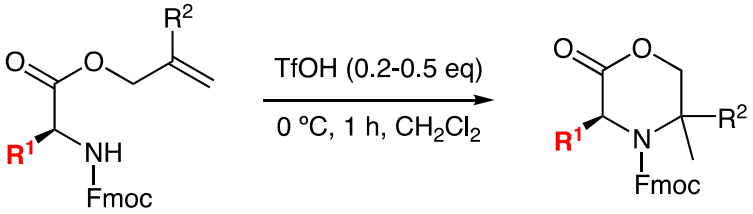
Morpholin-2-one Derivatives via Intramolecular Acid-Catalyzed Hydroamination

Abdul Hadi Aldmairi [a]
David W. Knight *[a]
Thomas Wirth *[a]

[a] School of Chemistry, Cardiff University, Park Place, Cardiff, CF10 3AT, UK.

knightdw@cf.ac.uk, wirth@cf.ac.uk



Received:
Accepted:
Published online:
DOI:

Abstract Substituted morpholin-2-one derivatives were readily obtained in two steps staring from commercially available *N*-protected amino acids. In a metal-free and practical method, a catalytic amount of trifluoromethanesulfonic acid was sufficient to generate morpholinones under mild reaction conditions in an intramolecular hydroamination reaction in good to excellent yields.

Key words amino acids, cyclization, hydroamination, morpholinone, trifluoromethanesulfonic acid

Morpholinone derivatives occur frequently as a central unit in drug discovery and medicinal chemistry.[1]

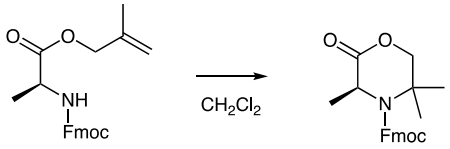
Substituted morpholin-2-ones are not only important derivatives in pharmaceutical industry with recent examples including anti-fungal agents[2] and compounds with potential in cancer chemotheraphy,[3] they can also be versatile precursors for ring-opening reactions. For example, the organocatalytic ring opening polymerization of *N*-acyl morpholin-2-ones can generate functionalized poly(aminoesters) with *N*-acylated amines,[4] while the alcoholysis of optically active morpholin-2-ones yielded hydroxy amides in a stereoselective way.[5]

Morpholin-2-ones are generally prepared by metal-catalyzed cyclizations. Palladium,[6] rhodium[7] and gold[8] catalysts have been employed as major strategies for generating morpholin-2-one derivatives. *N*-Substituted morpholin-2-ones were also prepared by alternative methods.[9] However, we are not aware of any report describing an acid-catalyzed synthesis of substituted morpholinones, probably due to the acid-sensitivity of *N,O*-morpholinones. Moreover, there are only a few reports on the syntheses 5,5-disubstituted morpholinone derivatives, although they are important pharmacophores in medicinal chemistry.[10]

We describe herein a simple and efficient two-step method to access substituted morpholin-2-ones starting from commercially available *N*-protected amino acids as building blocks under metal-free conditions.

In continuation to access small bioactive molecules containing oxygen and nitrogen heteroatoms through cyclizations,[11] we selected morpholin-2-ones as challenging acid sensitive heterocyclic frameworks. For initial investigations, commercially available Fmoc-L-alanine was reacted with methyl allyl chloride and potassium carbonate to yield the methylallyl ester **1** in 95% yield.

Table 1 Screening of various acidic catalysts for the synthesis of 3,5,5-trimethyl morpholin-2-one **2.**



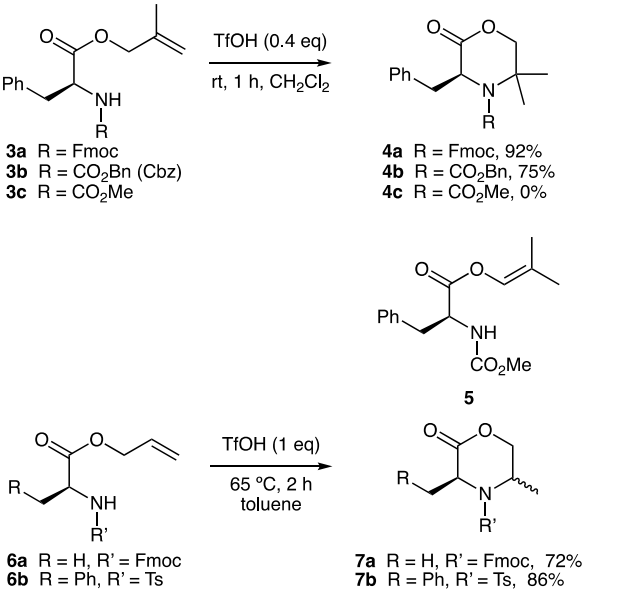
1 **2**

Entry	Reagent	Time (h)	Temperature (°C)	Yield (%)
1	Amberlyst-15[a]	24	20	no reaction
2	Nafion® NR50[a]	24	2	no reaction
3	Silica supported tungstic acid	20	20	no reaction
4	SiO_2[a]	20	20	no reaction
5	H_2SO_4 (0.25 eq)	1	20	85%
6	TfOH (0.2 eq)[b]	1	0	84%
7	TfOH (0.2 eq)[c]	0.33	0	93%

[a] 200 mg / mmol. [b] Added neat. [c] Added as 0.1 M solution in CH_2Cl_2.

The *N*-protected allyl-ester **1** was subjected to different acidic catalysts as shown in Table 1. While ion exchange resins (entries 1 and 2) and silica-supported tungstic acid (entry 3) were completely unreactive towards **1**, catalytic amounts of sulfuric or trifluoromethanesulfonic acid led to good conversions. High yields (93%) of 3,5,5-trimethyl morpholin-2-one **2** were obtained with 0.2 equivalents of trifluoromethanesulfonic acid at 0 °C for 20 min (entry 6).

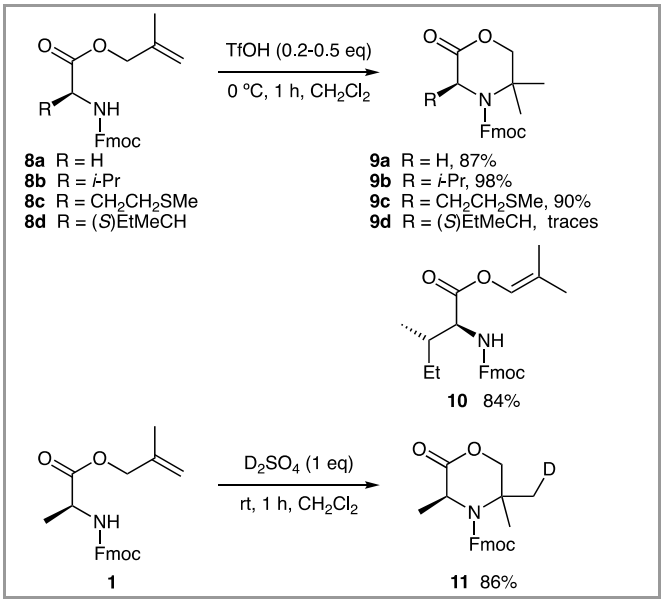
We then further studied the scope of the cyclization reaction with different protection groups on the nitrogen of phenylalanine esters **3**. As shown in Scheme 1, the Fmoc protected derivative **3a** cyclized as expected to the morpholin-2-one derivative **4a** in 92% yield. Another group such as the benzyloxycarbonyl (Cbz) protecting group were less efficient (**4b** formed in 75% yield, while the substrate with a methyloxycarbonyl group **3c** did not form any cyclized product. Interestingly, in this case only a double bond isomerization to compound **5** was observed under identical reaction conditions. As expected, allyl ester **6**, either protected as sulfonamide or as Fmoc, required a much longer exposure of one equivalent of trifluoromethanesulfonic acid in toluene at 65 °C for two hours to yield a 1:1 *cis/trans* mixture of inseparable diastereomers of both products, **7a** and **7b**. Allyl ester **6b** did neither react under similar conditions with Amberlyst-15 as catalyst nor at lower temperatures (40 °C).



Scheme 1 Synthesis of morpholin-2-one derivatives from phenylalanine precursors.

Other *N*-protected amino esters were synthesized according to a literature procedure[12] and then subjected to the reaction conditions shown in Table 1, Entry 7.

The *N*-Fmoc glycine ester **8a** gave the desired morpholinone **9a** in 87% yield after one-hour reaction time with 0.4 equivalents of trifluoromethanesulfonic acid. Valine derivative **8b** cyclized completely after 10 minutes to give 3-isopropyl-5,5-dimethyl morpholinone **9b** in quantitative yield. Surprisingly, *N*-Fmoc methionine **8c** was stable under the acidic conditions to give morpholinone **9c** in 90% yield. Compound **9d** did not cyclize under the reaction conditions but isomerized to compound **10**. Further investigations with alanine ester were carried out with deuterated sulfuric acid (solution 96-98 wt. % in D_2O). While 0.2 equivalents D_2SO_4 gave only 17% of the product **11** (determined by ^1H NMR), one equivalent of D_2SO_4 was needed to complete the cyclization and **11** was obtained in 86% yield.



Scheme 2 Synthesis of morpholin-2-one derivatives from other *N*-Fmoc protected amino acids.

In conclusion, we describe an efficient, general and transition-metal free methodology for the synthesis of substituted morpholin-2-ones using an intramolecular hydroamination reaction of allyl amino acid derivatives mediated by catalytic amounts of trifluoromethanesulfonic acid in good to excellent yields.

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

All reactions were carried out in oven–dried glassware under an atmosphere of nitrogen/argon using anhydrous solvents. All commercial reagents were used as received. Proton nuclear magnetic resonance ^1H NMR spectra were recorded at 300, 400 and 500 MHz. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethyl silane (δ 0.00). ^1H NMR splitting patterns are designated as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), multiplet (m). Carbon nuclear magnetic resonance ^{13}C NMR spectra were recorded at 100 MHz/125 MHz. Mass spectra (MS) were obtained using ESI mass spectrometers. IR spectra were recorded as neat for liquid and in KBr for solids. Melting points were determined using a hot stage apparatus and were uncorrected. Optical rotations were measured using a 10.0 mL cell with a 1.0 dm path length and are reported as [α] (c in g per 100 mL, solvent) at 20 °C.

Procedures

Synthesis of *N*-Fmoc protected allyl esters:

To the *N*-protected amino-acid (4.0 mmol) in dry DMF (20 mL) 3-chloro-2-methyl-1-propene (450 mg, 5.0 mmol) was added at room temperature. Next, anhydrous K_2CO_3 (1.0 g) was added in one portion. The reaction was stirred for 18 hours at room temperature. Once the TLC indicated consumption of the starting material, the mixture was diluted with EtOAc (100 mL) and the organic phase was washed by HCl solution (2.0 M), brine, and dried over anhydrous $MgSO_4$. The solvent removed under reduced pressure to give the crude residue. Flash silica gel chromatography (CH_2Cl_2/hexane 9:1) provided the allyl ester.

Acid-catalyzed cyclization:

The ester (1.00 mmol) was taken up in anhydrous CH_2Cl_2 (20 mL) and the solution was cooled to 0 °C. Trifluoromethanesulfonic acid (32 mg, 0.2

mmol) was then added. The completed reaction was quenched with sat. aq. potassium carbonate (5 mL). The aqueous layer was extracted with dichloromethane (2 x 10 mL) and the combined organic extracts were dried, filtered and evaporated to yield the product.

2-Methylallyl (((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-alaninate (1)

Synthesized according to the general procedure, Fmoc-Ala-OH (1.56 g, 5.0 mmol) gave the allyl ester as white solid, m.p. 116 – 118 °C (1.74 g, 95%). $[\alpha]_D^{20}$ –10 (c 0.2, CH_2Cl_2).

IR (neat): 2922, 2852, 1722, 1707, 1531, 1500, 1250 1040 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 7.5 Hz, 2H), 7.51 (dd, *J* = 7.1, 3.8 Hz, 2H), 7.34 – 7.27 (m, 2H), 7.22 (dd, *J* = 7.4, 1.1 Hz, 2H), 5.33 (d, *J* = 7.5 Hz, 1H), 4.90 (s, 1H), 4.86 (s, 1H), 4.49 (q, *J* = 13.1 Hz, 1H), 4.37 (dd, *J* = 14.4, 7.1 Hz, 1H), 4.29 (dd, *J* = 14.3, 8.8 Hz, 2H), 4.13 (t, *J* = 7.0 Hz, 2H), 1.67 (s, 3H), 1.38 (d, *J* = 7.2 Hz, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.8, 155.6, 143.9, 141.3, 139.4, 127.7, 127.1, 125.1, 119.9, 113.5, 68.6, 67.0, 49.7, 47.2, 19.4, 18.8. ppm

HRMS (EI) m/z calcd for $C_{22}H_{24}NO_4$ $[M]^+$ = 366.1705; found: 366.1693.

(*S*)-(9*H*-Fluoren-9-yl)methyl 3,5,5-trimethyl-2-oxomorpholine-4-carboxylate (2)

According to the general procedure, the ester **1** (365 mg, 1.0 mmol) and triflic acid (32 mg, 0.2 mmol) (20 min, 0 °C) gave the product as yellow oil (341 mg, 93%). $[\alpha]_D^{20}$ –2.5 (c 1.0, CH_2Cl_2).

According to the general procedure, the ester **1** (365 mg, 1.0 mmol) and sulfuric acid (25 mg, 0.25 mmol) (60 min, rt) gave the product as yellow oil (313 mg, 85%).

IR (neat): 2830, 2802, 1719, 1697, 1108, 1090, 1002 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 7.5 Hz, 2H), 7.47 – 7.42 (m, 2H), 7.25 (t, *J* = 7.5 Hz, 2H), 7.16 (dd, *J* = 7.5, 1.0 Hz, 2H), 4.33 – 4.27 (m, 1H), 4.25 (d, *J* = 6.9 Hz, 2H), 4.07 (t, *J* = 6.9 Hz, 1H), 3.94 – 3.86 (m, 2H), 1.32 (d, *J* = 7.1 Hz, 3H), 1.10 (s, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.3, 155.7, 143.8, 141.3, 127.8, 127.1, 125.1, 120.0, 72.7, 69.8, 67.1, 50.1, 47.1, 26.1, 18.4 ppm.

HRMS (EI) m/z calcd for $C_{22}H_{24}NO_4$ $[M]^+$ = 366.1705; found: 366.1698.

2-Methylallyl (((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-phenylalaninate (3a)

According to the general procedure, Fmoc-Phe-OH (1.94 g, 5.0 mmol) gave the allyl ester as white solid, m.p. 125 – 128 °C (2.00 g, 91%). $[\alpha]_D^{20}$ +31.4 (c 0.86, CH_2Cl_2).

IR (neat): 3228, 2846, 1738, 1502, 1248, 1014 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.5 Hz, 2H), 7.62 – 7.55 (m, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.35 – 7.28 (m, 2H), 7.14 (d, *J* = 6.7 Hz, 2H), 5.29 (d, *J* = 8.3 Hz, 1H), 4.99 (d, *J* = 8.4 Hz, 2H), 4.75 (dd, *J* = 14.1, 6.0 Hz, 1H), 4.57 (q, *J* = 12.9 Hz, 2H), 4.46 (dd, *J* = 10.6, 7.2 Hz, 1H), 4.37 (dd, *J* = 10.6, 7.0 Hz, 1H), 4.24 (t, *J* = 7.1 Hz, 1H), 3.27 – 3.22 (m, 2H), 1.75 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.3, 155.6, 143.9, 141.4, 139.4, 128.0, 127.8, 127.7, 127.6, 127.1, 125.1, 120.0, 113.7, 68.8, 67.0, 55.0, 47.0, 38.4, 19.4 ppm.

HRMS (CI) m/z calcd for $C_{28}H_{27}NO_4Na$ $[M]^+$ = 464.1838; found: 464.1840.

2-Methylallyl ((benzyloxy)carbonyl)-*L*-phenylalaninate (3b)

According to the general procedure, Cbz-Phe-OH (1.50 g, 5.0 mmol) gave the allyl ester as colorless oil (1.30 g, 73%). $[\alpha]_D^{20}$ +28.1 (c 0.64, CH_2Cl_2).

IR (neat): 3334, 1724, 1261, 1203, 1187 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.39 – 7.33 (m, 5H), 7.29 – 7.23 (m, 3H), 7.13 (dt, *J* = 11.6, 6.0 Hz, 2H), 5.26 (d, *J* = 8.1 Hz, 1H), 5.12 (d, *J* = 1.5 Hz, 2H), 4.98 (d, *J* = 7.5 Hz, 2H), 4.73 (dt, *J* = 8.2, 6.0 Hz, 2H), 4.55 (q, *J* = 13.0 Hz, 2H), 3.26 – 3.20 (m, 2H), 1.73 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.3, 155.6, 139.2, 136.2, 135.7, 129.3, 128.7, 128.2, 128.1, 127.8, 127.2, 127.1, 113.9, 68.8, 67.0, 54.9, 38.3, 19.5 ppm.

HRMS (CI) m/z calcd for $C_{21}H_{23}NO_4Na$ $[M]^+$ = 376.1525; found: 376.1529.

2-Methylallyl (methoxycarbonyl)-*L*-phenylalaninate (3c)

According to the general procedure, Moc-Phe-OH (1.12 g, 5.0 mmol) gave the allyl ester **3c** as colorless oil (1.00 g, 72%). $[\alpha]_D^{20}$ +3.33 (c 0.24, CH_2Cl_2).

IR (neat): 2356, 2923, 2811, 1736, 1711, 1305, 1054 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.32 – 7.27 (m, 3H), 7.15 (dd, *J* = 5.1, 2.8 Hz, 2H), 5.17 (d, *J* = 7.7 Hz, 1H), 4.99 – 4.94 (m, 2H), 4.74 – 4.65 (m, 1H), 4.53 (t, *J* = 4.7 Hz, 2H), 3.67 (s, 3H), 3.14 (t, *J* = 5.3 Hz, 2H), 1.72 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.3, 135.7, 129.3, 128.6, 127.2, 113.9, 19.6 ppm.

HRMS (EI) m/z calcd for $C_{21}H_{22}NO_4$ $[M]^+$ = 277.1314; found: 277.1305.

(*S*)-(9H-Fluoren-9-yl)methyl 3-benzyl-5,5-dimethyl-2-oxomorpholine-4-carboxylate (4a)

According to the general procedure, ester **3a** (220 mg, 0.5 mmol) and triflic acid (32 mg, 0.2 mmol, 0.4eq) gave the product as colourless oil (202 mg, 92%). $[\alpha]_D^{20}$ –16.7 (c 0.6, CH_2Cl_2).

IR (neat): 2824, 1729, 1411, 1278, 1027 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 7.68 (d, *J* = 7.5 Hz, 2H), 7.47 (dd, *J* = 6.9, 4.5 Hz, 2H), 7.35 – 7.27 (m, 2H), 7.27 – 7.16 (m, 5H), 4.61 (dd, *J* = 14.2, 6.7 Hz, 1H), 4.42 – 4.32 (m, 2H), 4.27 (dd, *J* = 10.6, 6.9 Hz, 2H), 4.12 (t, *J* = 6.9 Hz, 1H), 3.89 (q, *J* = 11.0 Hz, 2H), 3.11 – 3.03 (m, 2H), 1.08 (t, *J* = 8.0 Hz, 6H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.6, 154.9, 142.9, 140.3, 134.7, 128.2, 127.7, 126.7, 126.3, 126.0, 123.9, 119.1, 72.2, 68.4, 65.9, 53.7, 46.3, 37.4, 24.8 ppm.

HRMS (CI) m/z calcd for $C_{28}H_{27}NO_4Na$ [M]+ = 464.1838; found: 464.1853.

(*S*)-Benzyl 3-benzyl-5,5-dimethyl-2-oxomorpholine-4-carboxylate (4b)

According to the general procedure, ester **4a** (177 mg, 0.5 mmol) and triflic acid (32 mg, 0.2 mmol, 0.4eq) gave the product as colourless oil (132 mg, 75%). $[\alpha]_D^{20}$ +21.4 (c 1.4, CH_2Cl_2).

IR (neat): 2968, 1704, 1184, 1109, 1022 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.24 – 7.10 (m, 7H), 7.06 – 6.99 (m, 3H), 4.95 (*app.* s, 2H), 4.54 (dd, *J* = 14.3, 6.7 Hz, 1H), 3.87 – 3.74 (m, 2H), 2.98 – 2.74 (m, 29H), 1.04 (s, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.9, 155.5, 139.2, 130.7, 129.2, 74.6, 73.0, 54.7, 41.6, 26.3, 22.3, 18.5 ppm.

HRMS (CI) m/z calcd for $C_{21}H_{23}NO_4Na$ [M]+ = 376.1525; found: 376.1529.

2-Methylprop-1-en-1-yl (methoxycarbonyl)-*L*-phenylalaninate (5)

According to the general procedure, the ester **3c** (139 mg, 0.5 mmol) and triflic acid (32 mg, 0.2 mmol) gave the product **5** as colourless oil (130 mg, 94%). $[\alpha]_D^{20}$ –5.56 (c 0.54, CH_2Cl_2).

IR (neat): 2847, 1706, 1694, 1583, 1034 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.24 – 7.17 (m, 3H), 7.08 – 7.03 (m, 2H), 6.74 (dd, *J* = 2.9, 1.4 Hz, 1H), 5.14 (d, *J* = 13.5 Hz, 1H), 4.65 (d, *J* = 6.2 Hz, 1H), 4.50 – 4.39 (m, 1H), 3.59 (s, 3H), 3.07 (d, *J* = 5.9 Hz, 2H), 1.58 (d, *J* = 0.9 Hz, 3H), 1.54 (s, 3H) ppm.

HRMS (EI) m/z calcd for $C_{21}H_{22}NO_4$ $[M]^+$ = 277.1314; found: 277.1311.

Allyl (((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-alaninate (6a)

Fmoc-Ala-OH (1.87 g, 6 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C. Allylic alcohol (0.4 mL, 5.7 mmol) was added. The solution was cooled to −15 °C. A solution of DCC (1.2g, 5.7 mmol) and DMAP (70 mg, 0.6 mmol) in CH_2Cl_2 (50 mL) was added and the reaction was stirred at room temperature for 20 h. The precipitated *N,N*-dicyclohexyl urea was filtered off and washed with CH_2Cl_2. The organic layer was washed with 1 M HCl (10 mL) and saturated $NaHCO_3$ (10 mL) solution. The organic phase was dried over Na_2SO_4, filtered and the solvent was evaporated in *vacuo*. The crude product was purified by flash chromatography CH_2Cl_2/MeOH (10:0.2) to give the ester **6a** as a colourless oil (1.76 g, 88%). $[\alpha]_D^{20}$ –3.57 (c 0.28, CH_2Cl_2).

IR (neat): 3291, 2882, 2811, 1744, 1721, 1219, 1025 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 7.5 Hz, 2H), 7.50 (dd, *J* = 7.1, 3.5 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 2H), 7.21 (td, *J* = 7.4, 1.1 Hz, 2H), 5.81 (ddd, *J* = 22.7, 10.9, 5.7 Hz, 1H), 5.37 (d, *J* = 7.6 Hz, 1H), 5.23 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.15 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.55 (d, *J* = 5.4 Hz, 2H), 4.40 – 4.23 (m, 3H), 4.12 (t, *J* = 7.0 Hz, 1H), 1.35 (d, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.7, 141.3, 131.58, 127.7, 127.1, 125.2, 120.0, 118.8, 67.0, 66.0, 49.7, 47.2, 18.7 ppm.

HRMS (EI) m/z calcd for $C_{21}H_{22}NO_4$ $[M]^+$ = 352.1549; found: 352.1547.

Allyl tosyl-L-phenylalaninate (6b)[13]

Ts-Phe-OH (1.9 g, 6 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to 0 °C. Allylic alcohol (0.4 mL, 5.7 mmol) was added. The solution was cooled to −15 °C. A solution of DCC (1.2g, 5.7 mmol) and DMAP (70 mg, 0.6 mmol) in CH_2Cl_2 (50 mL) was added and the reaction was stirred at room temperature for 20 h. The precipitated *N,N*-dicyclohexyl urea was filtered off and washed with CH_2Cl_2. The organic layer was washed with 1 M HCl (10 mL) and sat. aq. $NaHCO_3$ (10 mL) solution. The organic phase was dried over Na_2SO_4, filtered and the solvent was evaporated in *vacuo*. The crude product was purified by flash chromatography CH_2Cl_2/MeOH (10 : 0.2) to give the ester **6b** as a colourless oil (1.44 g, 72%). $[\alpha]_D^{20}$ –6,7 (c 0.3, CH_2Cl_2).

IR (neat): 3252, 2990, 2824, 1734, 1584, 1219, 1017 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8.3 Hz, 2H), 7.13 – 7.06 (m, 5H), 7.01 – 6.94 (m, 2H), 5.55 (ddt, *J* = 17.6, 9.8, 5.9 Hz, 1H), 5.30 (d, *J* = 9.1 Hz, 1H), 5.07 (t, *J* = 4.0 Hz, 1H), 5.05 – 4.99 (m, 1H), 4.22 (dd, *J* = 12.0, 7.2 Hz, 2H), 4.10 (dt, *J* = 8.9, 6.2 Hz, 1H), 2.90 (d, *J* = 6.9 Hz, 2H), 2.27 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.5, 143.6, 134.9, 130.9, 129.6, 128.6, 66.1, 56.6, 39.5, 21.5 ppm.

HRMS (CI) m/z calcd for $C_{19}H_{21}NO_4SNa$ $[M]^+$ = 382.1089; found: 382.1080.

(9*H*-Fluoren-9-yl)methyl (3*S*)-3,5-dimethyl-2-oxomorpholine-4-carboxylate (7a)

The ester **6a** (176 mg, 0.5 mmol) and triflic acid (80 mg, 0.5 mmol) in dry toluene (20 mL) were heated for 2 h at 65 °C. The completed reaction was quenched with sat. aq. potassium carbonate (5 mL). The separated aqueous layer was extracted with toluene (2 x 10 mL) and the combined organic extracts were dried, filtered and evaporated to yield the product **7a** (126 mg, 72%) as a colourless oil 1:1 mixture of diastereoisomers, which could not be separated.

IR (neat): 2834, 2800, 1714, 1698, 1466, 1305 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.70 (dd, *J* = 7.5, 3.8 Hz, 2H), 7.52 (dd, *J* = 14.3, 7.6 Hz, 2H), 7.33 (dt, *J* = 12.7, 6.5 Hz, 2H), 7.10 – 7.06 (m, 1H), 7.03 – 7.00 (m, 1H), 4.49 – 4.43 (m, 1H), 4.43 – 4.37 (m, 1H), 4.36 – 4.30 (m, 2H), 4.18 – 4.14 (m, 2H), 4.09 (d, *J* = 5.9 Hz, 1H), 3.75 (dd, *J* = 7.2, 4.3 Hz, 1H), 1.29 – 1.24 (m, 3H), 0.87 – 0.81 (m, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 141.3, 129.2, 127.8, 127.2, 127.0, 124.9, 120.1, 119.7, 49.7, 28.7, 18.6, 12.8 ppm.

HRMS (EI) m/z calcd for $C_{21}H_{22}NO_4$ $[M]^+$ = 352.1549; found: 352.1546.

(3*S*)-3-Benzyl-5-methyl-4-tosylmorpholin-2-one (7b)

The ester **6b** (180 mg, 0.5 mmol) and triflic acid (80 mg, 0.5 mmol) in dry toluene (20 mL) were heated for 2 h at 65 °C. The completed reaction was quenched with sat. aq. potassium carbonate (5 mL). The separated aqueous layer was extracted with toluene (2 x 10 mL) and the combined organic extracts were dried, filtered and evaporated to yield the product **7b** (154 mg, 86%) as a yellow oil as a 1:1 mixture of diastereomers, which could not be separated.

IR (neat): 2823, 2801, 1717, 1522, 1112, 1017 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.29 – 7.24 (m, 4H), 7.15 (t, *J* = 6.2 Hz, 5H), 5.34 – 5.11 (m, 1H), 4.24 (d, *J* = 5.4 Hz, 1H), 3.98 (t, *J* = 7.5 Hz, 1H), 3.75 (t, *J* = 7.7 Hz, 1H), 3.14 (dd, *J* = 13.9, 5.2 Hz, 1H), 3.02 (dd, *J* = 14.0, 6.6 Hz, 1H), 2.33 (s, 3H), 0.91 (d, *J* = 7.5 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.0, 143.6, 136.7, 134.8, 129.6, 128.6, 127.2, 67.3, 56.5, 39.6, 21.7, 21.5, 10.2 ppm.

HRMS (CI) m/z calcd for $C_{19}H_{21}NO_4SNa$ $[M]^+$ = 382.1089; found: 382.1082.

2-Methylallyl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino) acetate (8a)

Synthesized according to the general procedure, Fmoc-Gly-OH (1.19 g, 4.0 mmol) gave the allyl ester **8a** as white solid m.p. 109 – 111 °C (1.21 g, 86%).

IR (neat): 3327, 1734, 1686, 1543, 1320, 1170 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 7.5 Hz, 2H), 7.52 (d, *J* = 7.4 Hz, 2H), 7.32 (dd, *J* = 7.5, 1.2 Hz, 2H), 7.23 (dd, *J* = 7.4, 1.2 Hz, 2H), 5.29 (t, *J* = 5.3 Hz, 1H), 4.92 – 4.85 (m, 2H), 4.50 (s, 2H), 4.32 (d, *J* = 7.1 Hz, 2H), 4.15 (t, *J* = 7.1 Hz, 1H), 3.96 (d, *J* = 5.6 Hz, 2H), 1.67 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 156.3, 143.8 (2C), 141.3 (2C), 139.2, 127.8 (2C), 127.0 (2C), 125.13 (2C), 120.0 (2C), 113.7, 68.7, 67.2, 47.1, 42.8, 19.5 ppm.

HRMS (EI) m/z calcd for $C_{21}H_{21}NO_4$ $[M]^+$ = 351.1471; found: 351.1476.

(*S*)-2-Methylallyl2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-methylbutanoate (8b)

Synthesized according to the general procedure, Fmoc-Val-OH (1.36 g, 4.0 mmol) gave the allyl ester **8b** (1.33 g, 85%). $[\alpha]_D^{20}$ –2.00 (c 0.5, CH_2Cl_2).

IR (neat): 2978, 2834, 1702, 1697, 1176, 1043 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.6 Hz, 2H), 7.63 (d, *J* = 7.3 Hz, 2H), 7.43 (dd, *J* = 7.5, 4.3 Hz, 2H), 7.35 (dd, *J* = 7.3, 4.3 Hz, 2H), 5.30 (d, *J* = 4.7 Hz, 1H), 5.04 (s, 1H), 4.99 (s, 1H), 4.60 – 4.53 (m, 2H), 4.43 (d, *J* = 6.7 Hz, 2H), 4.39 (dd, *J* = 9.2, 4.7 Hz, 1H), 4.26 (t, *J* = 7.1 Hz, 1H), 2.32 – 2.18 (m, 1H), 1.79 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.94 (t, *J* = 6.0 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.9, 156.2, 143.9, 143.8, 141.3, 139.2, 127.7, 127.0, 125.1, 119.9, 113.7, 68.6, 67.1, 59.1, 47.2, 31.4, 19.6, 19.1, 17.5 ppm.

HRMS (EI) m/z calcd for $C_{24}H_{27}NO_4$ [M]+ = 393.1949; found: 393.1952.

(*S*)-2-Methylallyl 2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-4-(methylthio)butanoate (8c)

According to general procedure, Fmoc-Met-OH (1.49 g, 4.0 mmol) gave the allyl ester **8c** as yellowish solid, m.p. 94 – 95 °C (1.30 g, 76%). $[\alpha]_D^{20}$ +59.2 (c 1.74, CH_2Cl_2).

IR (neat): 3325, 2943, 1724, 1711, 1238, 1054 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.4 Hz, 2H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 5.46 (d, *J* = 7.7 Hz, 1H), 5.02 (s, 1H), 4.99 (s, 1H), 4.61 – 4.54 (m, 3H), 4.44 (d, *J* = 6.6 Hz, 2H), 4.26 (t, *J* = 6.8 Hz, 1H), 2.57 (t, *J* = 6.9 Hz, 2H), 2.28 – 2.16 (m, 1H), 2.13 (s, 3H), 2.09 – 1.96 (m, 1H), 1.79 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.6, 155.7, 143.7, 141.2, 139.0, 127.6, 126.8, 125.1, 119.8, 113.6, 68.9, 66.9, 53.1, 47.0, 31.9, 29.8, 19.4, 15.4 ppm.

HRMS (EI) m/z calcd for $C_{24}H_{27}NO_4S$ $[M]^+$ = 425.1661; found: 425.1665.

2-Methylallyl (((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-isoleucinate (8d)

According to the general procedure, Fmoc-Ile-OH (1.41 g, 4.0 mmol) gave the allyl ester **8d** as colorless oil (1.40 g, 86%). $[\alpha]_D^{20}$ -6.8 (c 1.5, CH_2Cl_2).

IR (neat): 3304, 2911, 2820, 1720, 1698, 1287, 1165 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 7.5 Hz, 2H), 7.63 (d, *J* = 7.4 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 5.39 (d, *J* = 9.1 Hz, 1H), 5.02 (d, *J* = 7.9 Hz, 1H), 4.98 (s, 1H), 4.66 – 4.53 (m, 2H), 4.45 – 4.38 (m, 2H), 4.26 (t, *J* = 7.0 Hz, 1H), 1.99 – 1.94 (m, 1H), 1.79 (s, 3H), 1.54 – 1.39 (m, 1H), 1.33 – 1.13 (m, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 7.8 Hz, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 156.2, 143.9, 141.3, 139.3), 127.7, 127.1, 125.1, 120.0, 113.9, 68.6, 67.0, 58.5, 47.2, 38.1, 25.0, 19.6, 15.6, 11.7 ppm.

HRMS (CI) m/z calcd for $C_{25}H_{29}NO_4Na[M]+$ = 430.1994; found: 430.1998.

(9*H*-Fluoren-9-yl)methyl 5,5-dimethyl-2-oxomorpholine-4-carboxylate (9a)

According to the general procedure, the ester **8a** (176 mg, 0.5 mmol) and triflic acid (32 mg, 0.2 mmol) gave the product as colourless oil (153 mg, 87%).

IR (neat): 3348, 2974, 1707, 1701, 1522, 1448, 1274 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 7.5 Hz, 2H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.30 (dd, *J* = 10.9, 3.9 Hz, 2H), 7.24 – 7.16 (m, 2H), 4.35 – 4.25 (m, 2H), 4.15 – 4.07 (m, 1H), 3.95 – 3.89 (m, 3H), 1.13 (s, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 156.6, 143.8 (2C), 141.3 (2C), 127.8 (2C), 127.1 (2C), 125.1 (2C), 120.1 (2C), 72.6, 69.7, 67.3, 47.1, 42.8, 26.1 (2C) ppm.

HRMS (EI) m/z calcd for $C_{21}H_{21}NO_4$ $[M]^+$ = 351.1471; found: 351.1465.

(*S*)-(9*H*-Fluoren-9-yl)methyl-3-isopropyl-5,5-dimethyl-2-oxomorpholine-4-carboxylate (9b)

According to the general procedure, the ester **9a** (394 mg, 1.0 mmol) and triflic acid (32 mg, 0.2 mmol) gave the product as colourless oil (385 mg, 98%). $[\alpha]_D^{20}$ –1.18 (c 0.34, CH_2Cl_2).

IR (neat): 3228, 2924, 1717, 1677, 1432, 1198, 1034 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 7.5 Hz, 2H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.30 (dd, *J* = 7.2, 3.0 Hz, 2H), 7.21 (dd, *J* = 7.5, 3.0 Hz, 2H), 4.36 – 4.27 (m, 2H), 4.27 – 4.20 (m, 1H), 4.12 (t, *J* = 6.9 Hz, 1H), 3.98 – 3.90 (m, 2H), 2.22 – 2.10 (m, 1H), 1.15 (*app.* s, 6H), 0.89 (d, *J* = 8.3 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.2, 156.4, 143.8, 141.3, 127.8, 127.1, 125.1, 120.0, 72.7, 69.7, 67.1, 59.3, 47.2, 31.2, 26.2, 19.1, 17.7 ppm.

HRMS (EI) m/z calcd for $C_{24}H_{27}NO_4$ [M]+ = 393.1940; found: 393.1949.

(*S*)-(9*H*-Fluoren-9-yl)methyl 5,5-dimethyl-3-(2-(methylthio)ethyl)-2-oxomorpholine-4-carboxylate (9c)

According to the general procedure, ester **8c** (213 mg, 0.5 mmol) and triflic acid (40 mg, 0.25 mmol) gave the product as yellow oil (192 mg, 90%). $[\alpha]_D^{20}$ -74.4 (c 1.64, CH_2Cl_2).

IR (neat): 3325, 2943, 1724, 1711, 1238, 1054 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ= 7.67 (d, *J* = 7.4 Hz, 2H), 7.50 (d, *J* = 7.4 Hz, 2H), 7.33 – 7.28 (m, 2H), 7.22 (dd, *J* = 7.4, 3.0, 2H), 4.44 (dd, *J* = 12.8, 7.7 Hz, 1H), 4.36 – 4.30 (m, 2H), 4.13 (t, *J* = 6.8 Hz, 1H), 3.96 (s, 2H), 2.47 (t, *J* = 7.2 Hz, 2H), 2.17 – 2.04 (m, 1H), 2.01 (s, 3H), 1.96 – 1.91 (m, 1H), 1.15 (s, 6H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 155.9, 144.0, 141.2, 127.8, 127.1, 124.8, 119.9, 72.6, 69.8, 67.0, 53.6, 47.0, 31.5, 29.8, 26.1, 15.9 ppm.

HRMS (EI) m/z calcd for $C_{24}H_{27}NO_4S$ $[M]^+$ = 425.1661; found: 425.1667.

2-Methylprop-1-en-1-yl (((9*H*-fluoren-9-yl)methoxy)carbonyl)-*L*-isoleucinate (10)

According to the general procedure, ester **8d** (204 mg, 0.5 mmol) and triflic acid (50 mg, 0.5 mmol) gave the product **10** as colourless oil (172 mg, 84%). $[\alpha]_D^{20}$ +2.5 (c 1.6, CH_2Cl_2).

IR (neat): 3007, 2891, 2807, 1675, 1430, 1087 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 7.4 Hz, 2H), 7.53 (d, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.25 (t, *J* = 7.4 Hz, 2H), 6.79 (s, 1H), 5.32 (d, *J* = 7.8 Hz, 1H, 1H), 4.43 – 4.28 (m, 3H), 4.16 (t, *J* = 7.0 Hz, 1H), 1.99 – 1.77 (m, 1H), 1.62 (s, 3H), 1.59 (d, *J* = 1.4 Hz, 3H), 1.47 – 1.32 (m, 1H), 1.26 – 1.14 (m, 1H), 0.94 – 0.84 (m, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.5, 156.1, 143.9, 141.3, 129.5, 127.7, 127.1, 125.1, 120.0, 119.6, 67.1, 58.2, 47.2, 38.2, 25.1, 17.5, 15.5, 14.6, 11.7 ppm.

HRMS (CI) m/z calcd for $C_{25}H_{29}NO_4Na[M]^+$ = 430.1994; found: 430.1999.

(9*H*-Fluoren-9-yl)methyl (3*S*)-3,5-dimethyl-5-(methyl-*d*)-2-oxomorpholine-4-carboxylate (11)

According to the general procedure, ester **1** (183 mg, 0.5 mmol) and sulfuric acid-d2 solution 96-98 wt. % in D_2O (55 mg, 0.5 mmol) (rt, 1 h) gave the product as yellow oil (153 mg, 86%).

IR (neat): 2352, 2983, 1723, 1719, 1122, 1067 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 7.2 Hz, 2H), 7.41 – 7.22 (m, 2H), 7.24 – 7.13 (m, 4H), 4.35 – 4.26 (m, 3H), 4.10 (t, *J* = 6.9 Hz, 1H), 3.93 (q, *J* = 7.0 Hz, 2H), 1.35 (d, *J* = 7.0 Hz, 12H), 1.12 (d, *J* = 3.8 Hz, 2H), 1.12 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.0, 155.8, 143.7, 141.2, 127.5, 127.0, 125.0, 120.0, 72.7, 69.7, 67.1, 53.4, 49.8, 47.1, 26.0 (t, *J* = 6.9 Hz), 18.5, 17.5 ppm.

HRMS (EI) m/z calcd for $C_{22}H_{22}DNO_4$ $[M]^+$ = 366.1690; found: 366.1694.

Acknowledgment

Support from the School of Chemistry, Cardiff University, is gratefully acknowledged. We thank the EPSRC National Mass Spectrometry Facility, Swansea, for mass spectrometric data.

Supporting Information

Yes

Primary Data

No

References

(1) (a) Nilsson, J. W.; Kvarnström, I.; Musil, D.; Nilsson, I.; Samulesson, B. *J. Med. Chem.* **2003**, *46*, 3985. (b) Wijtmans, R.; Vink, M. K. S.; Schoemaker, H. E.; Deilt, F. L.; Blaauw, R. H. *Synthesis* **2004**, 641. (c) Couladours, E. A.; Moutsos, V. I.; Pitsinos, E. N. *Tetrahedron Lett.* **2004**, *45*, 7779. (d) Shikre, B. A.; Deshmukh, A. R. A. S. *Tetrahedron: Asymmetry* **2004**, *15*, 1081. (e) Ku, I. W.; Cho, S.; Doddareddy, M. R.; Jang, M. S.; Keum, G.; Lee, J.-H.; Chung, B. Y.; Kim, Y.; Rhima, H.; Kang, S. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5244.

(2) Bardiot, D.; Thevissen, K.; De Brucker, K.; Peeters, A.; Cos, P.; Taborda, C. P.; McNaughton, M.; Maes, L.; Chaltin, P.; Cammue, B. P. A.; Marchand, A. *J. Med. Chem.* **2015**, *58*, 1502.

(3) Gonzalez, A. Z.; Eksterowicz, J.; Bartberger, M. D.; Beck, H. P.; Canon, J.; Chen, A.; Chow, D.; Duquette, J.; Fox, B. M.; Fu, J.; Huang, X.; Houze, J. B.; Jin, L.; Li, Z.; Li, Z.; Ling, Y.; Lo, M.-C.; Long, A. M.; McGee, L. R.; McIntosh, J.; McMinn, D. L.; Oliner, J. D.; Osgood, T.; Rew, Y.; Saiki, A. Y.; Shaffer, P.; Wortman, S.; Yakowec, P.; Yan, X.; Ye, Q.; Yu, D.; Zhao, X.; Zhou, J.; Olson, S. H.; Medina, J. C.; Sun, D. *J. Med. Chem.* **2014**, *57*, 2472.

(4) Blake, T. R.; Waymouth, R. M. *J. Am. Chem. Soc.* **2014**, *136*, 9252.

(5) Kashima, C.; Harada, K. *J. Org. Chem.* **1989**, *54*, 789.

(6) (a) Chung, K.; Banik, S. M.; De Crisci, A. G.; Pearson, D. M.; Blake, T. R.; Olsson, J. V.; Ingram, A. J.; Zare, R. N.; Waymouth, R. M. *J. Am. Chem. Soc.* **2013**, *135*, 7593. (b) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. *Nature* **2014**, *510*, 129.

(7) (a) Endo, Y.; Bäckvall, J.-E. *Chem. Eur. J.* **2011**, *17*, 12596. (b) Zhang, J.; Balaraman, E.; Leitus, G.; Milstein, D. *Organometallics* **2011**, *30*, 5716. (c) Nicklaus, C. M.; Phua, P. H.; Buntara, T.; Noel, S.; Heeres, H. J.; de Vries, J. G. *Adv. Synth. Catal*. **2013**, *355*, 2839.

(8) Mitsudome, T.; Noujima, A.; Mizugaki, T.; Jitsukawa, K.; Kaneda, K. *Green Chem*. **2009**, *11*, 793.

(9) (a) Zhao, M. M.; McNamara, J. M.; Ho, G.-J.; Emerson, K. M.; Song, Z. J.; Tschaen, D. M.; Brands, K. M. J.; Dolling, U.-H.; Grabowski, E. J. J.; Reider, P. J.; Cottrell, I. F.; Ashwood, M. S.; Bishop, B. C. *J. Org. Chem.* **2002**, *67*, 6743. (b) Kasima, C.; Harada, K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 152. (c) Samanta, S.; Mal, A.; Halder, S.; Ghorai, M. K. *Synthesis* **2015**, *47*, 3776.

(10) Numajiri, Y.; Jiménez-Osés, G.; Wang, B.; Houk, K. N.; Stoltz, B. M. *Org. Lett.* **2015**, *17*, 1082.

(11) (a) Griffiths-Jones, C. M.; Knight, D. W. *Tetrahedron* **2010**, *66*, 4150. (b) Griffiths-Jones, C. M.; Knight, D. W. *Tetrahedron* **2011**, *67*, 8515. (c) Aldmairi, A. H.; Knight, D. W.; Wirth, T. *Synlett* **2017**, *28*, 2976. (d) Aldmairi, A. H.; Griffiths-Jones, C.; Dupauw, A.; Henderson, L.; Knight, D. W. *Tetrahedron Lett.* **2017**, *58*, 3690.

(12) Zhong, C.; Wang, Y.; Hung, A. W.; Schreiber, S. L.; Young D. W. *Org. Lett.* **2011**, *13*, 5556.

(13) Thomanek, H.; Schenk, S. T.; Stein, E.; Kogel, K.-H.; Schikora, A.; Maison, W. *Org. Biomol. Chem*. **2013**, *11*, 6994.