}H_{23}N_2O_4S$ $[M + H]^+$: 363.1373. Found: 363.1388.

*(±)-Ethyl 3-(4-Fluorophenyl)-2-(N-methylpyridine-2-sulfonamido)propanoate [(±)-**XXI**].* Following the typical procedure, (±)-**XIII** (1.24 g, 3.51 mmol) reacted with MeI (656.3 μL, 10.54 mmol) in the presence of K_2CO_3 (971.4 mg, 7.03 mmol) in MeCN (10 mL) to give, after column chromatography (*n*-hexane−EtOAc 8:2), (±)-**XXI** as a white solid; yield: 1.027 g (80%); mp: 121−123 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 7.76 (td, *J* = 7.7, 1.7 Hz, 1H), 7.71 (ddd, *J* = 7.9, 1.5, 0.9 Hz, 1H), 7.37 (ddd, *J* = 7.4, 4.7, 1.5 Hz, 1H), 7.14−7.04 (m, 2H), 6.83 (t, *J* = 8.7 Hz, 2H), 4.85 (dd, *J* = 8.7, 6.9 Hz, 1H), 3.88 (q, *J* = 7.1 Hz, 2H), 3.14 (dd, *J* = 14.2, 6.9 Hz, 1H), 2.99 (s, 3H), 2.86 (dd, *J* = 14.2, 8.7 Hz, 1H), 0.97 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.6, 161.5 (d, $J_{C\text{-}F}$ = 244.8 Hz), 157.1, 149.6, 137.6, 131.9 (d, $J_{C\text{-}F}$ = 0.7 Hz), 130.4 (d, $J_{C\text{-}F}$ = 8.0 Hz), 126.3, 121.8, 115.1 (d, $J_{C\text{-}F}$ = 21.3 Hz), 61.0, 60.8 (d, $J_{C\text{-}F}$ = 1.3 Hz), 34.7, 31.00, 13.7. ^{19}F{^{1}H} NMR: δ −115.99 (s). ESI-HRMS: Calcd for $C_{17}H_{20}FN_2O_4S$ $[M + H]^+$: 367.1122. Found: 367.1113.

*(±)-Ethyl 3-(4-Chlorophenyl)-2-(N-methylpyridine-2-sulfonamido)propanoate [(±)-**XXII**].* Following the typical procedure, (±)-**XIV** (1422 mg, 3.85 mmol) reacted with MeI (719.9 μL, 11.56 mmol) in the presence of K_2CO_3 (1.07 g, 7.71 mmol) in MeCN (10 mL) to give, after column chromatography (*n*-hexane−EtOAc 8:2), (±)-**XXII** as a white solid; yield: 145 mg (98%); mp: 122−124 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 7.81 (ddd, *J* = 7.8, 7.3, 1.7 Hz, 1H), 7.75 (ddd, *J* = 7.9, 1.5, 0.9 Hz, 1H), 7.43 (ddd, *J* = 7.3, 4.7, 1.5 Hz, 1H), 7.19−7.07 (m, 4H), 4.92 (dd, *J* = 8.8, 6.8 Hz, 1H), 3.98 (q, *J* = 7.1 Hz, 2H), 3.21 (dd, *J* = 14.2, 6.8 Hz, 1H), 3.05 (s, 3H), 2.92 (dd, *J* = 14.2, 8.8 Hz, 1H), 1.08 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.9, 157.5, 149.8, 137.7, 134.9, 132.8, 130.5, 128.7, 126.4, 122.0, 61.4, 60.9, 35.1, 31.3, 14.0. ESI-HRMS: Calcd for $C_{17}H_{20}ClN_2O_4S$ $[M + H]^+$: 383.0832. Found: 383.0827.

*(±)-Ethyl 3-(4-Bromophenyl)-2-(N-methylpyridine-2-sulfonamido)propanoate [(±)-**XXIII**].* Following the typical procedure, (±)-**XV** (1.22 g, 2.94 mmol) reacted with MeI (549.8 μL, 8.83 mmol) in the presence of K_2CO_3 (813.7 mg, 5.89 mmol) in MeCN (10 mL) to give, after column chromatography (*n*-hexane−EtOAc 8:2), (±)-**XXIII** as a white solid; yield: 1.19 g (95%); mp: 118−120 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 7.80 (ddd, *J* = 7.9, 7.4, 1.7 Hz, 1H), 7.73 (ddd, *J* = 7.9, 1.4, 0.9 Hz, 1H), 7.43 (ddd, *J* = 7.4, 4.7, 1.4 Hz, 1H), 7.33−7.27 (m, 2H), 7.07−6.99 (m, 2H), 4.91 (dd, *J* = 8.9, 6.7 Hz, 1H), 3.98 (q, *J* = 7.1 Hz, 2H), 3.18 (dd, *J* = 14.2, 6.7 Hz, 1H), 3.04 (s, 3H), 2.89 (dd, *J* = 14.2, 8.9 Hz, 1H), 1.07 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.8, 157.4, 149.8, 137.7, 135.4, 131.6, 130.8, 126.4, 121.9, 120.8, 61.4, 60.8, 35.2, 31.2, 14.0. ESI-HRMS: Calcd for $C_{17}H_{20}BrN_2O_4S$ $[M + H]^+$: 427.0322. Found: 427.0314.

*(±)-Ethyl 3-(3-Fluorophenyl)-2-(N-methylpyridine-2-sulfonamido)propanoate [(±)-**XXIV**].* Following the typical procedure, (±)-**XVI** (352.4 mg, 1.00 mmol) reacted with MeI (186.8 μL, 3.00 mmol) in the presence of K_2CO_3 (276.3 mg, 2.00 mmol) in MeCN (10 mL) to give, after column chromatography (*n*-hexane−EtOAc 8:2), (±)-**XXIV** as a colorless oil; yield: 311.4 mg (85%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.66 (d, *J* = 4.7 Hz, 1H), 7.86 (m, 2H), 7.48 (m, 1H), 7.24 (m, 1H), 7.03 (d, *J* = 7.7 Hz, 1H), 6.93 (m, 2H), 4.99 (t, *J* = 8.0 Hz, 1H), 4.01 (c, *J* = 7.1 Hz, 2H), 3.27 (dd, *J* = 7.2, 14.0 Hz, 1H), 3.10 (s, 3H), 3.00 (dd, *J* = 8.3, 14.0 Hz, 1H), 1.12 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.8, 162.7 (d, $J_{C\text{-}F}$ = 46.0 Hz), 157.3, 149.8, 138.9 (d, $J_{C\text{-}F}$ = 7.1 Hz), 137.8, 130.0 (d, $J_{C\text{-}F}$ = 9.2 Hz), 126.5, 124.8 (d, $J_{C\text{-}F}$ = 3.0 Hz), 121.9, 115.9 (d, $J_{C\text{-}F}$ = 21.4 Hz), 113.8 (d, $J_{C\text{-}F}$ = 20.9 Hz), 61.2, 60.8, 35.5, 31.2, 13.9. ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$): δ −113.0. ESI-HRMS: Calcd for $C_{17}H_{20}FN_2O_4S$ $[M + H]^+$: 367.1122. Found: 367.1128.

*(±)-Ethyl 2-(N-Methylpyridine-2-sulfonamido)-3-(naphthalen-1-yl)propanoate [(±)-**XXV**].* Following the typical procedure, (±)-**XVII** (384.5 mg, 1.00 mmol) reacted with MeI (186.8 μL, 3.00 mmol) in the presence of K_2CO_3 (276.3 mg, 2.00 mmol) in MeCN (10 mL) to give, after column chromatography (*n*-hexane−EtOAc 8:2), (±)-**XXV** as a colorless oil; yield: 354.6 mg (89%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.46 (d, *J* = 4.3 Hz, 1H), 7.81 (m, 1H), 7.73 (m, 2H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.59−7.51 (m, 2H), 7.50−7.46 (m, 2H), 7.35 (dd, *J* = 1.1, 8.6 Hz, 1H), 7.20 (m, 1H), 5.12 (dd, *J* = 6.8, 8.9 Hz, 1H), 4.05 (c, *J* = 7.2 Hz, 2H), 3.44 (dd, *J* = 6.7, 14.0 Hz, 1H), 3.18 (s, 3H), 3.13 (dd, *J* = 9.8, 14.0 Hz, 1H), 1.13 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.0, 157.3, 149.5, 137.3, 133.9, 133.3, 132.4, 128.2, 127.8, 127.6, 127.1, 126.0, 125.7, 121.5, 61.3, 61.1, 35.9, 31.3, 14.0. ESI-HRMS: Calcd for $C_{21}H_{23}N_2O_4S$ $[M + H]^+$: 399.1379. Found: 399.1372.

*(±)-Ethyl 2-(N-Methylpyridine-2-sulfonamido)-3-(naphthalen-2-yl)propanoate [(±)-**XXVI**].* Following the typical procedure, (±)-**XVIII** (384.5 mg, 1.00 mmol) reacted with MeI (186.8 μL, 3.00 mmol) in the presence of K_2CO_3 (276.3 mg, 2.00 mmol) in MeCN (10 mL) to give, after column chromatography (*n*-hexane−EtOAc 8:2), (±)-**XXVI** as a colorless oil; yield: 318.8 mg (80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.58 (d, *J* = 4.5 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.74−7.69 (m, 3H), 7.61−7.50 (m, 2H), 7.39 (m, 1H), 7.32−7.28 (m, 2H), 5.17 (t, *J* = 7.3 Hz, 1H), 3.98 (c, *J* = 7.0 Hz, 2H), 3.74 (dd, *J* = 8.0, 14.0 Hz, 1H), 3.50 (dd, *J* = 7.3, 14.0 Hz, 2H), 3.26 (s, 3H), 1.03 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 170.2, 157.3, 149.6, 137.6, 133.8, 132.2, 131.8, 128.9, 127.9, 127.7, 126.4, 126.3, 125.7, 125.3, 123.4, 121.8, 61.1, 60.0, 33.4, 31.2, 13.9. ESI-HRMS: Calcd for $C_{21}H_{23}N_2O_4S$ $[M + H]^+$: 399.1379. Found: 399.1375.

*N-((1R,2S)-1-Methoxy-1-phenylpropan-2-yl)-N-methylpyridine-2-sulfonamide [(−)-**20**].* Potassium hydride (1.04 g of a 35% suspension in oil, 364 mg, 9.1 mmol) was weighed into a 100 mL 3-neck round-bottom flask. The KH was washed with hexane (3 × 4 mL) to remove the mineral oil, and THF (7 mL) was added to the dry KH powder. To the resulting suspension, cooled to 0 °C, was added dropwise (over 10 min) a soln of L-norpseudoephedrine (1.37 g, 9.1 mmol) in THF (15 mL). The reaction was stirred at room temperature for 10 min before MeI (0.567 mL, 9.1 mmol) was added. The mixture was stirred for 1.5 h before a 2 N soln of sodium thiosulfate (25 mL) was added. The mixture was extracted with diethyl ether (3 × 50 mL), and the combined organic phase was dried ($MgSO_4$) and concentrated to dryness. The resulting methyl ether intermediate [(1*R*,2*S*)-**XXVII**] was of sufficient purity for use in the next step.

To a solution of crude (1*R*,2*S*)-**XXVII** (9.1 mmol) and pyridine (1.08 mL, 13.65 mmol) in dry THF (20 mL), cooled to −5 °C and under an Ar atmosphere, was added dropwise a solution of 2-pyridylsulfonyl chloride (2.4 g, 13.65 mmol) in dry THF (5 mL). The mixture was stirred at room temperature for 18 h, and then it was filtered through a small pad of silica gel and the filtrate concentrated to dryness. The resulting solid residue was triturated in a 1:1 mixture of *n*-hexane−water (20 mL) and filtered, to give (1*R*,2*S*)-**XXVIII** as a white solid that was used in the next step without further purification.

To a solution of (1*R*,2*S*)-**XXVIII** (9.1 mmol) and K_2CO_3 (2.51 g, 18.2 mmol) in MeCN (20 mL) at room temperature was added methyl iodide (1.0 mL, 16.1 mmol). The reaction mixture was refluxed for 16 h before it was concentrated to dryness. The residue was purified by column chromatography (*n*-hexane−EtOAc 8:2) to afford the desired compound (1*R*,2*S*)-**20** as a colorless oil; yield: 2.011g (69%).

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^{1}H NMR (300 MHz, $CDCl_3$): δ 8.45 (d, J = 4.8 Hz, 1H), 7.83−7.51 (m, 2H), 7.23 (ddd, J = 7.4, 4.7, 1.4 Hz, 1H), 7.18−6.88 (m, 5H), 4.29 (d, J = 3.5 Hz, 1H), 4.00 (dd, J = 7.0, 3.4 Hz, 1H), 3.05 (s, 3H), 2.83 (s, 3H), 0.79 (d, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 155.6, 147.6, 136.8, 135.4, 125.9, 125.2, 124.3, 123.9, 120.0, 85.3, 56.1, 54.8, 28.6, 8.1. ESI-HRMS: Calcd for $C_{16}H_{21}N_2O_3S$ $(M + H)^+$: 321,1267. Found: 321,1261. $[\alpha]_D^{298}$ = −68.23 (c 0.68, $CHCl_3$).

*Typical Procedure for the C−H Activation Reaction: Synthesis of (S,E)-Butyl 3-(2-(3-Ethoxy-2-(N-methylpyridine-2-sulfonamido)-3-oxopropyl)phenyl)acrylate [(S)-**2**].* A screw-capped test tube was charged with *N*-(2-pyridyl)sulfonyl phenylalanine ethyl ester derivative (*S*)-**1** (52.3 mg, 0.15 mmol), 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol), and $Pd(OAc)_2$ (3.4 mg, 0.015 mmol). The tube was sealed with a rubber septum and then evacuated and backfilled with nitrogen (3×) before acetic acid (1 mL) and butyl acrylate (43.0 μL, 0.30 mmol) were successively added. The septum was replaced with a Teflon-coated screw cap, and the resulting solution was heated and vigorously stirred at 110 °C for 6 h (for the rest of substrates the reaction time was extended to overnight, typically 18 h). Then, it was cooled to room temperature and diluted with CH_2Cl_2 (5 mL). The resulting suspension was filtered through a plug of Celite (washed with CH_2Cl_2). The clear solution was washed with a sat. aq soln of $NaHCO_3$ (2 × 10 mL), dried with anhydrous $MgSO_4$, and then concentrated to dryness. The residue was then purified by column chromatography (*n*-hexane−EtOAc 85:15) to afford (*S*)-**2** as a yellow oil; yield: 59.8 mg (84%).

$[\alpha]_D^{20}$= −13.7 (c 0.89, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (dd, J = 0.6, 7.5 Hz, 1H), 7.98 (d, J = 15.0 Hz, 1H), 7.75−7.70 (m, 2H), 7.55−7.40 (m, 1H), 7.40−7.35 (m, 2H), 7.30−7.10 (m, 2H), 6.73 (d, J = 15.0 Hz, 1H), 4.80 (t, J = 8.0 Hz, 1H), 3.95−3.80 (m, 2H), 3.33 (dd, J = 7.3 Hz, 1H), 3.10 (dd, J = 7.3 Hz, 1H), 3.01 (s, 3H), 1.73 (m, 2H), 1.48 (m, 2H), 1.10 (t, J = 7.0 Hz, 3H), 0.98 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.7, 166.8, 157.4, 149.8, 141.3, 137.6, 135.8, 133.8, 130.6, 130.0, 127.5, 126.9, 126.3, 122.0, 120.8, 64.5, 61.3, 60.7, 32.6, 31.4, 30.8, 19.2, 13.9, 13.8. ESI-HRMS: Calcd for $C_{24}H_{31}N_2O_6S$ $[M + H]^+$: 475.1897. Found: 475.1891. HPLC: Daicel Chiralpak AD, hexane−isopropanol 90−10, flow rate 0.7 mL/min (ë = 254 nm), t_R: 28.0 min (3*R*)-**2** and 33.8 min (3*S*)-**2**.

*(±)-(E)-Methyl 3-(2-(3-Ethoxy-2-(N-methylpyridine-2-sulfonamido)-3-oxopropyl)phenyl)acrylate [(±)-**3**].* Following the typical procedure, (±)-**1** (52.3 mg, 0.15 mmol) reacted with methyl acrylate (27.0 μL, 0.30 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol) in acetic acid (1 mL), to afford, after purification by column chromatography (*n*-hexane−EtOAc 85:15), product (±)-**3** as yellow oil; yield: 49.5 mg (77%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (d, J = 4.5 Hz, 1H), 7.96 (d, J = 15.9 Hz, 1H), 7.80−7.70 (m, 3H), 7.45 (d, J = 7.7 Hz, 1H), 7.35 (m, 1H), 7.25−7.15 (m, 2H), 6.29 (d, J = 15.9 Hz, 1H), 4.84 (m, 1H), 3.88 (dc, J = 2.2, 7.0 Hz, 2H), 3.70 (s, 3H), 3.31 (dd, J = 7.0, 14.0 Hz, 1H), 3.06 (dd, J = 7.0, 14.0 Hz, 1H), 3.01 (s, 3H), 0.99 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.7, 167.1, 157.4, 149.8, 141.6, 137.7, 135.9, 133.8, 130.7, 130.1, 127.6, 126.9, 126.3, 122.1, 120.4, 61.3, 60.8, 51.7, 32.7, 31.4, 13.9. ESI-HRMS: Calcd for $C_{21}H_{25}N_2O_6S$ $[M + H]^+$: 433.1428. Found: 433.1420.

*(±)-(E)-Ethyl 3-(2-(2-(Dimethoxyphosphoryl)vinyl)phenyl)-2-(N-methylpyridine-2-sulfonamido)propanoate [(±)-**4**].* Following the typical procedure, (±)-**1** (52.3 mg, 0.15 mmol) reacted with dimethyl vinylphosphonate (35.6 μL, 0.30 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol) in acetic acid (1 mL), to afford, after purification by column chromatography (*n*-hexane−EtOAc 50:50), product (±)-**4** as a yellow oil, yield: 49.3 mg (68%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (m, 1H), 7.82−7.74 (m, 3H), 7.44 (dd, J = 1.9, 7.7 Hz, 1H), 7.36 (m, 1H), 7.25−7.15 (m, 3H), 6.12 (t, J = 7.7 Hz, 1H), 4.88 (m, 1H), 3.73 (d, J = 5.0 Hz, 2H), 3.71 (d, J = 4.8 Hz, 6H), 3.31 (dd, J = 6.6, 14.2 Hz, 1H), 3.07 (dd, J = 8.5, 14.2 Hz, 1H), 3.01 (s, 3H), 0.98 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.7, 157.3, 149.9, 146.3 (d, $J_{C\text{-}P}$ = 5.0 Hz), 137.7, 135.5, 134.4 (d, $J_{C\text{-}P}$ = 43.7 Hz), 130.7, 130.2, 127.6, 126.8, 126.4, 122.1, 115.5 (d, $J_{C\text{-}P}$ = 160.6 Hz), 61.3, 60.7, 52.6, 32.7, 31.4, 13.9. ESI-HRMS: Calcd for $C_{21}H_{28}N_2O_7PS$ $[M + H]^+$: 483.1349. Found: 483.1356.

*(S,E)-Ethyl 2-(N-Methylpyridine-2-sulfonamido)-3-(2-(2-(phenylsulfonyl)vinyl)phenyl)-propanoate [(S)-**5**].* Following the typical procedure, (*S*)-**1** (52.3 mg, 0.15 mmol) reacted with phenyl vinyl sulfone (50.46 mg, 0.30 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol) in acetic acid (1 mL), to afford, after purification by column chromatography (*n*-hexane−EtOAc 80:20), product (*S*)-**5** as a yellow oil, yield: 61.1 mg (79%).

$[\alpha]_D^{20}$= −11.0 (c 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (dd, J = 0.6, 4.5 Hz, 1H), 7.98 (d, J = 15.0 Hz, 1H), 7.93 (d, J = 7.9 Hz, 2H), 7.75−7.70 (m, 2H), 7.55−7.40 (m, 3H), 7.40−7.35 (m, 2H), 7.30−7.10 (m, 3H), 6.73 (d, J = 15.0 Hz, 1H), 4.80 (t, J = 8.0 Hz, 1H), 3.95−3.80 (m, 2H), 3.33 (dd, J = 7.3 Hz, 1H), 3.10 (dd, J = 7.3 Hz, 1H), 3.01 (s, 3H), 0.98 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.5, 157.2, 149.9, 140.5, 139.4, 137.7, 136.6, 133.8, 131.7, 131.1, 131.0, 129.6, 129.4, 127.9, 127.7, 127.4, 126.5, 122.1, 61.4, 61.0, 32.7, 31.4, 13.9. ESI-HRMS: Calcd for $C_{25}H_{27}N_2O_6S_2$ $[M + H]^+$: 515.1305. Found: 515.1310. HPLC: Daicel Chiralpak AD, hexane−isopropanol 85−15, flow rate 0.7 mL/min (ë = 254 nm), t_R: 87.0 min (3*S*)-**5** and 93.4 min (3*R*)-**5**.

*(±)-(E)-Ethyl 2-(N-Methylpyridine-2-sulfonamido)-3-(2-(2-(phenoxysulfonyl)vinyl)phenyl)-propanoate [(±)-**6**].* Following the typical procedure, (±)-**1** (52.3 mg, 0.15 mmol) reacted with phenyl vinyl sulfonate (55.2 mg, 0.30 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol) in acetic acid (1 mL), to afford, after purification by column chromatography (*n*-hexane−EtOAc 80:20), product (±)-**6** as a yellow oil, yield: 58.1 mg (73%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (m, 1H), 7.83 (d, J = 15.1 Hz, 1H), 7.76−7.48 (m, 2H), 7.45−7.20 (m, 10H), 6.73 (d, J = 15.1 Hz, 1H), 4.77 (dd, J = 6.3, 8.8 Hz, 1H), 3.88 (dc, J = 1.6, 7.6 Hz, 2H), 3.21 (dd, J = 6.3, 14.5 Hz, 1H), 2.99−2.90 (m, 4H), 0.98 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.3, 157.2, 149.8, 149.6, 143.3, 137.7, 136.9, 131.4, 131.3, 131.0, 129.9, 127.9, 127.4, 127.2, 126.4, 123.1, 122.5, 122.1, 61.5, 60.9, 32.4, 31.9, 13.9. ESI-HRMS: Calcd for $C_{25}H_{27}N_2O_7S_2$ $[M + H]^+$: 531.1254. Found: 531.1259.

*(±)-(E)-Ethyl 2-(N-Methylpyridine-2-sulfonamido)-3-(2-(3-oxobut-1-en-1-yl)phenyl)propanoate [(±)-**7**].* Following the typical procedure, (±)-**1** (52.3 mg, 0.15 mmol) reacted with 3-buten-2-one (24.3 μL, 0.30 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol) in acetic acid (1 mL), to afford, after purification by column chromatography (diethyl ether−hexane 50:50), product (±)-**7** as a yellow oil, yield: 26.5 mg (43%).

^{1}H NMR (300 MHz, $CDCl_3$): 8.62 (dt, J = 4.7, 1.4 Hz, 1H), 7.94 (d, J = 16.1 Hz, 1H), 7.87−7.81 (m, 2H), 7.61−7.55 (m, 1H), 7.44 (q, J = 4.6 Hz, 1H), 7.31−7.22 (m, 2H), 6.64 (d, J = 16.1 Hz, 1H), 4.90 (dd, J = 8.3, 6.9 Hz, 1H), 3.90 (q, J = 7.1 Hz, 2H), 3.40 (dd, J = 14.0, 8.3 Hz, 1H), 3.23 (dd, J = 14.0, 6.9 Hz, 1H), 3.09 (s, 3H), 2.44 (s, 3H), 0.98 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 199.1, 169.6, 157.3, 149.9, 140.3, 137.9, 136.0, 134.1, 131.3, 130.2, 130.1, 127.9, 127.0, 126.6, 122.4, 61.3, 60.7, 33.7, 31.4, 27.4, 14.0. ESI-HRMS: Calcd for $C_{21}H_{24}N_2O_5S$ $[M + H]^+$: 417.1479. Found: 417.1510.

*(±)-(E)-Ethyl 2-(N-Methylpyridine-2-sulfonamido)-3-(2-(3-oxoprop-1-en-1-yl)phenyl)propanoate [(±)-**8**].* Following the typical procedure, (±)-**1** (52.3 mg, 0.15 mmol) reacted with acrolein (20.1 μL, 0.30 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol) in acetic acid (1 mL), to afford, after purification by column chromatography (diethyl ether−hexane 50:50), product (±)-**8** as a yellow oil, yield: 15.3 mg (25%).

^{1}H NMR (300 MHz, $CDCl_3$): 9.77 (d, J = 7.7 Hz, 1H), 8.63 (d, J = 4.3 Hz, 1H), 8.05 (d, J = 15.7 Hz, 1H), 7.91−7.84 (m, 2H), 7.66−7.60 (m, 1H), 7.46 (td, J = 5.1, 3.0 Hz, 1H), 7.36−7.27 (m, 3H), 6.69 (dd, J = 15.7, 7.7 Hz, 1H), 4.90 (dd, J = 8.9, 6.1 Hz, 1H), 3.92 (qd, J = 7.1, 1.0 Hz, 2H), 3.43 (dd, J = 13.9, 8.9 Hz, 1H), 3.28 (dd, J = 13.9, 6.2 Hz,

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1H), 3.08 (s, 3H), 0.98 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 94.3, 169.5, 157.3, 149.9, 149.4, 137.9, 136.3, 133.5, 131.6, 131.0, 130.8, 128.0, 127.2, 126.7, 122.5, 61.4, 60.8, 33.8, 31.4, 14.0. ESI-HRMS: Calcd for $C_{20}H_{23}N_2O_5S$ $[M + H]^+$: 403.1328. Found: 403.1322.

*(±)-(E)-Ethyl 2-(N-Methylpyridine-2-sulfonamido)-3-(2-(2-(perfluorophenyl)vinyl)phenyl)-propanoate [(±)-**9**].* Following the typical procedure, (±)-**1** (52.3 mg, 0.15 mmol) reacted with 2,3,4,5,6-pentafluorostyrene (41.4 μL, 0.30 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol) in acetic acid (1 mL), to afford, after purification by column chromatography (diethyl ether−hexane 50:50), product (±)-**9** as a yellow oil, yield: 45.0 mg (56%).

^1H NMR (300 MHz, $CDCl_3$): 8.58 (s, 1H), 7.83−7.71 (m, 2H), 7.76 (d, J = 16.5 Hz, 1H), 7.56 (dd, J = 6.9, 1.8 Hz, 1H), 7.44−7.37 (m, 1H), 7.29−7.20 (m, 3H), 6.86 (d, J = 16.5 Hz, 1H), 4.94 (dd, J = 8.5, 6.7 Hz, 1H), 3.96 (q, J = 7.1 Hz, 2H), 3.42 (dd, J = 14.3, 6.7 Hz, 1H), 3.11 (dd, J = 14.3, 6.7 Hz, 1H), 3.11 (s, 3H), 1.06 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 169.8, 157.3, 149.6, 144.8 (q, $J_{C\text{-}F}$ = 252.12 Hz), 139.8 (q, $J_{C\text{-}F}$ = 252.12 Hz), 137.6, 137.6 (q, $J_{C\text{-}F}$ = 252.12 Hz), 136.0, 134.7, 134.5 (td, $J_{C\text{-}F}$ = 8.1, 2.4 Hz), 130.6, 128.8, 127.6, 126.3, 126.1, 121.9, 115.3 (d, $J_{C\text{-}F}$ = 3.2 Hz), 112.43 (m), 61.2, 60.5, 33.2, 31.3, 13.8. $^{19}F\{^1H\}$ NMR: δ −142.55 (dd, $J_{C\text{-}F}$ = 21.2, 7.6 Hz, 2F), −156.30 (t, $J_{C\text{-}F}$ = 20.8 Hz, 1F), −162.94 (td, $J_{C\text{-}F}$ = 21.2, 7.6 Hz, 2F). ESI-HRMS: Calcd for $C_{25}H_{22}F_5N_2O_4S$ $[M + H]^+$: 541.1215. Found: 541.1251.

*(±)-(E)-Ethyl 2-(N-Methylpyridine-2-sulfonamido)-3-(2-(3-nitrostyryl)phenyl)propanoate [(±)-**10**].* Following the typical procedure, (±)-**1** (52.3 mg, 0.15 mmol) reacted with 3-nitrostyrene (41.8 μL, 0.30 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol) in acetic acid (1 mL), to afford, after purification by column chromatography (diethyl ether−hexane 50:50), product (±)-**10** as a yellow oil, yield: 36.3 mg (49%).

^1H NMR (300 MHz, $CDCl_3$): 8.58 (dt, J = 4.7, 1.4 Hz, 1H), 8.38 (t, J = 2.1 Hz, 1H), 8.10−8.05 (m, 1H), 7.95 (dt, J = 8.0, 1.5 Hz, 1H), 7.84−7.80 (m, 2H), 7.71 (d, J = 16.0 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.49 (t, J = 7.9 Hz, 1H), 7.45−7.38 (m, 1H), 7.30−7.24 (m, 1H), 7.22−7.18 (m, 2H), 7.08 (d, J = 15.8 Hz, 1H), 5.00 (dd, J = 8.5, 6.7 Hz, 1H), 3.94 (q, J = 7.1 Hz, 2H), 3.40 (dd, J = 13.8, 8.5 Hz, 1H), 3.28 (dd, J = 13.8, 6.7 Hz, 1H), 3.10 (s, 3H), 1.00 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 169.8, 157.2, 149.8, 148.9, 139.3, 137.8, 136.0, 134.5, 132.6, 131.1, 129.6, 129.0, 128.7, 128.4, 127.8, 126.6, 126.2, 122.5, 122.2, 121.7, 61.2, 60.5, 34.0, 31.2, 14.0. ESI-HRMS: Calcd for $C_{25}H_{26}N_3O_6S$ $[M + H]^+$: 496.1537. Found: 496.1541.

*(±)-(E)-Ethyl 2-(N-Methylpyridine-2-sulfonamido)-3-(2-(3-(trifluoromethyl)styryl)phenyl)-propanoate [(±)-**11**].* Following the typical procedure, (±)-**1** (52.3 mg, 0.15 mmol) reacted with 3-(trifluoromethyl)styrene (44.5 μL, 0.30 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol) in acetic acid (1 mL), to afford, after purification by column chromatography (diethyl ether−hexane 50:50), product (±)-**11** as a yellow oil, yield: 28.7 mg (37%).

^1H NMR (300 MHz, $CDCl_3$): 8.56 (s, 1H), 7.86−7.73 (m, 4H), 7.62 (d, J = 15.6 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.52−7.48 (m, 1H), 7.48−7.43 (m, 1H), 7.43−7.35 (m, 1H), 7.31−7.23 (m, 1H), 7.21−7.16 (m, 2H), 7.05 (d, J = 16.1 Hz, 1H), 5.00 (dd, J = 8.3, 6.9 Hz, 1H), 3.93 (q, J = 7.1 Hz, 2H), 3.39 (dd, J = 13.9, 8.3 Hz, 1H), 3.26 (dd, J = 13.8, 6.8 Hz, 1H), 3.11 (s, 3H), 1.00 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 169.93, 157.30, 149.83, 138.29, 137.79), 136.38, 134.33, 131.09 (q, $J_{C\text{-}F}$ = 32.24 Hz), 131.05, 129.99, 129.20, 128.14, 127.71, 127.52, 126.54, 126.17, 124.25 (q, $J_{C\text{-}F}$ = 3.8 Hz), 123.77 (q, $J_{C\text{-}F}$ = 3.77 Hz), 122.44, 61.23, 60.47, 33.93, 31.31, 13.97. The CF_3 carbon was not observed, in spite of the use of long accumulation trials. $^{19}F\{^1H\}$ NMR: δ −62.75. ESI-HRMS: Calcd for $C_{26}H_{25}F_3N_2O_4S$ $[M + H]^+$: 519.1560. Found: 519.1578.

*(±)-(E)-Butyl 3-(2-(3-Ethoxy-2-(N-methylpyridine-2-sulfonamido)-3-oxopropyl)-5-methoxyphenyl)-acrylate [(±)-**12**].* Following the typical procedure, sulfonamide (±)-**XIX** (56.8 mg, 0.15 mmol) reacted with butyl acrylate (43.0 μL, 0.30 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol) in acetic acid (1 mL), to afford, after purification by column chromatography (*n*-hexane−EtOAc 80:20), product (±)-**12** as a yellow oil, yield: 53.7 mg (71%).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.54 (d, J = 4.5 Hz, 1H), 7.90 (d, J = 15.6 Hz, 1H), 7.80−7.65 (m, 2H), 7.35 (m, 1H), 7.07 (d, J = 8.3 Hz, 1H), 6.94 (d, J = 2.6 Hz, 1H), 6.75 (dd, J = 2.6, 8.3 Hz, 1H), 6.26 (d, J = 15.6 Hz, 1H), 4.79 (dd, J = 2.8, 8.7 Hz, 1H), 4.14 (t, J = 6.6 Hz, 2H), 3.90 (dc, J = 1.0, 7.9 Hz, 2H), 3.73 (s, 3H), 3.25 (dd, J = 6.6, 14.1 Hz, 1H), 3.01 (m, 4H), 1.62 (m, 2H), 1.36 (m, 2H), 1.00 (t, J = 7.1 Hz, 3H), 0.89 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 169.7, 166.7, 158.7, 157.5, 149.7, 141.3, 137.6, 134.8, 131.8, 128.1, 126.2, 122.0, 120.8, 116.1, 111.5, 64.5, 61.2, 60.9, 55.3, 31.9, 31.4, 30.8, 19.2, 13.9, 13.7. ESI-HRMS: Calcd for $C_{25}H_{33}N_2O_7S$ $[M + H]^+$, 505.2003. Found 505.2009.

*(±)-(E)-Butyl 3-(2-(3-Ethoxy-2-(N-methylpyridine-2-sulfonamido)-3-oxopropyl)-5-methylphenyl)-acrylate [(±)-**13**].* Following the typical procedure, sulfonamide (±)-**XX** (54.5 mg, 0.15 mmol) reacted with butyl acrylate (43.0 μL, 0.30 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol) in acetic acid (1 mL), to afford, after purification by column chromatography (*n*-hexane−EtOAc 80:20), product (±)-**13** as a yellow oil; yield: 31.3 mg (43%).

^1H NMR (300 MHz, $CDCl_3$): δ 8.61 (dt, J = 4.8, 1.5 Hz, 1H), 7.98 (d, J = 15.7 Hz, 1H), 7.85−7.75 (m, 2H), 7.42 (ddd, J = 6.7, 4.7, 2.1 Hz, 1H), 7.33 (d, J = 1.8 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.08 (dd, J = 7.8, 1.8 Hz, 1H), 6.34 (d, J = 15.7 Hz, 1H), 4.89 (dd, J = 8.8, 6.6 Hz, 1H), 4.21 (t, J = 6.7 Hz, 2H), 3.97 (qd, J = 7.1, 1.4 Hz, 2H), 3.35 (dd, J = 14.4, 6.6 Hz, 1H), 3.08 (s, 3H), 3.07 (dd, J = 14.4, 8.8 Hz, 1H), 2.32 (s, 3H), 1.73−1.64 (m, 2H), 1.48−1.40 (m, 2H), 1.07 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 169.9, 167.0, 157.5, 149.8, 141.5, 137.7, 137.1, 133.6, 133.0, 131.0, 130.7, 127.5, 126.3, 122.1, 120.5, 64.6, 61.4, 60.9, 32.3, 31.5, 30.9, 21.2, 19.3, 14.0, 13.9. ESI-HRMS: Calcd for $C_{25}H_{32}N_2NaO_6S$ $[M + Na]^+$: 511.1873. Found: 511.1867.

*(±)-(E)-Butyl 3-(2-(3-Ethoxy-2-(N-methylpyridine-2-sulfonamido)-3-oxopropyl)-5-fluorophenyl)-acrylate [(±)-**14**].* Following the typical procedure, sulfonamide (±)-**XXI** (55.0 mg, 0.15 mmol) reacted with butyl acrylate (43.0 μL, 0.30 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol) in acetic acid (1 mL), to afford, after purification by column chromatography (*n*-hexane−EtOAc 80:20), product (±)-**14** as a yellow oil; yield: 29.6 mg (40%).

^1H NMR (300 MHz, $CDCl_3$): δ 8.65 (d, J = 3.7 Hz, 1H), 7.98 (d, J = 15.8 Hz, 1H), 7.90−7.80 (m, 2H), 7.47 (m, 1H), 7.30−7.13 (m, 2H), 7.01 (m, 1H), 6.37 (d, J = 15.8 Hz, 1H), 4.91 (m, 1H), 4.25 (t, J = 6.8 Hz, 2H), 4.01 (m, 2H), 3.40 (dd, J = 6.4, 14.5 Hz, 1H), 3.16−3.10 (m, 4H), 1.73 (m, 2H), 1.48 (m, 2H), 1.11 (t, J = 7.2 Hz, 3H), 1.00 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 169.5, 166.4, 157.4, 149.8, 140.1 (2C), 137.7, 135.7 (d, $J_{C\text{-}F}$ = 7.3 Hz), 132.4 (d, $J_{C\text{-}F}$ = 7.3 Hz), 131.7, 126.3, 122.0, 121.9, 116.9 (d, $J_{C\text{-}F}$ = 22.0 Hz), 113.2 (d, $J_{C\text{-}F}$ = 22.6 Hz), 64.7, 61.4, 60.9, 32.0, 31.4, 30.7, 19.2, 13.9, 13.7. $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$): δ −114.7. ESI-HRMS: Calcd for $C_{24}H_{30}FN_2O_6S$ $[M + H]^+$: 493.1803. Found: 493.1805.

*(±)-(E)-Butyl 3-(5-Chloro-2-(3-ethoxy-2-(N-methylpyridine-2-sulfonamido)-3-oxopropyl)phenyl)-acrylate [(±)-**15**].* Following the typical procedure, sulfonamide (±)-**XXII** (57.5 mg, 0.15 mmol) reacted with butyl acrylate (43.0 μL, 0.30 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol) in acetic acid (1 mL), to afford, after purification by column chromatography (*n*-hexane−EtOAc 80:20), product (±)-**15** as yellow oil; yield: 18.2 mg (24%). It should be noted that the difficulty in the complete chromatographic separation of the products from the starting material and trace amount of unidentified byproducts resulted in low yields upon isolation.

^1H NMR (300 MHz, $CDCl_3$): δ 8.60 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 7.91 (d, J = 15.7 Hz, 1H), 7.82 (td, J = 7.7, 1.7 Hz, 1H), 7.76 (tt, J = 7.9, 1.0 Hz, 1H), 7.46 (d, J = 2.1 Hz, 1H), 7.44 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 7.20 (dd, J = 8.3, 2.1 Hz, 1H), 7.17−7.15 (m, 1H), 6.34 (d, J

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= 15.7 Hz, 1H), 4.87 (dd, J = 9.0, 6.4 Hz, 1H), 4.21 (t, J = 6.7 Hz, 2H), 4.03−3.98 (m, 2H), 3.35 (dd, J = 14.5, 6.4 Hz, 1H), 3.08 (dd, J = 14.5, 9.0 Hz, 1H), 3.07 (s, 3H), 1.71−1.65 (m, 2H), 1.46−1.40 (m, 2H), 1.09 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR: δ 169.5, 166.5, 157.4, 149.9, 139.9, 137.8, 135.6, 134.4, 133.4, 132.1, 129.9, 126.8, 126.4, 122.1, 122.0, 64.7, 61.6, 60.8, 32.1, 31.5, 30.8, 19.3, 14.0, 13.8. ESI-HRMS: Calcd for $C_{24}H_{30}ClN_2O_6S$ $[M + H]^+$: 509.1508. Found: 509.1499.

*(±)-(E)-Butyl 3-(5-Bromo-2-(3-ethoxy-2-(N-methylpyridine-2-sulfonamido)-3-oxopropyl)phenyl)-acrylate [(±)-**16**].* Following the typical procedure, sulfonamide (±)-**XXIII** (64.0 mg, 0.15 mmol) reacted with butyl acrylate (43.0 μL, 0.30 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol) in acetic acid (1 mL), to afford, after purification by column chromatography (*n*-hexane−EtOAc 80:20), product (±)-**16** as a yellow oil; yield: 23.8 mg (29%). It should be noted that the difficulty in the complete chromatographic separation of the products from the starting material and trace amount of unidentified byproducts resulted in low yields upon isolation.

^1H NMR (300 MHz, $CDCl_3$): δ 8.60 (ddd, J = 4.6, 1.6, 0.8 Hz, 1H), 7.90 (d, J = 15.7 Hz, 1H), 7.82 (td, J = 7.7, 1.7 Hz, 1H), 7.75 (tt, J = 7.9, 1.0 Hz, 1H), 7.61 (d, J = 2.1 Hz, 1H), 7.44 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 7.33 (ddd, J = 8.7, 7.4, 2.0 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.33 (d, J = 15.7 Hz, 1H), 4.88 (dd, J = 9.0, 6.3 Hz, 1H), 4.21 (t, J = 6.7 Hz, 2H), 4.03−3.99 (m, 2H), 3.33 (dd, J = 14.5, 6.3 Hz, 1H), 3.07 (s, 3H), 3.07 (dd, J = 14.5, 5.9 Hz, 1H), 1.73−1.64 (m, 2H), 1.47−1.41 (m, 2H), 1.10 (t, J = 7.2 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR: δ 169.6, 166.5, 157.4, 149.9, 139.8, 137.8, 135.9, 134.9, 132.8, 132.3, 129.8, 126.4, 122.2, 122.0, 121.5, 64.8, 61.6, 60.7, 32.2, 31.5, 30.8, 19.3, 14.1, 13.8. ESI-HRMS: Calcd for $C_{24}H_{30}BrN_2O_6S$ $[M + H]^+$: 553.1002. Found: 553.1027.

*(±)-(E)-Butyl 3-(2-(3-Ethoxy-2-(N-methylpyridine-2-sulfonamido)-3-oxopropyl)-6-fluorophenyl)-acrylate [(±)-**17a**] and (±)-(E)-Butyl 3-(2-(3-Ethoxy-2-(N-methylpyridine-2-sulfonamido)-3-oxopropyl)-4-fluorophenyl)acrylate [(±)-**17b**].* Following the typical procedure, sulfonamide (±)-**XXIV** (55.0 mg, 0.15 mmol) reacted with butyl acrylate (43.0 μL, 0.30 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol) in acetic acid (1 mL), to afford a 1:1.3 isomeric mixture of (**17a** + **17b**), which was separated upon purification by column chromatography (*n*-hexane−EtOAc 80:20).

Product (±)-**17a** was obtained as a yellow oil; yield: 22.6 mg (31%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.53 (d, J = 4.5 Hz, 1H), 7.70−7.65 (m, 2H), 7.65 (d, J = 16.0 Hz, 1H), 7.35 (m, 1H), 7.15 (m, 1H), 7.00 (d, J = 7.5 Hz, 1H), 6.90 (m, 1H), 6.47 (d, J = 16.0 Hz, 1H), 4.84 (dd, J = 6.0, 9.0 Hz, 1H), 4.14 (t, J = 6.7 Hz, 2H), 3.90 (dc, J = 2.0, 4.6 Hz, 2H), 3.32 (dd, J = 9.0, 14.5 Hz, 1H), 3.06 (dd, J = 9.0, 14.5 Hz, 1H), 3.00 (m, 3H), 1.62 (m, 2H), 1.36 (m, 2H); 1.01 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 169.5, 166.9, 157.4, 149.8, 138.4, 137.6, 134.9, 130.5 (d, $J_{C\text{-}F}$ = 13.0 Hz), 126.3, 126.2 (d, $J_{C\text{-}F}$ = 23.4 Hz), 125.5, 125.3, 121.9, 115.1, 114.1, 64.6, 61.4, 60.6, 32.7, 31.5, 30.7, 19.2, 13.9, 13.7. $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$): δ −110.2. ESI-HRMS: Calcd for $C_{24}H_{30}FN_2O_6S$ $[M + H]^+$: 493.1803. Found: 493.1808.

Product (±)-**17b** was obtained as a yellow oil; yield: 30.5 mg (41%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.55 (m, 1H), 7.87 (d, J = 15.8 Hz, 1H), 7.76−7.74 (m, 2H), 7.45 (dd, J = 6.0, 8.4 Hz, 1H), 7.37 (m, 1H), 6.90−6.83 (m, 2H), 6.24 (d, J = 15.8 Hz, 1H), 4.84 (dd, J = 4.7, 8.6 Hz, 1H), 4.14 (t, J = 6.5 Hz, 2H), 3.91 (c, J = 6.0 Hz, 2H), 3.30 (dd, J = 6.7, 14.3 Hz, 1H), 3.06 (m, 1H), 3.00 (s, 3H), 1.62 (m, 2H), 1.35 (m, 2H); 1.01 (t, J = 7.1 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 169.5, 166.7, 162.4, 157.3, 149.9, 140.1, 138.5, 137.7, 130.1, 128.9 (d, $J_{C\text{-}F}$ = 8.3 Hz), 126.4, 122.0, 120.6 (d, $J_{C\text{-}F}$ = 1.9 Hz), 117.5 (d, $J_{C\text{-}F}$ = 22.0 Hz), 114.8 (d, $J_{C\text{-}F}$ = 22.0 Hz), 64.6, 61.5, 60.7, 32.6, 31.5, 30.8, 19.2, 13.9, 13.8. $^{19}F\{^1H\}$ NMR (282 MHz, $CDCl_3$): δ −110.5. ESI-HRMS: Calcd for $C_{24}H_{30}FN_2O_6S$ $[M + H]^+$: 493.1803. Found: 493.1800.

*(±)-(E)-Butyl 3-(3-(3-Ethoxy-2-(N-methylpyridine-2-sulfonamido)-3-oxopropyl)naphthalen-2-yl)acrylate [(±)-**18**].* Following the typical procedure, sulfonamide (±)-**XXVI** (59.8 mg, 0.15 mmol) reacted with butyl acrylate (43.0 μL, 0.30 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol) in acetic acid (1 mL), to afford, after purification by column chromatography (*n*-hexane−EtOAc 80:20), product (±)-**18** as yellow oil; yield: 40.9 mg (52%).

^1H NMR (300 MHz, $CDCl_3$): δ 8.47 (d, J = 4.2 Hz, 1H), 8.16−8.11 (m, 2H), 7.75 (d, J = 6.7 Hz, 1H), 7.69−7.63 (m, 2H), 7.56−7.45 (m, 3H), 7.30 (m, 1H), 6.32 (d, J = 15.7 Hz, 1H), 5.01 (t, J = 7.4 Hz, 1H), 4.15 (t, J = 6.7 Hz, 2H), 3.90−3.75 (m, 3H), 3.56 (dd, J = 7.6, 14.5 Hz, 1H), 3.10 (s, 3H), 1.62 (m, 2H), 1.38 (m, 2H), 0.90 (m, 6H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 169.8, 166.9, 157.2, 149.7, 142.1, 137.6, 134.3, 133.0, 132.1, 131.6, 128.9, 128.3, 127.3, 126.8, 126.3, 124.4, 123.6, 121.9, 120.9, 64.5, 61.3, 60.4, 31.8, 30.8, 28.8, 19.2, 13.8. ESI-HRMS: Calcd for $C_{28}H_{33}N_2O_6S$ $[M + H]^+$: 525.2054. Found: 525.2059

*(±)-(E)-Butyl 3-(1-(3-Ethoxy-2-(N-methylpyridine-2-sulfonamido)-3-oxopropyl)naphthalen-2-yl)acrylate [(±)-**19**].* Following the typical procedure, sulfonamide compound (±)-**XXV** (59.8 mg, 0.15 mmol) reacted with butyl acrylate (43.0 μL, 0.30 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol) in acetic acid (1 mL), to afford, after purification by column chromatography (*n*-hexane−EtOAc 80:20), product (±)-**19** as a yellow oil; yield: 54.3 mg (69%).

^1H NMR (300 MHz, $CDCl_3$): δ 8.33 (d, J = 4.5 Hz, 1H), 8.03 (d, J = 15.7 Hz, 1H), 7.89 (s, 1H), 7.70 (m, 1H), 7.61 (m, 1H), 7.55−7.35 (m, 5H), 7.07 (m, 1H), 6.42 (d, J = 15.7 Hz, 1H), 4.95 (dd, J = 6.0, 9.1 Hz, 1H), 4.27 (t, J = 6.7 Hz, 2H), 3.94 (dc, J = 1.5, 7.0 Hz, 2H), 3.47 (dd, J = 6.0, 14.5 Hz, 1H), 3.15 (dd, J = 6.0, 14.5 Hz, 1H), 3.10 (m, 3H), 1.62 (m, 2H), 1.40 (m, 2H), 1.01 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 169.8, 166.7, 157.5, 149.5, 141.6, 137.3, 133.8, 132.7, 132.4, 132.3, 129.3, 128.0, 127.5, 127.0, 126.9, 126.4, 125.9, 121.5, 121.4, 64.6, 61.4, 60.7, 33.0, 31.5, 30.8, 19.2, 14.0, 13.8. ESI-HRMS: Calcd for $C_{28}H_{33}N_2O_6S$ $[M + H]^+$: 525.2054. Found: 525.2059.

*(E)-Butyl 3-(2-((1R,2S)-1-Methoxy-2-(N-methylpyridine-2-sulfonamido)propyl)phenyl)acrylate [(−)-**21**].* Following the typical procedure, (−)-**20** (48.1 mg, 0.15 mmol) reacted with butyl acrylate (21.5 μL, 0.15 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol) in acetic acid (1 mL), to afford, after purification by column chromatography (*n*-hexane−EtOAc 80:20), product (−)-**21** as colorless oil; yield: 51.4 mg (74%).

$[\alpha]_D^{298}$= −73.8 (*c* 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.77−8.63 (m, 1H), 8.25 (d, J = 15.7 Hz, 1H), 8.05−7.93 (m, 1H), 7.87 (td, J = 7.7, 1.7 Hz, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.52−7.25 (m, 4H), 6.38 (d, J = 15.7 Hz, 1H), 4.85 (d, J = 4.3 Hz, 1H), 4.23 (dt, J = 8.7, 5.5 Hz, 2H), 3.25 (s, 3H), 3.07 (s, 3H), 1.87−1.60 (m, 3H), 1.03 (d, J = 7.0 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 166.7, 158.0, 149.8, 141.3, 137.9, 137.7, 133.8, 129.6, 127.9, 127.4, 126.8, 126.1, 122.5, 121.2, 84.5, 64.4, 57.2, 57.1, 31.3, 30.7, 19.1, 13.7, 11.1. ESI-HRMS: Calcd for $C_{23}H_{31}N_2O_5S$ $[M + H]^+$: 447.1948. Found: 447.1952.

*N-((1R,2S)-1-Methoxy-1-(2-((E)-2-(phenylsulfonyl)vinyl)phenyl)-propan-2-yl)-N-methylpyridine-2-sulfonamide [(−)-**22**].* Following the typical procedure, (−)-**20** (48.1 mg, 0.15 mmol) reacted with phenyl vinyl sulfone (25.2 mg, 0.15 mmol) in the presence of $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), and 1-fluoro-2,4,6-trimethylpyridinium triflate (130.2 mg, 0.45 mmol) in acetic acid (1 mL), to afford, after purification by column chromatography (*n*-hexane−EtOAc 80:20), product (−)-**22** as colorless oil; yield: 56.9 mg (78%).

$[\alpha]_D^{298}$ = −63.51 (*c* 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.84−8.60 (m, 1H), 8.27 (d, J = 15.1 Hz, 1H), 8.15−8.03 (m, 2H), 8.05−7.95 (m, 1H), 7.90 (td, J = 7.7, 1.8 Hz, 1H), 7.73−7.35 (m, 7H), 7.31 (td, J = 7.2, 1.9 Hz, 1H), 6.85 (d, J = 15.2 Hz, 1H), 4.84 (d, J = 4.7 Hz, 1H), 4.18 (tt, J = 7.0, 3.5 Hz, 1H), 3.21 (s, 3H), 3.04 (s, 3H), 1.05 (d, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 157.8, 149.9, 140.5, 139.6, 138.7, 137.8, 133.2, 131.6, 130.6, 129.7, 129.2, 128.2, 128.1, 128.0, 127.4, 126.3, 122.6, 84.7, 57.5, 57.2, 31.2, 11.5.

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ESI-HRMS: Calcd for $C_{24}H_{27}N_2O_5S_2$ $[M + H]^+$: 487.1356. Found: 487.1351.

Typical Procedure for the Zn-Promoted Reductive N-Desulfonylation: Synthesis of (1R,3S*)-Ethyl 1-(2-Butoxy-2-oxoethyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate [(±)-**23**].* A suspension of (±)-**2** (47.5 mg, 0.1 mmol) and Zn powder (346 mg, 5 mmol) in a 1:1 mixture of THF and sat. aq NH_4Cl solution (2 mL) was stirred at 65 °C until consumption of the starting material (TLC monitoring, 72 h). The mixture was diluted with EtOAc (15 mL) and filtered over a plug of Celite to remove the Zn (washed with EtOAc). The combined filtrate was washed with brine (10 mL), and the combined organic phase was dried ($MgSO_4$) and concentrated to dryness. The residue was purified by flash chromatography (*n*-hexane−EtOAc 9:1) to afford the tetrahydroisoquinoline derivative (±)-**23** as a yellow oil (80:20 mixture of diastereomers); yield: 22.4 mg (71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10−7.00 (m, 4H), 4.31 (t, J = 6.8 Hz, 1H), 4.14 (m, 1H), 4.10−3.95 (m, 3H), 3.77 (dd, J = 5.6, 7.6 Hz, 1H), 3.04 (dd, J = 16.3, 7.5 Hz, 1H), 2.93 (dd, J = 16.5, 5.5 Hz, 1H), 2.73 (dd, J = 14.9, 6.5 Hz, 1H), 2.63 (dd, J = 15.0, 6.2 Hz, 1H), 2.41 (s, 3H), 1.49 (m, 2H), 1.23 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H), 0.84 (m, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 172.6, 171.7, 137.0, 132.2, 128.8, 126.9, 126.4, 126.3, 64.3, 60.5, 60.3, 58.4, 42.1, 39.1, 28.5, 27.5, 19.1, 14.2, 13.7. ESI-HRMS: Calcd for $C_{19}H_{28}NO_4$ $[M + H]^+$: 334.2013. Found: 334.2016.

*(1S,3S)-Ethyl 2-Methyl-1-((phenylsulfonyl)methyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate [(+)-**24**].* Following the typical procedure, (*S*)-**5** (51.4 mg, 0.1 mmol) and Zn powder (346 mg, 5 mmol) to afford, after flash chromatography (*n*-hexane−EtOAc 9:1), product (+)-**24** as a yellow oil (80:20 mixture of diastereomers); yield: 26.2 mg (74%) (95% ee for a pure sample of *anti*-(+)-**24**).

$[\alpha]_D^{298}$ = +38.88 (*c* 0.18, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03−7.97 (m, 2H), 7.70−7.55 (m, 3H), 7.26−7.08 (m, 4H), 4.53 (m, 1H), 4.09 (c, J = 7.1 Hz, 2H), 3.75−3.64 (m, 2H), 3.50 (dd, J = 4.0, 15.0 Hz, 1H), 3.02 (dd, J = 16.5, 7.8 Hz, 1H), 2.95 (dd, J = 6.1, 17.1 Hz, 1H), 2.36 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 171.7, 140.5, 135.2, 133.3, 132.5, 129.0, 128.9, 128.2, 127.4, 127.1, 127.0, 63.0, 60.6, 58.8, 57.6, 38.3, 27.5, 14.2. ESI-HRMS: Calcd for $C_{20}H_{24}NO_4S$ $[M + H]^+$: 374.1421. Found: 374.1427. HPLC: Daicel Chiralpak IA, hexane−isopropanol 90−10, flow rate 0.7 mL/min (ë = 254 nm), t_R: 22.7 min (1*R*,3*R*)-**24** and 34.7 min (1*S*,3*S*)-**24**.

■ ASSOCIATED CONTENT

Supporting Information

HPLC traces for enantioenriched compounds, copies of ^{1}H NMR and ^{13}C NMR of new compounds, copies of NOE experiments for relative stereochemistry determination of compounds **23** and **24**, and catalyst system optimization studies. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ramon.gomez@uam.es (R.G.-A.).

*E-mail: juancarlos.carretero@uam.es (J.C.C.).

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For general recent reviews on C−H functionalization: (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (b) Bruckl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* **2012**, *45*, 826. (c) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362. (d) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (e) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236. (f) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (g) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (h) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Tetrahedron* **2012**, *68*, 5130. (i) Mousseau, J. J.; Charette, A. B. *Acc. Chem. Res.* **2013**, *46*, 412. (j) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (k) Sharma, A.; Vacchani, D.; Van der Eycken, E. *Chem.—Eur. J.* **2013**, *19*, 1158. For a review on stoichiometric and catalytic cyclometalation strategies: (l) Cuesta, L.; Urriolabeitia, E. P. *Comments Inorg. Chem.* **2012**, *33*, 55.

(2) For a review on Pd-catalyzed remote C−H functionalization: Franzoni, I.; Mazet, C. *Org. Biomol. Chem.* **2014**, *12*, 233.

(3) For reviews on removable directing groups in C−H activation, see: (a) Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450. (b) Wang, C.; Huang, Y. *Synlett* **2013**, *24*, 145. (c) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726.

(4) For the wide range significance of α-amino acids, see: Hughes, A. B., Ed. *Amino Acids, Peptides and Proteins in Organic Chemistry*; Wiley-VCH: Weinheim, 2009−2013; Vol. *1*−*5*.

(5) For a general review on C−H functionalization in the synthesis of amino acids and peptides, see: Noisier, A. F. M.; Brimble, M. A. *Chem. Rev.* **2014**, *114*, 8775.

(6) For representative examples of functionalization of α-amino acid derivatives using a stoichiometric amount of metal: (a) Vicente, J.; Saura-Llamas, I.; García-López, J. A.; Bautista, D. *Organometallics* **2009**, *28*, 448. (b) Arnau, P.; Nieto, S.; Serrano, E.; Navarro, R.; Soler, T.; Cativiela, C.; Urriolabeitia, E. P. *Inorg. Chem.* **2009**, *48*, 11963. (c) Vicente, J.; Saura-Llamas, I.; García-López, J. A.; Bautista, D. *Organometallics* **2010**, *29*, 4320. (d) Nieto, S.; Sayago, F. J.; Laborda, P.; Soler, T.; Cativiela, C.; Urriolabeitia, E. P. *Tetrahedron* **2011**, *67*, 4185. (e) García-López, J. A.; Saura-Llamas, I.; McGrady, J. E.; Bautista, D.; Vicente, J. *Organometallics* **2012**, *31*, 8333. (f) Oliva-Madrid, M. J.; García-López, J. A.; Saura-Llamas, I.; Bautista, D.; Vicente, J. *Organometallics* **2012**, *31*, 3647. (g) Laga, E.; Cativiela, C.; Urriolabeitia, E. P. *Beilstein J. Org. Chem.* **2012**, *8*, 1569. (h) Laga, E.; García-Montero, A.; Sayago, F. J.; Soler, T.; Moncho, S.; Cativiela, C.; Martinez, M.; Urriolabeitia, E. P. *Chem.—Eur. J.* **2013**, *19*, 17398.

(7) For catalytic C(sp^2)−H functionalization of aromatic α-amino acid derivatives, see: (a) Li, J. J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. (b) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806. (c) Meyer, F.-M.; Liras, S.; Guzman-Perez, A.; Perreault, C.; Bian, J.; James, K. *Org. Lett.* **2010**, *12*, 3870. (d) Vickers, C. J.; Mei, T.-S.; Yu, J.-Q. *Org. Lett.* **2010**, *12*, 2511. (e) López, B.; Rodriguez, A.; Santos, D.; Albert, J.; Ariza, X.; Garcia, J.; Granell, J. *Chem. Commun.* **2011**, *47*, 1054. (f) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3. (g) Albert, J.; Ariza, X.; Calvet, T.; Font-Bardia, M.; Garcia, J.; Granell, J.; Lamela, A.; López, B.; Martinez, M.; Ortega, L.; Rodriguez, A.; Santos, D. *Organometallics* **2013**, *32*, 649. (h) Mei, T.-S.; Leow, D.; Xiao, H.; Laforteza, B. N.; Yu, J.-Q. *Org. Lett.* **2013**, *15*, 3058. (i) Zhu, Y.; Bauer, M.; Ploog, J.; Ackermann, L. *Chem.—Eur. J.* **2014**, *20*, 13099.

(8) For the catalytic activation of C(sp^3)−H bonds of α-amino acid derivatives, see: (a) Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149. (b) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391. (c) Zhao, L.; Baslé, O.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 4106. (d) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (e) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192. (f) Tran, L. D.; Daugulis, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 5188. (g) Aspin, S.; Goutierre, A.-S.; Larini, P.; Jazzar, R.; Baudoin, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 10808. (h) Fan, M.; Ma, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 12152. (i) Rodríguez, N.; Romero-Revilla, J. A.; Fernández-Ibáñez, M. A.; Carretero, J. C. *Chem. Sci.* **2013**, *4*, 175. (j) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124. (k) Chen, K.; Hu, F.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 3906. (l) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. *Nature*

DOI: 10.1021/jo502912m
J. Org. Chem. 2015, 80, 3321−3331

2014, *150*, 129. (m) Li, Q.; Zhang, S.-Y.; He, G.; Nack, W. A.; Chen, G. *Adv. Synth. Catal.* **2014**, *356*, 1544. (n) Chan, K. S. L.; Wasa, M.; Chu, L.; Laforteza, B. N.; Miura, M.; Yu, J.-Q. *Nat. Chem.* **2014**, *6*, 146. (o) Chen, K.; Zhang, S.-Q.; Xu, J.-W.; Hu, F.; Shi, B.-F. *Chem. Commun.* **2014**, *50*, 13924. (p) Zhu, R.-Y.; He, J.; Wang, X.-C.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 13194. (q) Gong, W.; Zhang, G.; Liu, T.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 16940. (r) He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. *Science* **2014**, *343*, 1216. (s) Poveda, A.; Alonso, I.; Fernández-Ibáñez, M. A. *Chem. Sci.* **2014**, *5*, 3873. (t) Zhang, L.-S.; Chen, G.; Wang, X.; Guo, Q.-Y.; Zhang, X.-S.; Pan, F.; Chen, K.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 3899. (u) Chen, K.; Shi, B.-F. *Angew. Chem., Int. Ed.* **2014**, *53*, 11950. See also ref 7f.

(9) For examples of C−H olefination, followed by *N*-functionalization, see: (a) Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem.* **1998**, *63*, 5211. (b) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680. (c) Stowers, K. J.; Fortner, K. C.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 6541. (d) Ji, X.; Huang, H.; Li, Y.; Chen, H.; Jiang, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 7292. (e) Wang, N.-J.; Mei, S.-T.; Shuai, L.; Yuan, Y.; Wei, Y. *Org. Lett.* **2014**, *16*, 3040. (f) Cai, S.; Chen, C.; Shao, P.; Xi, C. *Org. Lett.* **2014**, *16*, 3142. (g) Martínez, A. M.; Rodríguez, N.; Gómez Arrayás, R.; Carretero, J. C. *Chem. Commun.* **2014**, *50*, 6105. (h) Ye, X.; Shi, X. *Org. Lett.* **2014**, *16*, 4448. (i) Grigorjeva, L.; Daugulis, O. *Org. Lett.* **2014**, *16*, 4684. (j) Suzuki, C.; Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Adv. Synth. Catal.* **2014**, *356*, 1521. (k) Shi, Z.; Boultadakis-Arapinis, M.; Koester, D. C.; Glorius, F. *Chem. Commun.* **2014**, *50*, 2650. (l) Parthasarathy, K.; Bolm, C. *Chem.—Eur. J.* **2014**, *20*, 4896.

(10) See, for instance: (a) Rauf, W.; Thompson, A. L.; Brown, J. M. *Chem. Commun.* **2009**, 3874. (b) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 6169. (c) Li, G.; Leow, D.; Wan, L.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 1245. (d) Chan, L. Y.; Kim, S.; Ryu, T.; Lee, P. H. *Chem. Commun.* **2013**, *49*, 4682.

(11) For recent reviews on Fujiwara−Moritani reaction: (a) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170. (b) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (c) Kozhushkov, S. I.; Ackermann, L. *Chem. Sci.* **2013**, *4*, 886. (d) Wu, Y.; Wang, J.; Mao, F.; Kwong, F. Y. *Chem.—Asian J.* **2014**, *9*, 26. (e) Zhou, L.; Lu, W. *Chem.—Eur. J.* **2014**, *20*, 634.

(12) For selected very recent examples: (a) Li, G.; Leow, D.; Wan, L.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 1245. (b) Huang, X.; Huang, J.; Du, C.; Zhang, X.; Song, F.; You, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12970. (c) Ma, W.; Ackermann, L. *Chem.—Eur. J.* **2013**, *19*, 13925. (d) Wesch, T.; Leroux, F. R.; Colobert, F. *Adv. Synth. Catal.* **2013**, *355*, 2139. (e) Cheng, G.-J.; Yang, Y.-F.; Liu, P.; Chen, P.; Sun, T.-Y.; Li, G.; Zhang, X.; Houk, K. N.; Yu, J.-Q.; Wu, Y.-D. *J. Am. Chem. Soc.* **2014**, *136*, 894. (f) Wang, B.; Shen, C.; Yao, J.; Yin, H.; Zhang, Y. *Org. Lett.* **2014**, *16*, 46. (g) Zhou, J.; Li, B.; Qian, Z.-C.; Shi, B.-F. *Adv. Synth. Catal.* **2014**, *356*, 1038. (h) Yang, G.; Lindovska, P.; Zhu, D.; Kim, J.; Wang, P.; Tang, R.-Y.; Movassaghi, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 10807. (i) Vora, H. U.; Silvestri, A. P.; Engelin, C. J.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 268. (j) Fabry, D. C.; Zoller, J.; Raja, S.; Rueping, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10228. (k) Becker, P.; Priebbenow, D. L.; Pirwerdjan, R.; Bolm, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 269. (l) She, Z.; Shi, Y.; Huang, Y.; Cheng, Y.; Song, F.; You, J. *Chem. Commun.* **2014**, *50*, 13914. (m) Deb, A.; Bag, S.; Kancherla, R.; Maiti, D. *J. Am. Chem. Soc.* **2014**, *136*, 13602. For aerobic oxidative coupling of arenes with olefins, see: (n) Babu, B. P.; Meng, X.; Bäckvall, J.-E. *Chem.—Eur. J.* **2013**, *19*, 4140. (o) Gigant, N.; Bäckvall, J.-E. *Org. Lett.* **2014**, *16*, 1664.

(13) For previous examples on the use of *N*-SO_2Py directing group in C−H functionalizations, see: (a) García-Rubia, A.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 6511. (b) García-Rubia, A.; Urones, B.; Gómez Arrayás, R.; Carretero, J. C. *Chem.—Eur. J.* **2010**, *16*, 9676. (c) García-Rubia, A.; Urones, B.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10927. (d) Urones, B.; Gómez Arrayás, R.; Carretero, J. C. *Org. Lett.* **2013**, *15*, 1120. (e) Urones, B.; Martínez, A. M.; Rodríguez, N.; Gómez Arrayás, R.; Carretero, J. C. *Chem. Commun.* **2013**, *49*, 11044. (f) Yan, Z.-L.; Chen, W.-L.; Gao, Y.-R.; Mao, S.; Zhang, Y.-L.; Wang, Y.-Q. *Adv. Synth. Catal.* **2014**, *356*, 1085. See also refs 7h, 8i, and 8s.

(14) *N*-Fluoro-2,4,6-trimethylpyridinium triflate has been used as oxidant in Pd-catalyzed C−H fluorination, trifluoromethylation, and aminations, presumably through Pd^{II}/Pd^{IV} mechanisms. For early success: (a) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520. For a review: (b) Engle, K. M.; Mei, T.-S.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 1478.

(15) No products resulting from competing Heck-coupling were detected in the crude reaction mixtures of products **15** or **16**. In agreement with this observation, no Heck-type side reaction was either observed in our previously reported alkenylation of aniline derivatives with electron-defficient alkenes in substrates holding a chloro or bromo-substitutent (see ref 13c).

(16) For a recent review on synthesis and biological significance of the 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) core, see: Kotha, S.; Deodhar, D.; Khedkar, P. *Org. Biomol. Chem.* **2014**, *12*, 9054.

(17) The relative configuration of the tetrahydroisoquinoline products has been established by ^{1}H NMR, mainly by NOE experiments (see the Supporting Information for details).

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