Synthesis Z. Qureshi et al. Special Topic

Introduction of Hindered Electrophiles via C–H Functionalization in a Palladium-Catalyzed Multicomponent Domino Reaction

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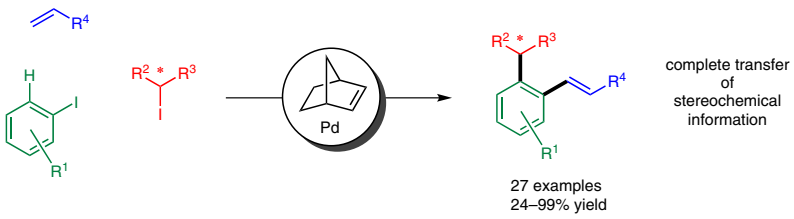

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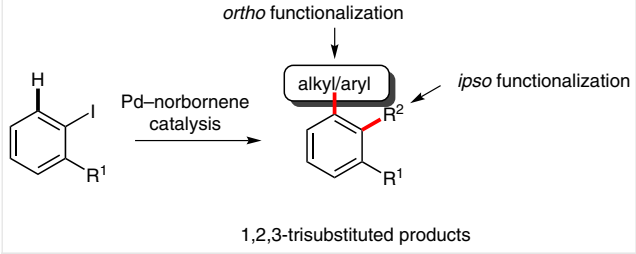
Abstract A general method for the incorporation of secondary alkyl iodides in a palladium-catalyzed multicomponent domino reaction is reported. With the relatively inexpensive $Pd(OAc)_2$ as the catalyst and norbornene as a mediator, a variety of 1,2,3-trisubstituted aromatic compounds were synthesized. The reaction was shown to be scalable, producing excellent isolated yields on up to 5 mmol scale. Chiral alkyl iodides were also incorporated without any loss of stereochemical information. The developed method offers an expedient and mild C–H functionalization strategy for the synthesis of sterically congested aromatic compounds in a one-pot process.

Key words multicomponent reaction, palladium, Catellani reaction, domino reaction, C–H functionalization

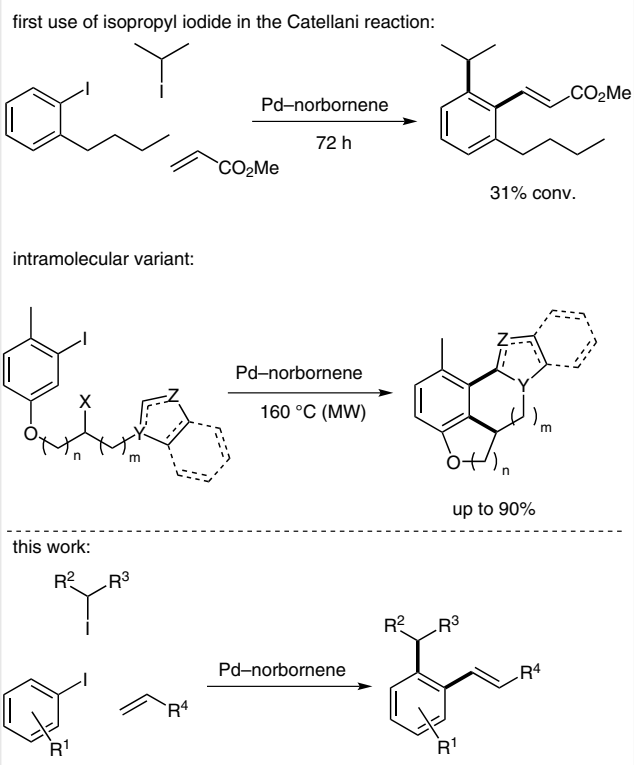
In the recent past, there has been an ongoing drive to develop directed C–H functionalization methods. Transition metals such as palladium, rhodium, and ruthenium have been shown to perform C–H functionalizations in a selective manner, provided that there is a suitable directing group.[1] However, these types of C–H activation strategies are very sensitive to sterically congested systems. Few examples of 1,2,3-trisubstituted aromatic compounds have been reported using these methods, the most common of which has been the method developed by Catellani.[2] Since 2000, our group has explored the power of this methodology, which utilizes a palladium catalyst, to functionalize an iodinated aromatic substrate at the *ortho*- and *ipso*-positions. The standard Catellani reaction involves an aryl iodide that is either alkylated or arylated *ortho* to the starting iodide, and a catalytic cycle terminator, generally an olefin, which undergoes a Mizoroki–Heck coupling (Scheme 1).



Scheme 1 General Catellani reaction scheme

During the course of our studies, we have published accounts detailing the utility of this remarkable reaction, most recently demonstrating its synthetic utility in the complex natural product synthesis of (+)-linoxepin.[3] Shortly after this publication, the group of Gu reported an elegant synthesis of (±)-rhazinal by utilizing an *ortho* arylation strategy of an iodinated pyrrole.[4] These reports testify to the reliability of the Catellani reaction to provide complex molecular scaffolds in useful quantities while reducing the number of synthetic steps, resulting in concise syntheses. Despite these advances, technological limitations of the method prevent further strategic applications. The vast majority of reports utilizing this type of reaction have been restricted to simple primary alkyl halides. The few reports that have utilized hindered alkyl halides suffer from low conversions, harsh reaction conditions, and poor modularity. The first report of the incorporation of isopropyl iodide in the Catellani reaction gave 31% conversion over three days.[5] In 2000, a more practical procedure was reported that produced sterically hindered 2,6-diisopropyl biphenyl in 71% yield after 144 hours.[6] In 2007, our group utilized a tethering strategy to improve the utilization of secondary alkyl halides (Scheme 2). Good yields were obtained, but the reaction required microwave irradiation with extreme temperatures (150–180 °C).[7,8] Moreover, the need for a

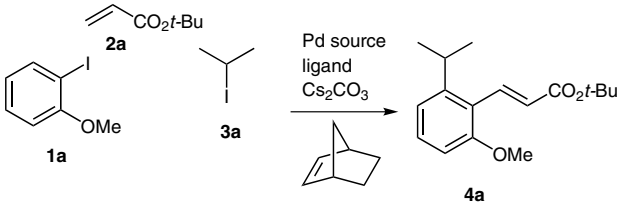
tether limits the scope of the reaction because the starting materials have to be prepared in a number of steps. Demonstrations of a scalable intermolecular multicomponent reaction with secondary halides remain scarce. To advance this methodology, we looked for ways to improve the incorporation of hindered alkyl iodides. In an effort to maximize modularity, our studies focused primarily on the reaction conditions. In particular, we looked to decrease reaction temperature. Lastly, we wanted to develop a method that would be easily scalable.



Scheme 2 Previous reported use of secondary alkyl halides

We began our studies on the incorporation of secondary alkyl halides with an excess (10 equiv) of isopropyl iodide. Relatively inexpensive $Pd(OAc)_2$ (10 mol%) with triphenyl phosphine (22 mol%) as ligand/reducing agent[9] was chosen as the starting catalyst. The reaction has been well documented[10] to require an excess of inorganic base and, as such, anhydrous Cs_2CO_3 was selected and used in a 5-fold excess to the starting *ortho*-substituted aryl iodide, 2-iodoanisole. Although norbornene is catalytic in the reaction, five equivalents were used to ensure selectivity over *tert*-butyl acrylate, which was used as the catalytic cycle terminator in 5-fold excess. A polar aprotic solvent, anhydrous and degassed acetonitrile, was used as solvent. The reaction was set up in a sealed vial with a Teflon-coated cap in a preheated (90 °C) oil bath. Gratifyingly, the reaction was com-

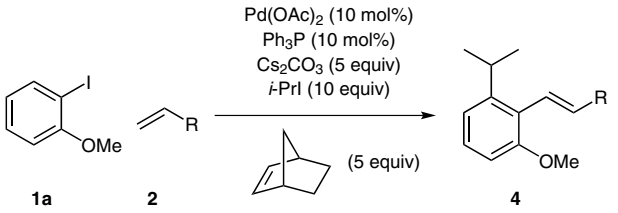
Table 1 Reaction Optimization[a]



Entry	*i*PrI (equiv)	Catalyst (mol%)	Solvent	Time (h)	Yield (%)
1	**10**	**10**	**MeCN**	**4**	**92**
2	10	5	MeCN	6	72
3	10	2.5	MeCN	16	52
4	10	1	MeCN	24	–
5	**5**	**10**	**MeCN**	**6**	**96**
6	2.5	10	MeCN	6	47
7	2.5	10	DMF	6	70
8	1	10	MeCN	6	36
9	1	10	DMF	6	58

[a] Reaction conditions: 2-iodoanisole (1 equiv), catalyst, PPh_3 (22 mol%), Cs_2CO_3 (5 equiv), *tert*-butyl acrylate (5 equiv), norbornene (5 equiv), sealed tube, 90 °C, solvent (3 mL).

Table 2 Heck Acceptor Screen[a]



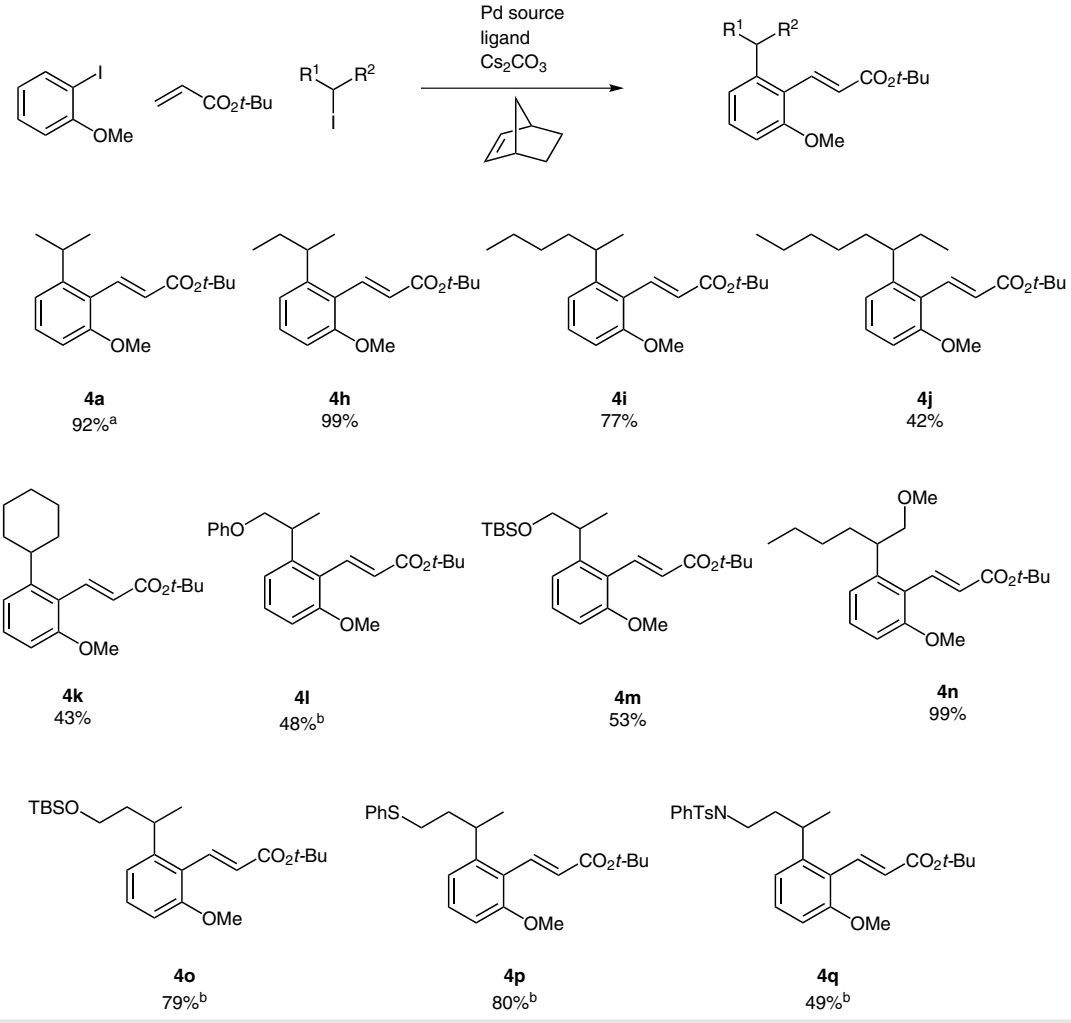
Entry	Compound	Heck acceptor	Olefin (equiv)	Yield (%)
1	**4a**	*tert*-butyl acrylate	5	92
2	**4a**	*tert*-butyl acrylate	2.5	58
3	**4a**	*tert*-butyl acrylate	1	36
4	**4b**	methyl acrylate	5	24
5	**4c**	ethyl acrylate	5	39
6	**4d**	benzyl acrylate	5	44
7	**4e**	hexyl acrylate	5	66
8	**4f**	*tert*-butyl acrylamide	5	49
9	**4g**	styrene	5	33

[a] Reaction conditions: 2-iodoanisole (0.13 mL, 1 mmol), *i*-PrI (1ml, 10 mmol), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), Ph_3P (57.6 mg, 0.22 mmol), Cs_2CO_3 (1.63 g, 5 mmol), norbornene (470 mg, 5 mmol), sealed tube, 90 °C, MeCN (3 mL).

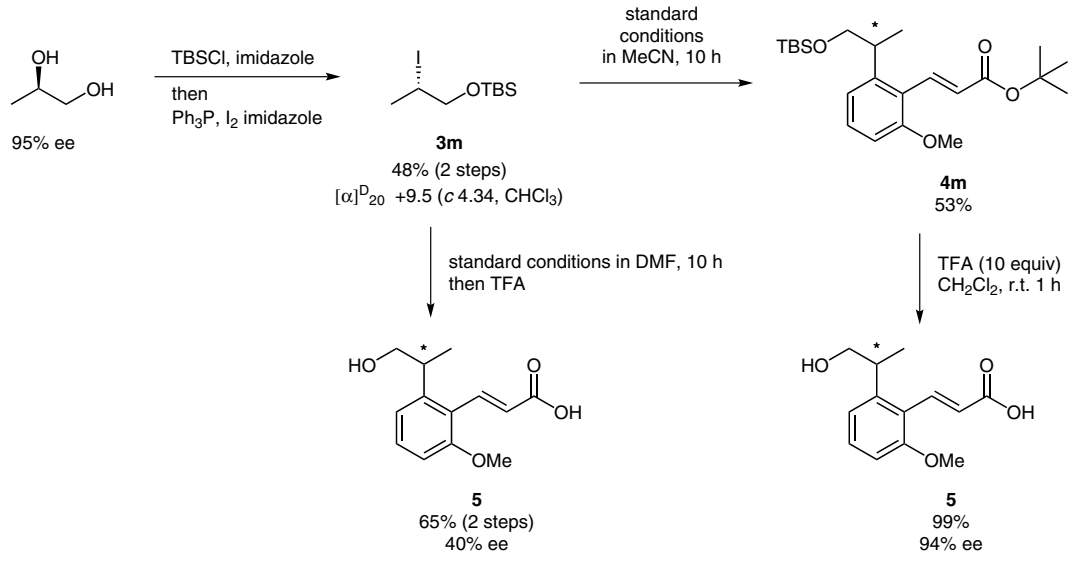
plete within four hours and provided the 1,2,3-trisubstituted aromatic compound in an isolated yield of 92% (Table 1, entry 1). Attempts to reduce the catalyst loading resulted in a decrease in the yield, and the reaction required longer to reach full conversion (entries 2–4). Reducing the number of equivalents of isopropyl iodide to five equivalents gave a similar yield (entry 5) but we observed a drop in yield when less than five equivalents was used (entries 6–9). The use of *N*,*N*-dimethylformamide (DMF) as solvent partially offset this decrease (compare entries 6 and 7 to 8 and 9). For our subsequent reactions, ten equivalents of iodide were used, foreseeing difficulty with more hindered substrates. With these results in hand, we screened a range of olefins as the chain terminator.

Decreasing the number of equivalents of *tert*-butyl acrylate resulted in a decrease in yield (Table 2, entries 1–3). By varying the size of the ester it became readily apparent that steric effects in the ester played a significant role in determining the product yield. Our hypothesis is that, under the reaction conditions, the less sterically hindered acrylates are hydrolyzed prior to the final Heck reaction, which leads to lower overall yields (entries 4–7). Both *tert*-butyl acrylamide and styrene were competent in the reaction, although with decreased yield. To ensure we had developed a reliable and scalable reaction, we repeated our conditions on 5 mmol scale and were able to isolate the desired product in 90% yield (Scheme 3). With the conditions optimized, a range of alkyl halides were then tested.

Straight-chain alkyl iodides worked well in the reaction (Scheme 3), with yields ranging from 42% for 3-octyl, to near quantitative for 2-butyl. Cycloalkyl substituents could also be incorporated (43%). Substrates with β-heteroatoms were participants, giving good to excellent yields (48, 53, and 99%). γ-Heteroatoms were also amenable in the reac-



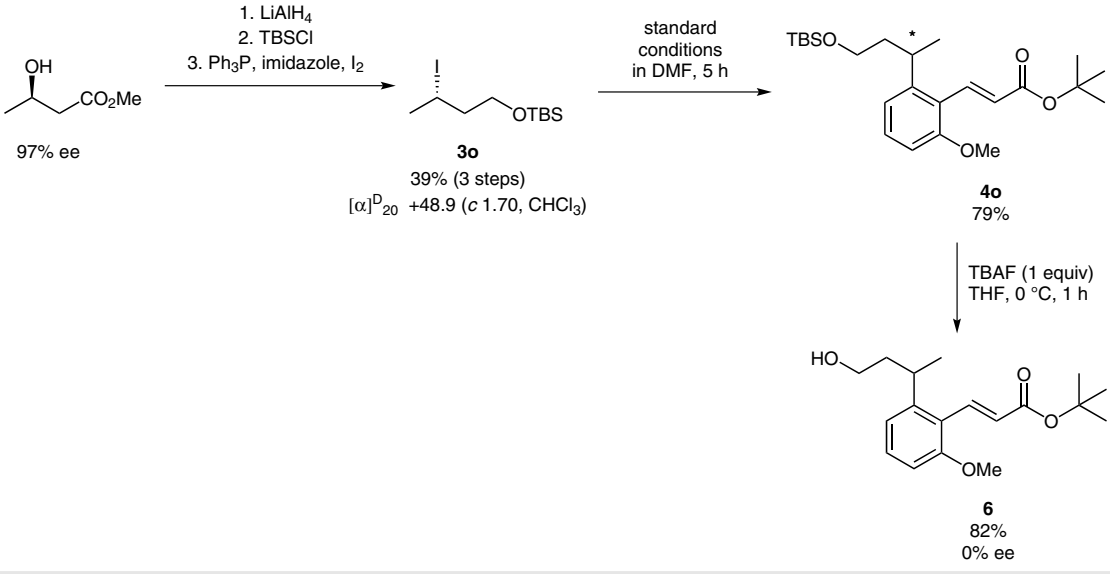
Scheme 3 *Reagents and conditions*: 2-iodoanisole (0.13 mL, 1 mmol), *tert*-butyl acrylate (0.72 mL, 5 mmol), alkyl iodide (10 mmol), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), Ph_3P (57.6 mg, 0.22 mmol), Cs_2CO_3 (1.63 g, 5 mmol), norbornene (470 mg, 5 mmol), sealed tube, 90 °C, MeCN (3mL). All alkyl iodides used were either commercially available or prepared by reported methods. [a] Yield: 90% on 5 mmol scale. [b] Reaction carried out in DMF (3 mL).



Scheme 4 Catellani reaction with chiral alkyl iodide with β-heteroatom

tion, giving good yields for the oxygen-, sulfur-, and nitrogen-containing substrates. Although all of these reactions required 10 equivalents of the alkyl iodide, the nonvolatile iodides could be recovered through flash column chromatography.

Our next goal was to probe the alkylation step. In a previous report, our group reported the use of chiral, tethered alkyl iodides in which the alkylation step was shown to proceed without loss of stereochemical information.[7] To build a synthetically useful methodology, we needed to determine whether this was also the case in our intermolecular reaction. Enantioenriched propane diol, prepared in 95% ee by using the method of Jacobsen, was silylated at the primary hydroxyl group (Scheme 4).[11,12] The Appel reaction was utilized to convert the secondary alcohol into iodide **3m**.[13] When this substrate was introduced into the reaction with MeCN as solvent, the product was obtained in 53% yield. Since **4m** was inseparable by chiral HPLC, the TBS group and the *tert*-butyl ester were cleaved by treatment with trifluoroacetic acid (10 equiv). The resulting acid **5**, was found to have 94% ee. The excess iodide was recovered with little erosion of the ee. In contrast, racemization was



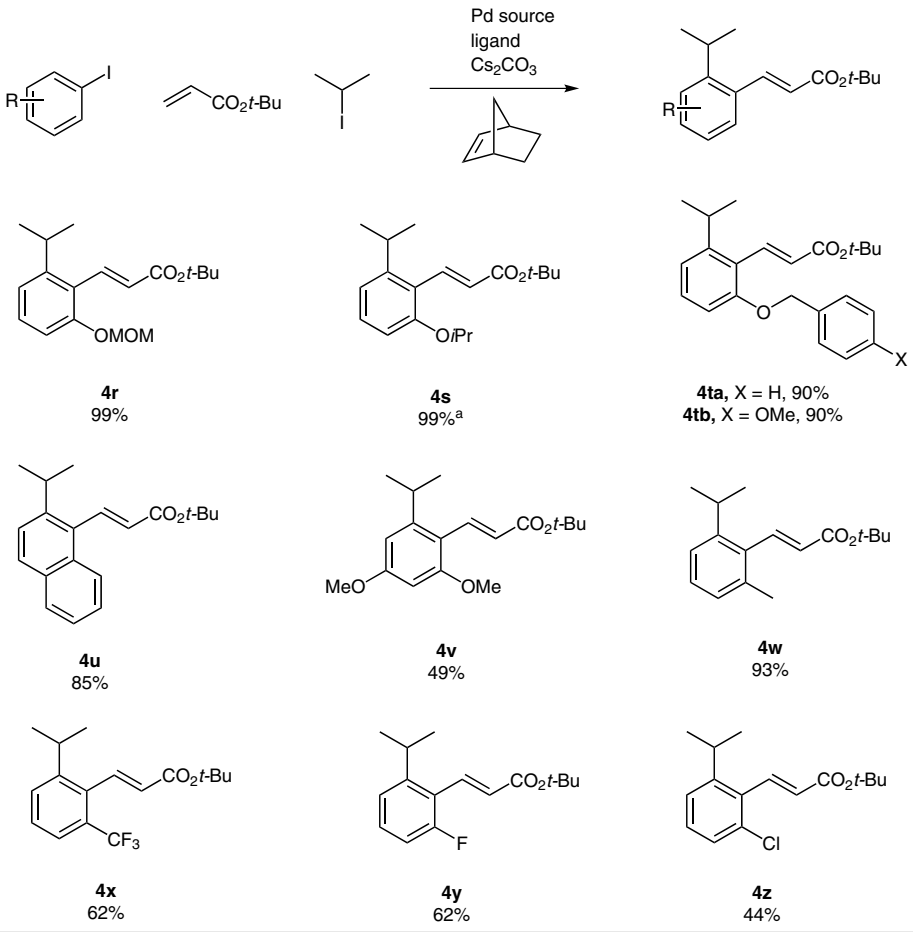
Scheme 5 Catellani reaction with chiral alkyl iodide without β-heteroatom

observed when the reaction was performed in DMF; the product after deprotection had 40% ee. Moreover, the recovered iodide was almost completely racemized. Although the alkyl iodide was shown to racemize in DMF, the product was obtained in higher yield compared with that obtained when the reaction was performed in MeCN (Scheme 4). To determine the absolute stereochemistry of **5**, both samples (from MeCN and DMF) were subjected to crystallization conditions. The sample with 94% ee failed to crystallize despite numerous attempts. The sample with 40% ee produced crystals; however, the crystals obtained were racemic.[14]

We took a similar approach to obtain **4o** (Scheme 5). Enantioenriched iodide **3o**, was synthesized starting from commercial methyl (*R*)-3-hydroxybutyrate. Reduction with $LiAlH_4$,[15] followed by protection of the primary hydroxyl group under cryogenic conditions led to an intermediate alcohol, which was transformed into iodide **3o**. Introducing **3o** into the reaction mixture with MeCN as solvent produced trace amounts of **4o**. In DMF, **4o** was obtained in 79% yield, but with 0% ee (ee determined for the free alcohol). The excess starting material was also recovered as the racemate. Under these conditions, β-heteroatoms thus appear to be essential for providing access to enriched products (Scheme 5).

Finally, we looked at the influence of the aryl iodide. Both electron-rich and electron-poor substrates gave good yields (Scheme 6). Notably, when 2-iodophenyl acetate was introduced into the reaction mixture, the product obtained was not the acetylated phenol. Rather, the acetyl group was cleaved in situ and the resultant phenoxide was converted into the corresponding isopropyl ether, **4s**. The incorporation of the chlorinated aromatic compound provides an extra handle for derivatization.[16]

In conclusion, we have developed a general procedure with which to incorporate hindered secondary alkyl iodides in the Catellani reaction in an intermolecular fashion. The optimized procedure allows for the incorporation of various



Scheme 6 Scope of the reaction with respect aryl iodide. *Reagents and conditions*: 2-iodoaromatic (1 mmol), *tert*-butyl acrylate (0.72 mL, 5 mmol), *i*-PrI (1 mL, 10 mmol), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), Ph_3P (57.6 mg, 0.22 mmol), Cs_2CO_3 (1.63 g, 5 mmol), norbornene (470 mg, 5 mmol), sealed tube, 90 °C, MeCN (3 mL). All aryl iodides used were either commercially available or prepared by reported methods. [a] 2-Iodophenyl acetate used as starting material.

alkyl iodide electrophiles starting from a range of aryl iodides. The termination step was shown to be flexible, and a range of olefins could be used. The multicomponent reaction offers a highly modular approach for the synthesis of sterically congested 1,2,3-trisubstituted aromatic compounds. Excellent isolated yields were obtained on reaction scales up to 5 mmol. Chiral products could also be produced from readily available starting materials, with complete transfer of stereochemical information.

TLC was performed with EMD TLC silica gel 60 F254 aluminum sheets. Visualization was accomplished with 254 nm UV light followed by staining with potassium permanganate or vanillin solution. Flash and gradient column chromatography were carried out using Silicycle Ultra-Pure 230–400 mesh silica gel. Melting points were measured with a Fisher–Johns melting-point apparatus and are uncorrected. IR spectra were obtained with a Perkin–Elmer Spectrum 1000 FTIR spectrophotometer as neat films or as solutions ($CHCl_3$) on a NaCl plate. Data are presented as frequency of absorption (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded at 23 °C in $CDCl_3$ with a Bruker Avance 400 spectrometer, Varian Mercury 400 spectrometer, Varian Unity 500 spectrometer, or Agilent DD2-600 spectrometer. Shifts for protons are reported in parts per million (δ scale) and are referenced to residual proton signals in the NMR solvent ($CDCl_3$: δ = 7.26 ppm). Chemical shifts for carbon resonances are reported in parts per million (δ scale) and are referenced to the carbon resonances of the solvent ($CDCl_3$: δ = 77.16 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, pent = pentet, m = multiplet), coupling constant (*J*, Hz) and integration. HPLC chromatograms were recorded with an Agilent 1100 series instrument, controlled by ChemStation LC 3D software, v. 10.02. High-resolution mass spectra were obtained with a SI2 Micromass 70S-250 mass spectrometer (EI) or an ABI/Sciex Qstar mass spectrometer (ESI).

General Procedure

$Pd(OAc)_2$ (22.4 mg, 0.10 mmol, 0.1 equiv), Ph_3P (57.6 mg, 0.22, 0.22 equiv), and Cs_2CO_3 (1.63 g, 5 mmol, 5 equiv) were added to a flame-dried, sealable vial under argon. Dry, degassed MeCN or DMF (3 mL) was added and the yellow mixture was stirred under argon for approximately 5 min. Aryl iodide (1.00 mmol, 1 equiv), alkyl iodide (10.00 mmol, 10 equiv), and olefin (5.00 mmol, 5 equiv) were added successively to the reaction mixture under argon. The mixture was stirred for 5 min, then solid norbornene (470 mg, 5.00 mmol, 5 equiv) was added. After a final argon purge, the vial was capped and placed in an oil bath that had been preheated to 90 °C. After 4–10 h, the mixture was cooled to r.t. Reactions performed in MeCN were filtered over a short pad of Celite (eluting with CH_2Cl_2) and concentrated in vacuo. Reactions performed in DMF were diluted with EtOAc–hexanes (1:1) and washed with brine twice. After drying with $MgSO_4$, the organic layer was filtered and concentrated. The crude products were purified by flash column chromatography (CH_2Cl_2–hexanes, 1:5, then Et_2O–hexanes, 1:100→1:25).

Large-Scale Reaction

$Pd(OAc)_2$ (112 mg, 0.5 mmol, 0.1 equiv), Ph_3P (288 mg, 1.1 mmol, 0.22 equiv), and Cs_2CO_3 (8.15 g, 25 mmol, 5 equiv) were added to a flame-dried 150 mL pressure flask under argon. Dry, degassed MeCN (15 mL) was added and the yellow mixture was stirred under argon for approximately 10 min. 2-Iodoanisole (0.65 mL, 5 mmol, 1 equiv), 2-iodopropane (5 mL, 50 mmol, 10 equiv), and *tert*-butyl acrylate (3.6 mL, 25 mmol, 5 equiv) were added successively to the reaction mixture by using a syringe. The mixture was stirred for 10 min, then solid norbornene (2.35 g, 25 mmol, 5 equiv) was added. After a final argon purge, the flask was capped and placed in an oil bath that had been preheated to 90 °C. After 4 h, the mixture was cooled to r.t., filtered over a pad of Celite (eluting with CH_2Cl_2), and concentrated in vacuo. The crude oil was purified by flash column chromatography (CH_2Cl_2–hexanes, 1:5, then again with Et_2O–hexanes, 1:100→1:25) to obtain the desired product (1.24 g, 4.5 mmol, 90%) as a clear oil.

tert-Butyl (*E*)-3-(2-Isopropyl-6-methoxyphenyl)acrylate (4a)

Yield: 254 mg (92%); clear oil.

IR (neat): 2965, 1722, 1623, 1595, 1572, 1470, 1456, 1447, 1436, 1391, 1367, 1311, 1263, 1061, 753 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 16.15 Hz, 1 H), 7.27 (t, *J* = 8.06 Hz, 1 H), 6.96 (d, *J* = 7.97 Hz, 1 H), 6.77 (d, *J* = 8.30 Hz, 1 H), 6.49 (d, *J* = 16.12 Hz, 1 H), 3.85 (s, 3 H), 3.37 (hept, *J* = 6.82 Hz, 1 H), 1.56 (s, 9 H), 1.25 (d, *J* = 6.85 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.30, 158.53, 149.86, 137.53, 129.93, 124.94, 121.78, 117.90, 108.31, 80.19, 55.54, 29.44, 28.36, 23.91.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{17}H_{25}O_3$: 277.18037; found: 277.18024.

Methyl (*E*)-3-(2-Isopropyl-6-methoxyphenyl)acrylate (4b)

Yield: 56 mg (24%); clear oil.

IR (neat): 2960, 2927, 2869, 2358, 1733, 1717, 1595, 1572, 1471, 1460, 1456, 1436, 1309, 1263, 1219, 1194, 1166, 1061, 1047, 772 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 16.2 Hz, 1 H), 7.29 (t, *J* = 8.1 Hz, 1 H), 6.96 (dd, *J* = 7.8, 1.1 Hz, 1 H), 6.77 (d, *J* = 8.3 Hz, 1 H), 6.56 (d, *J* = 16.2 Hz, 1 H), 3.85 (s, 3 H), 3.81 (s, 3 H), 3.35 (hept, *J* = 6.8 Hz, 1 H), 1.24 (d, *J* = 6.8 Hz, 7 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.36, 158.62, 150.04, 138.97, 130.26, 122.91, 121.69, 118.01, 108.44, 55.64, 51.72, 29.55, 23.97.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{14}H_{19}O_3$: 235.13342; found: 235.13352.

Ethyl (*E*)-3-(2-Isopropyl-6-methoxyphenyl)acrylate (4c)

Yield: 97 mg (39%); clear oil.

IR (neat): 2963, 2938, 2871, 2838, 2358, 25331, 2323, 1699, 1668, 1623, 1595, 1572, 1471, 1462, 1456, 1436, 1365, 1201, 1109, 1095, 1060, 407, 986, 791, 754 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 16.1 Hz, 1 H), 7.28 (t, *J* = 8.1 Hz, 1 H), 6.96 (dd, *J* = 7.9, 1.0 Hz, 1 H), 6.77 (d, *J* = 8.0 Hz, 1 H), 6.55 (d, *J* = 16.2 Hz, 1 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 3.85 (s, 3 H), 3.35 (hept, *J* = 6.8 Hz, 1 H), 1.35 (t, *J* = 7.1 Hz, 3 H), 1.24 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.97, 158.60, 150.02, 138.70, 138.69, 130.18, 123.31, 123.30, 121.75, 117.99, 108.40, 60.47, 55.64, 29.53, 23.97, 14.52.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{15}H_{21}O_3$: 249.14907; found: 249.14853.

Benzyl (*E*)-3-(2-Isopropyl-6-methoxyphenyl)acrylate (4d)

Yield: 136 mg (44%); clear oil.

IR (neat): 2958, 2930, 2871, 2859, 2358, 2331, 2323, 2312, 1711, 1627, 1595, 1572, 1471, 1460, 1437, 1035, 1263, 1231, 1183, 166, 1060, 1050, 957, 868, 791, 753 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 16.1 Hz, 1 H), 7.49–7.26 (m, 6 H), 6.96 (dd, *J* = 7.9, 1.0 Hz, 1 H), 6.77 (dd, *J* = 8.3, 1.3 Hz, 1 H), 6.64 (d, *J* = 16.2 Hz, 1 H), 5.27 (s, 2 H), 3.85 (s, 3 H), 3.36 (hept, *J* = 6.8 Hz, 1 H), 1.24 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.85, 158.73, 150.15, 139.26, 139.25, 136.45, 130.35, 128.68, 128.41, 128.40, 128.28, 122.77, 122.77, 121.56, 117.99, 108.43, 66.34, 55.62, 29.54, 23.97.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{20}H_{23}O_3$: 311.16472; found: 311.16499.

Hexyl (*E*)-3-(2-Isopropyl-6-methoxyphenyl)acrylate (4e)

Yield: 201 mg (66%); clear oil.

IR (neat): δ = 2963, 2940, 2871, 2837, 2358, 2331, 2323, 2312, 1697, 1683, 1622, 1595, 1572, 1497, 1472, 1456, 1437, 1373, 1364, 1389, 1321, 1184, 1109, 1059, 1050, 957, 868, 753 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 16.2 Hz, 1 H), 7.28 (dd, *J* = 8.3, 7.8 Hz, 1 H), 6.96 (dd, *J* = 7.9, 1.0 Hz, 1 H), 6.77 (dd, *J* = 8.3, 1.3 Hz, 1 H), 6.56 (d, *J* = 16.1 Hz, 1 H), 4.20 (t, *J* = 6.8 Hz, 2 H), 3.85 (s, 3 H), 3.35 (hept, *J* = 6.8 Hz, 1 H), 1.71 (ddt, *J* = 8.9, 7.9, 6.7 Hz, 2 H), 1.45–1.37 (m, 2 H), 1.37–1.29 (m, 4 H), 1.24 (s, 3 H), 1.23 (s, 3 H), 0.94–0.88 (m, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.06, 158.62, 150.01, 138.63, 130.18, 123.30, 123.29, 121.72, 117.98, 108.41, 64.73, 55.64, 31.64, 29.55, 28.87, 25.83, 23.96, 22.71, 14.16.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{19}H_{29}O_3$: 305.21167; found: 305.21134.

***N*-(*tert*-Butyl) (*E*)-3-(2-Isopropyl-6-methoxyphenyl)acrylamide (4f)**

Yield: 135 mg (49%); white solid; mp 156–157 °C.

IR (neat): 3267, 2964, 2929, 2869, 1651, 1619, 1614, 1595, 1572, 1547, 15374, 1532, 1470, 1453, 1437, 1390, 1363, 1359, 1334, 1265, 1256, 1223, 1204, 1811, 1062, 1048, 987, 791, 771, 751 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 15.6 Hz, 1 H), 7.25 (t, *J* = 8.0 Hz, 1 H), 6.95 (dd, *J* = 7.9, 1.0 Hz, 1 H), 6.76 (dd, *J* = 8.1, 1.2 Hz, 1 H), 6.44 (d, *J* = 15.6 Hz, 1 H), 5.40 (s, 1 H), 3.84 (s, 3 H), 3.39 (hept, *J* = 6.8 Hz, 1 H), 1.44 (s, 10 H), 1.22 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.11, 158.37, 150.02, 134.11, 129.49, 126.82, 122.19, 118.05, 108.41, 55.68, 51.55, 29.42, 29.12, 24.01.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{17}H_{26}NO_2$: 276.1958; found: 276.1971.

(*E*)-1-Isopropyl-3-methoxy-2-styrylbenzene (4g)

Yield: 83 mg (33%); clear oil.

IR (neat): 2963, 2936, 2880, 2869, 2834, 2358, 2331, 2323, 2312, 1595, 1570, 1493, 1469, 1459, 1436, 1253, 1062, 1045, 1028, 980, 786, 751, 691 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.54 (ddd, *J* = 7.8, 1.3, 0.6 Hz, 2 H), 7.42–7.35 (m, 2 H), 7.31–7.23 (m, 1 H), 7.24–7.19 (m, 2 H), 6.99 (dd, *J* = 7.9, 1.0 Hz, 1 H), 6.95 (d, *J* = 16.5 Hz, 1 H), 6.81–6.77 (m, 1 H), 3.85 (s, 3 H), 3.44 (hept, *J* = 6.8 Hz, 1 H), 1.27 (d, *J* = 6.9 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.59, 148.58, 138.32, 134.06, 128.71, 128.04, 127.45, 126.54, 125.17, 123.09, 118.03, 108.21, 55.74, 29.53, 24.08.

HRMS (ESI): *m*/*z* [M + H] calcd for $C_{18}H_{21}O_2$: 253.1587; found: 253.1591.

***tert*-Butyl (*E*)-3-[2-(*sec*-butyl)-6-methoxyphenyl]acrylate (4h)**

Yield: 288 mg (99%); clear oil.

IR (neat): 2964, 2933, 1705, 1627, 1595, 1572, 1471, 1465, 1367, 1311, 1261, 1149, 1062, 983, 875, 752 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 16.11 Hz, 1 H), 7.26 (m, 1 H), 6.90 (dd, *J* = 1.02, 7.92 Hz, 1 H), 6.76 (dd, *J* = 1.28, 8.2 Hz, 1 H), 6.45 (d, *J* = 16.13 Hz, 1 H), 3.85 (s, 3 H), 3.31 (hept, *J* = 6.97 Hz, 1 H), 1.61 (m, 2 H), 1.55 (s, 9 H), 1.21 (d, *J* = 6.85 Hz, 6 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.32, 158.51, 149.95, 137.77, 129.83, 125.04, 122.52, 118.45, 108.19, 80.22, 55.57, 36.38, 31.00, 28.40, 21.85, 12.26.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{18}H_{27}O_3$: 291.19602; found: 291.19637.

***tert*-Butyl (*E*)-3-[2-(Hexan-2-yl)-6-methoxyphenyl]acrylate (4i)**

Yield: 245 mg (77%); clear oil.

IR (neat): 2961, 2928, 2865, 1708, 1632, 1599, 1573, 1473, 1436, 1390, 1369, 1315, 1265, 1152, 1068, 985, 881, 793, 768, 756 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 16.1 Hz, 1 H), 7.30–7.19 (m, 1 H), 6.90 (dd, *J* = 7.9, 1.0 Hz, 1 H), 6.75 (dd, *J* = 8.2, 1.1 Hz, 1 H), 6.43 (d, *J* = 16.1 Hz, 1 H), 3.84 (s, 3 H), 3.16 (hept, *J* = 6.9 Hz, 1 H), 1.63–1.57 (m, 2 H), 1.54 (s, 9 H), 1.31–1.24 (m, 3 H), 1.21 (d, *J* = 6.8 Hz, 3 H), 1.18–1.11 (m, 1 H), 0.84 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.27, 158.45, 149.23, 137.77, 129.83, 125.15, 125.14, 122.46, 118.48, 108.14, 80.24, 55.60, 38.06, 34.71, 29.95, 28.42, 22.96, 22.28, 14.16.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{20}H_{31}O_3$: 319.22732; found: 319.23010.

***tert*-Butyl (*E*)-3-[2-Methoxy-6-(octan-3-yl)phenyl]acrylate (4j)**

Yield: 145 mg (42%); clear oil.

IR (neat): 2958, 2929, 2857, 1706, 1700, 1628, 1595, 1577, 1468, 1464, 1456, 1367, 1310, 1259, 1149, 1063, 981, 878, 847, 770 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.83 (dd, *J* = 16.1, 0.5 Hz, 1 H), 7.29–7.17 (m, 1 H), 6.85 (dd, *J* = 7.9, 1.0 Hz, 1 H), 6.74 (ddt, *J* = 8.2, 1.0, 0.4 Hz, 1 H), 6.43 (d, *J* = 16.1 Hz, 1 H), 3.85 (s, 3 H), 2.98 (tt, *J* = 8.7, 5.6 Hz, 1 H), 1.76–1.62 (m, 2 H), 1.54 (s, 9 H), 1.37–1.05 (m, 7 H), 0.92–0.85 (m, 1 H), 0.82 (t, *J* = 6.9 Hz, 3 H), 0.76 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.30, 158.36, 147.68, 138.16, 138.16, 129.69, 125.16, 123.62, 108.00, 80.20, 55.56, 36.66, 32.20, 29.79, 28.43, 27.20, 22.67, 14.20, 12.12.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{22}H_{35}O_3$: 347.25862; found: 347.25808.

***tert*-Butyl (*E*)-3-(2-Cyclohexyl-6-methoxyphenyl)acrylate (4k)**

Yield: 136 mg (43%); clear oil.

IR (neat): 2949, 2934, 1706, 1595, 1583, 1472, 1367, 1307, 1267, 1237, 1219, 1066, 1052, 982, 776, 753 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 16.10 Hz, 1 H), 7.26 (m, 1 H), 6.93 (dd, *J* = 1.03, 7.91 Hz, 1 H), 6.76 (dd, *J* = 1.25, 8.30 Hz, 1 H), 6.48 (d, *J* = 16.12 Hz, 1 H), 3.85 (s, 3 H), 2.91 (m, 1 H), 1.80 (m, 5 H), 1.55 (s, 9 H), 1.43 (m, 4 H), 1.27 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.36, 158.71, 149.05, 137.49, 129.88, 124.95, 121.83, 118.65, 108.40, 80.21, 55.62, 40.34, 34.41, 28.44, 27.03, 26.39.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{20}H_{29}O_3$: 317.21167; found: 317.21227.

tert-Butyl (*E*)-3-[2-Methoxy-6-(1-phenoxypropan-2-yl)phenyl]acrylate (4l)

Yield: 177 mg (48%); clear oil.

IR (neat): 2976, 2933, 1724, 1705, 1626, 1599, 1496, 1469, 1456, 1367, 1311, 1244, 1149, 1039, 754, 692 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ (mixture of rotomers) = 7.88 (d, *J* = 16.1 Hz, 0.64 H), 7.87 (d, *J* = 16.2 Hz, 0.22 H), 7.31–7.18 (m, 3 H), 6.98 (dd, *J* = 7.9, 1.0 Hz, 0.26 H), 6.95–6.85 (m, 3.59 H), 6.84–6.78 (m, 1 H), 6.63 (d, *J* = 16.1 Hz, 0.64 H), 6.46 (d, *J* = 16.1 Hz, 0.23 H), 4.59 (hept, *J* = 6.2 Hz, 0.71 H), 4.09 (dd, *J* = 9.1, 6.1 Hz, 0.24 H), 3.98 (dd, *J* = 9.1, 7.4 Hz, 0.24 H), 3.87 (s, 1.82 H), 3.86 (s, 0.81 H), 3.73 (hept, *J* = 7.0 Hz, 0.27 H), 3.29 (dd, *J* = 14.0, 6.7 Hz, 0.70 H), 2.97 (dd, *J* = 14.0, 6.4 Hz, 0.70 H), 1.54 (s, 2.50 H), 1.54 (s, 5.79 H), 1.38 (d, *J* = 6.9 Hz, 0.70 H), 1.29 (d, *J* = 6.1 Hz, 2.05 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ (mixture of rotomers) = 167.31, 166.98, 159.16, 159.01, 158.48, 157.92, 144.71, 140.06, 137.54, 137.53, 129.88, 129.78, 129.58, 129.51, 125.85, 125.00, 123.74, 123.19, 122.87, 120.84, 120.79, 118.82, 116.21, 114.74, 109.47, 108.99, 80.39, 80.26, 74.47, 72.91, 55.68, 55.60, 40.66, 34.88, 28.39, 19.77, 18.85.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{28}O_4Na$: 391.1880; found: 391.1894.

tert-Butyl (*S*)-(2-Iodopropoxy)dimethylsilane (3m)

To a solution of propandiol (4 g, 52.6 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added imidazole (3.58 g, 52.6 mmol) followed by *tert*-butyldimethylsilyl chloride (7.89 g, 52.6 mmol). The reaction was stirred at 0 °C for 30 min, then the imidazole·HCl salt was filtered. In a separate flask, triphenylphosphine (13.79 g, 52.6 mmol) and imidazole (3.58 g, 52.6 mmol) are dissolved in CH_2Cl_2 (100 mL) at 0 °C. Molecular iodine (13.37 g, 52.6 mmol) was added and the reaction was stirred at 0 °C for 15 min. The solution of the monosilylated diol was added dropwise over 5 min and the mixture was stirred for 30 min at 0 °C. The mixture was washed with an aqueous solution of Na_2SO_3, and the organic layer was separated and concentrated. The residue was purified by column chromatography (hexanes) to give the (*S*)-iodide **3m**.

Yield: 7.28 g (46%, 2 steps); clear oil; $[\alpha]_D^{20}$ +9.5 (*c* = 4.34, $CHCl_3$). Enantiomers could not be separated on HPLC.

IR (neat): 2955, 2928, 2885, 2856, 1464, 1450, 1386, 1379, 1253, 1170, 1139, 1111, 1078, 1045, 1004, 989, 837, 777, 669 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.15–4.03 (m, 1 H), 3.81 (dd, *J* = 10.5, 5.5 Hz, 1 H), 3.61 (dd, *J* = 10.5, 7.8 Hz, 1 H), 1.86 (d, *J* = 6.8 Hz, 3 H), 0.90 (s, 9 H), 0.07 (s, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 70.59, 28.28, 26.00, 24.46, 18.43, –5.03, –5.13.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{19}H_{22}IOSi$: 301.0486; found: 301.04820.

tert-Butyl (*S*,*E*)-3-(2-{1-[(*tert*-Butyldimethylsilyl)oxy]propan-2-yl}-6-methoxyphenyl)acrylate (4m)

Yield: 215 mg (53%); clear oil; $[\alpha]_D^{20}$ +11.9 (*c* = 2.28, $CHCl_3$). Enantiomers could not be separated on HPLC.

IR (neat): 2956, 2928, 2875, 1724, 1653, 1456, 1437, 1390, 1367, 1309, 1257, 1149, 1091, 1057, 837, 752 cm^{-1}.

^{1}H NMR (399 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 16.2 Hz, 1 H), 7.25 (t, *J* = 8.0 Hz, 1 H), 6.90 (dd, *J* = 8.0, 1.0 Hz, 1 H), 6.81–6.75 (m, 1 H), 6.42 (d, *J* = 16.2 Hz, 1 H), 3.84 (s, 3 H), 3.68 (dd, *J* = 9.8, 6.1 Hz, 1 H), 3.60 (dd, *J* = 9.7, 7.3 Hz, 1 H), 3.43–3.33 (m, 1 H), 1.54 (s, 9 H), 1.24 (d, *J* = 6.9 Hz, 3 H), 0.84 (s, 9 H), –0.03 (s, 3 H), –0.05 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.85, 158.17, 145.47, 137.71, 129.38, 125.49, 123.20, 118.91, 108.46, 80.07, 68.71, 55.51, 37.32, 28.24, 25.86, 18.01, –5.48.

HRMS (DART) *m*/*z* [M + H] calcd for $C_{22}H_{39}O_4Si$: 407.26176; found: 407.26260.

(*E*)-3-[2-(1-Hydroxypropan-2-yl)-6-methoxyphenyl]acrylic Acid (5)

The starting *tert*-butyl ester **4m** (51 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (5 mL) and TFA (96 µL, 130 µmol). The mixture was stirred for 1 h at r.t., then concentrated. The resulting acid was purified by column chromatography (EtOAc–hexanes, 1:1) to give the acid **5** (29 mg, 99%) as a clear oil, which was crystallized by slow evaporation from hexanes as white crystals.

IR (neat): 2968, 2875, 2841, 2359, 1786, 1689, 1681, 1622, 1595, 1573, 1471, 1456, 1438, 1369, 1346, 1307, 1261, 1219, 1165, 1057, 983, 873, 775, 754 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 16.1 Hz, 1 H), 7.34 (t, *J* = 8.1 Hz, 1 H), 6.91 (dd, *J* = 7.9, 1.0 Hz, 1 H), 6.86 (dd, *J* = 8.4, 1.2 Hz, 1 H), 6.58 (d, *J* = 16.1 Hz, 1 H), 4.45 (dd, *J* = 10.8, 6.6 Hz, 1 H), 4.40 (dd, *J* = 10.8, 7.3 Hz, 1 H), 3.88 (s, 3 H), 3.78–3.63 (m, 1 H), 1.35 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.73, 157.48, 142.54, 139.99, 130.67, 123.12, 122.34, 118.38, 109.60, 71.83, 55.61, 33.76, 18.08.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{13}H_{17}O_4$: 237.11268; found: 237.11279.

$[\alpha]_D^{20}$ +28.8 (*c* = 0.18 $CHCl_3$)

HPLC (Chiralpak AD-H column; flow: 0.5 mL/min; hexane–2-propanol, 98:2): t_R = 35.6 (major), 40.1 (minor) min; 94% ee from reaction in MeCN. t_R = 35.2 (major), 39.5 (minor) min; $[\alpha]_D^{20}$ +5.4 (*c* = 0.22, $CHCl_3$), 40% ee from reaction in DMF.

Compound crystallizes as a racemate; mp 127–128 °C (crystals obtained from reaction in DMF).

tert-Butyl (*E*)-3-[2-Methoxy-6-(1-methoxypentyl)phenyl]acrylate (4n)

Yield: 345 mg (99%); clear oil.

IR (neat): 2956, 2931, 2872, 2860, 1705, 1626, 1595, 1573, 1469, 1456, 1367, 1311, 1265, 1151, 1093, 983, 875, 754 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 16.1 Hz, 1 H), 7.20 (t, *J* = 8.1 Hz, 1 H), 6.85 (dd, *J* = 7.5, 1.0 Hz, 1 H), 6.80 (d, *J* = 8.3 Hz, 1 H), 6.61 (dd, *J* = 16.1, 0.6 Hz, 1 H), 3.86 (s, 3 H), 3.30 (m, 4 H), 3.06 (dd, *J* = 13.8, 6.3 Hz, 1 H), 2.78 (dd, *J* = 13.8, 6.5 Hz, 1 H), 1.53 (s, 9 H), 1.49–1.37 (m, 2 H), 1.31–1.20 (m, 2 H), 0.90–0.82 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.29, 159.14, 140.93, 137.51, 129.66, 124.91, 123.96, 122.64, 109.22, 82.07, 80.21, 57.52, 55.59, 38.61, 33.82, 28.42, 27.66, 22.96, 14.20.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{20}H_{31}O_4$: 349.23788; found: 349.23724.

tert-Butyl (*E*)-3-(2-{4-[(*tert*-Butyldimethylsilyl)oxy]butan-2-yl}-6-methoxyphenyl)acrylate (4o)

Yield: 332 mg (79%); clear oil. Enantiomers could not be separated on HPLC.

IR (neat): 2956, 2929, 2856, 1708, 1624, 1595, 1572, 1471, 1437, 1390, 1367, 1311, 1149, 1099, 1060, 983, 835, 775 cm^{-1}.

^{1}H NMR (399 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 16.2 Hz, 1 H), 7.25 (t, *J* = 7.5 Hz, 1 H), 6.89 (d, *J* = 7.9 Hz, 1 H), 6.74 (d, *J* = 8.2 Hz, 1 H), 6.40 (dd, *J* = 16.1, 0.8 Hz, 1 H), 3.83 (s, 3 H), 3.61–3.44 (m, 2 H), 3.33 (hept, *J* = 7.0 Hz, 1 H), 1.98–1.72 (m, 2 H), 1.53 (d, *J* = 0.9 Hz, 9 H), 1.22 (d, *J* = 6.8 Hz, 3 H), 0.85 (d, *J* = 0.9 Hz, 9 H), –0.02 (d, *J* = 0.9 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.00, 158.41, 148.28, 137.67, 129.79, 125.24, 122.61, 118.53, 108.24, 80.14, 61.41, 55.57, 40.68, 31.28, 28.37, 26.08, 22.65, 18.38, –5.23, –5.28.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{24}H_{41}O_4Si$: 421.27741; found: 421.27942.

tert-Butyl (*E*)-3-(2-{4-Hydroxybutan-2-yl}-6-methoxyphenyl)acrylate (6)

To a solution of **4o** (33 mg, 79 μmol) in anhydrous THF (3 mL) at 0 °C was added TBAF (1 M in THF, 79 μL, 79 μmol). The mixture was stirred at 0 °C for 1 h under Ar, then aqueous NH_4Cl was added. The aqueous phase was extracted with EtOAc (3×) and dried with Mg_2SO_4. After filtration, the organic layer was concentrated and the residue was purified by column chromatography (EtOAc–hexanes, 1:20) to give **6**.

Yield: 14.7 mg (61%); clear oil.

IR (neat): 2958, 2926, 2872, 1734, 1716, 1653, 1558, 1435, 1394, 1367, 1261, 1219, 1062, 1049, 773 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 16.1 Hz, 1 H), 7.27 (t, *J* = 8.0 Hz, 1 H), 6.92 (dd, *J* = 7.9, 1.0 Hz, 1 H), 6.76 (dd, *J* = 8.2, 1.2 Hz, 1 H), 6.46 (d, *J* = 16.1 Hz, 1 H), 3.85 (s, 3 H), 3.55 (td, *J* = 6.6, 3.4 Hz, 2 H), 3.38 (hept, *J* = 7.0 Hz, 1 H), 1.93–1.78 (m, 2 H), 1.53 (s, 9 H), 1.26 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.39, 158.55, 148.18, 137.55, 130.04, 125.25, 122.40, 118.48, 108.46, 80.46, 61.09, 55.61, 41.10, 31.24, 28.39, 22.19.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{18}H_{27}O_4$: 307.19093; found: 307.18999.

HPLC (Chiralpak AD-H column; flow: 1.0 mL/min; hexane–2-propanol, 90:10): t_R (racemic sample) = 6.1, 7.7 min; t_R (chiral sample) = 6.1, 7.6 min; 0% ee.

tert-Butyl (*E*)-3-{2-Methoxy-6-[4-(phenylthio)butan-2-yl]phenyl}acrylate (4p)

Yield: 318 mg (80%); clear oil.

IR (neat): 2966, 2926, 1683, 1653, 1581, 1570, 1475, 1437, 1292, 1274, 1247, 1053, 1024, 1016, 914, 742, 688, 648 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ (mixture of rotomers) = 7.82 (d, *J* = 16.1 Hz, 0.8 H), 7.77 (d, *J* = 16.1 Hz, 0.2 H), 7.39–7.34 (m, 0.3 H), 7.30–7.24 (m, 1 H), 7.25–7.23 (m, 4 H), 7.17–7.11 (m, 0.7 H), 6.86 (dd, *J* = 7.9, 1.0 Hz, 0.8 H), 6.82 (dd, *J* = 7.6, 1.1 Hz, 0.2 H), 6.81–6.74 (m, 1 H), 6.60 (d, *J* = 16.1 Hz, 0.2 H), 6.42 (d, *J* = 16.1 Hz, 0.8 H), 3.86 (s, 0.6 H), 3.85 (s, 2.4 H), 3.42–3.29 (m, 0.8 H), 3.30–3.18 (m, 0.2 H), 2.92 (t, *J* = 7.9 Hz, 0.4 H), 2.76 (t, *J* = 7.8 Hz, 1.6 H), 2.00–1.84 (m, 2 H), 1.55 (s, 7 H), 1.53 (s, 2 H), 1.33 (d, *J* = 6.7 Hz, 0.6 H), 1.23 (d, *J* = 6.8 Hz, 2.4 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ (mixture of rotomers) = 167.34, 167.11, 159.30, 158.48, 147.30, 143.50, 137.51, 137.11, 136.58, 135.23, 132.01, 130.00, 129.96, 129.05, 128.93, 126.81, 125.84, 125.57, 124.82, 122.81, 122.52, 118.31, 109.08, 108.55, 80.40, 80.25, 55.64, 42.87, 38.29, 37.44, 34.16, 31.48, 28.43, 22.39, 21.27.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{24}H_{31}O_3S$: 399.19939; found: 399.19876.

tert-Butyl (*E*)-3-(2-Methoxy-6-{4-(*N*-phenyl 4-methylphenylsulfonamido)butan-2-yl}phenyl)acrylate (4q)

Yield: 262 mg (49%); clear oil.

IR (neat): 2966, 2928, 2870, 1705, 1699, 1629, 1595, 1573, 1494, 1471, 1456, 1367, 1350, 1311, 1261, 1165, 1151, 1082, 1070, 1606, 979, 815, 754, 698, 655, 574, 545 cm^{-1}.

^{1}H NMR (399 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 16.2 Hz, 1 H), 7.40 (d, *J* = 8.1 Hz, 2 H), 7.32–7.15 (m, 6 H), 7.06–6.92 (m, 2 H), 6.82–6.72 (m, 2 H), 6.35 (d, *J* = 16.1 Hz, 1 H), 3.83 (s, 3 H), 3.48 (ddd, *J* = 13.1, 9.0, 6.3 Hz, 1 H), 3.37 (ddd, *J* = 13.0, 8.9, 6.4 Hz, 1 H), 3.16 (hept, *J* = 6.9 Hz, 1 H), 2.40 (s, 3 H), 1.75 (dtd, *J* = 8.8, 6.6, 3.9 Hz, 2 H), 1.57 (d, *J* = 0.8 Hz, 9 H), 1.17 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.04, 158.41, 147.23, 143.33, 139.20, 137.47, 135.23, 130.00, 129.45, 129.16, 129.04, 128.79, 128.35, 127.87, 127.85, 125.50, 122.51, 118.23, 108.54, 80.44, 55.64, 48.87, 36.13, 32.24, 30.10, 29.84, 28.42, 22.44, 21.65.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{31}H_{38}NO_5S$: 536.24707; found: 536.24831.

tert-Butyl (*E*)-3-[2-Isopropyl-6-(methoxymethoxy)phenyl]acrylate (4r)

Yield: 320 mg (99%); clear oil.

IR (neat): 2976, 2933, 2872, 2369, 1708, 1627, 1592, 1573, 1472, 1459, 1388, 1368, 1310, 1255, 1200, 1152, 1102, 1009, 983, 867, 754 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 16.2 Hz, 1 H), 7.25–7.21 (m, 1 H), 7.01–6.97 (m, 2 H), 6.40 (d, *J* = 16.2 Hz, 1 H), 5.21 (s, 2 H), 3.48 (s, 3 H), 3.38–3.26 (m, 1 H), 1.55 (s, 9 H), 1.23 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.10, 155.92, 149.72, 137.77, 137.77, 129.85, 125.34, 125.33, 122.90, 119.10, 112.11, 94.72, 80.35, 56.31, 29.57, 28.38, 23.93.

HRMS (DART): *m*/*z* [M + NH_4] calcd for $C_{18}H_{30}NO_4$: 324.21748; found: 324.21795.

tert-Butyl (*E*)-3-(2-Isopropoxy-6-isopropylphenyl)acrylate (4s)

Yield: 302 mg (99%); clear oil.

IR (neat): 2965, 2928, 2870, 1708, 1626, 1594, 1572, 1472, 1453, 1437, 1394, 1362, 1315, 1260, 1201, 1154, 1068, 985, 875, 754 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 16.2 Hz, 1 H), 7.22 (t, *J* = 8.0 Hz, 1 H), 6.91 (dd, *J* = 7.9, 1.0 Hz, 1 H), 6.76 (dd, *J* = 8.1, 1.4 Hz, 1 H), 6.49 (d, *J* = 16.1 Hz, 1 H), 4.61–4.50 (m, 1 H), 3.34 (hept, *J* = 6.7 Hz, 1 H), 1.54 (s, 9 H), 1.36 (d, *J* = 6.0 Hz, 6 H), 1.23 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.33, 156.82, 149.91, 137.71, 137.71, 129.59, 124.71, 124.70, 122.68, 117.56, 110.94, 79.96, 70.80, 29.38, 28.26, 23.82, 22.14.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{19}H_{29}O_3$: 305.21167; found: 305.21205.

tert-Butyl (*E*)-3-[2-(Benzyloxy)-6-isopropylphenyl]acrylate (4ta)

Yield: 317 mg (90%); clear oil.

IR (neat): 2963, 2936, 2871, 1722, 1695, 1636, 1623, 1596, 1569, 1470, 1447, 1367, 1311, 1148, 1044, 1028, 984, 878, 845, 751, 735 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 16.2 Hz, 1 H), 7.47–7.43 (m, 2 H), 7.42–7.36 (m, 2 H), 7.35–7.29 (m, 1 H), 7.27–7.21 (m, 1 H), 6.98 (dd, *J* = 7.9, 1.0 Hz, 1 H), 6.82 (ddd, *J* = 8.3, 1.0, 0.5 Hz, 1 H), 6.54 (d, *J* = 16.2 Hz, 1 H), 5.14 (s, 2 H), 3.38 (hept, *J* = 6.8 Hz, 1 H), 1.55 (s, 9 H), 1.26 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.20, 157.39, 149.92, 137.49, 137.09, 129.83, 128.60, 127.87, 127.09, 125.61, 125.60, 122.48, 118.28, 110.05, 80.16, 70.54, 29.58, 28.38, 23.94.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{23}H_{28}O_3Na$: 375.1930; found: 375.1928.

tert-Butyl (*E*)-3-{2-Isopropyl-6-[(4-methoxybenzyl)oxy]phenyl}acrylate (4tb)

Yield: 344 mg (90%); clear oil.

IR (neat): 2963, 2928, 2870, 2358, 2329, 2323, 1706, 1698, 1515, 1456, 1367, 1310, 1304, 1247, 1219, 1173, 1148, 034, 770 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 16.2 Hz, 1 H), 7.35 (dt, *J* = 8.8, 0.6 Hz, 2 H), 7.23 (t, *J* = 8.1 Hz, 1 H), 6.95 (dd, *J* = 7.9, 1.0 Hz, 1 H), 6.93–6.87 (m, 2 H), 6.84–6.79 (m, 1 H), 6.47 (s, 1 H), 5.06 (s, 2 H), 3.81 (s, 3 H), 3.35 (hept, *J* = 6.4 Hz, 1 H), 1.52 (s, 9 H), 1.24 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.29, 159.43, 157.57, 149.98, 137.52, 129.84, 129.18, 128.81, 125.53, 122.53, 118.27, 114.06, 110.24, 80.16, 70.46, 55.43, 29.60, 28.42, 23.97.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{24}H_{30}O_4Na$: 405.2050; found: 405.2056.

tert-Butyl (*E*)-3-(2-Isopropylnaphthalen-1-yl)acrylate (4u)

Yield: 237 mg (85%); clear oil.

IR (neat): 2961, 2932, 2871, 1725, 1713, 1700, 1697, 1468, 1456, 1391, 1367, 1331, 1301, 1281, 1257, 1149, 846, 818, 770, 748 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 16.3 Hz, 1 H), 8.02–7.97 (m, 1 H), 7.84–7.70 (m, 2 H), 7.56–7.40 (m, 3 H), 6.09 (d, *J* = 16.3 Hz, 1 H), 3.39 (hept, *J* = 6.8 Hz, 1 H), 1.59 (s, 9 H), 1.28 (d, *J* = 6.9 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.95, 144.11, 141.91, 132.10, 131.50, 130.11, 128.85, 128.25, 127.91, 127.90, 126.42, 125.52, 125.39, 123.69, 80.96, 30.40, 28.43, 23.84.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{20}H_{25}O_2$: 297.18545; found: 297.18584.

tert-Butyl (*E*)-3-(2-Isopropyl-4,6-dimethoxyphenyl)acrylate (4v)

Yield: 150 mg (49%); clear oil.

IR (neat): 2966, 2933, 1701, 1600, 1456, 1365, 1313, 1271, 1203, 1147, 1062, 983, 835 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (dd, *J* = 16.0, 0.6 Hz, 1 H), 6.59–6.39 (m, 2 H), 6.34 (d, *J* = 2.4 Hz, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.40 (hept, *J* = 6.8 Hz, 1 H), 1.53 (s, 9 H), 1.23 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.04, 161.41, 160.62, 151.79, 137.12, 122.31, 114.64, 102.92, 95.81, 80.01, 55.63, 55.36, 29.68, 28.47, 23.89.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{18}H_{27}O_4$: 307.19093; found: 307.19028.

tert-Butyl (*E*)-3-(2-Isopropyl-6-methylphenyl)acrylate (4w)

Yield: 242 mg (93%); clear oil.

IR (neat): 2961, 2871, 1713, 1639, 1470, 1456, 1383, 1367, 1311, 1287, 1254, 1150, 980, 846, 771, 753 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78 (dd, *J* = 16.4, 0.7 Hz, 1 H), 7.22–7.11 (m, 2 H), 7.09–6.96 (m, 1 H), 5.91 (d, *J* = 16.3 Hz, 1 H), 3.16 (hept, *J* = 6.8 Hz, 1 H), 2.30 (s, 3 H), 1.55 (s, 9 H), 1.20 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.05, 147.15, 142.76, 135.93, 133.73, 128.28, 127.86, 126.35, 122.98, 80.72, 29.98, 28.37, 23.98, 21.41.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{17}H_{25}O_2$: 261.18545; found: 261.18561.

tert-Butyl (*E*)-3-[2-Isopropyl-6-(trifluoromethyl)phenyl]acrylate (4x)

Yield: 195 mg (62%); clear oil.

IR (neat): 2965, 2933, 2873, 1713, 1700, 1647, 1456, 1393, 1367, 1316, 1289, 1257, 1150, 1129, 1098, 978, 910, 875, 843, 807, 773, 753, 739, 715 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.92–7.67 (m, 1 H), 7.62–7.45 (m, 2 H), 7.44–7.32 (m, 1 H), 5.91 (dq, *J* = 16.3, 0.5 Hz, 1 H), 3.17 (dq, *J* = 13.6, 6.8 Hz, 1 H), 1.54 (s, 9 H), 1.20 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.26, 148.38, 139.88, 133.29 (q, *J* = 1.67 Hz), 129.13 (q, *J* = 1.1 Hz), 128.54 (q, *J* = 29.4 Hz), 128.17, 128.14–128.10 (m), 124.17 (q, *J* = 273.9 Hz), 123.56 (q, *J* = 5.6 Hz), 81.07, 29.85, 28.33, 23.84.

^{19}F NMR (564 MHz, $CDCl_3$): δ = –58.11.

HRMS (DART): *m*/*z* [M + NH_4] calcd for $C_{17}H_{25}F_3NO_2$: 332.18374; found: 332.18393.

tert-Butyl (*E*)-3-(2-Fluoro-6-isopropylphenyl)acrylate (4y)

Yield: 164 mg (62%); clear oil.

IR (neat): 2966, 2931, 1708, 1631, 1610, 1471, 1456, 1367, 1317, 1244, 1151, 983, 945, 794, 752 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76–7.71 (m, 1 H), 7.25 (td, *J* = 8.0, 5.6 Hz, 1 H), 7.09 (dd, *J* = 7.9, 1.2 Hz, 1 H), 6.92 (dddd, *J* = 11.1, 8.2, 1.2, 0.6 Hz, 1 H), 6.44 (dd, *J* = 16.2, 1.8 Hz, 1 H), 3.36–3.23 (m, 1 H), 1.53 (s, 9 H), 1.24 (d, *J* = 6.9 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.69 (d, *J* = 1.0 Hz), 162.68, 160.18, 150.56, 134.77 (d, *J* = 0.9 Hz), 130.30 (d, *J* = 9.7 Hz), 126.43 (d, *J* = 12.4 Hz), 121.17 (d, *J* = 3.2 Hz), 121.00 (d, *J* = 11.1 Hz), 113.44 (d, *J* = 23.4 Hz), 80.74, 29.65 (d, *J* = 2.4 Hz), 28.48–28.15 (m), 23.71.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –111.52.

HRMS (DART): *m*/*z* [M + H] calcd for $C_{16}H_{22}FO_2$: 265.16038; found: 265.16106.

***tert*-Butyl (*E*)-3-(2-Chloro-6-isopropylphenyl)acrylate (4z)**

Yield: 123 mg (44%); clear oil.

IR (neat): 2966, 2930, 1713, 1700, 1643, 1367, 1312, 1292, 1257, 1150, 977, 739 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 16.3 Hz, 1 H), 7.30–7.13 (m, 3 H), 6.08 (d, *J* = 16.3 Hz, 1 H), 3.20 (hept, *J* = 6.8 Hz, 1 H), 1.55 (s, 9 H), 1.21 (d, *J* = 7.0 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (mixture of rotomers) = 165.61, 149.26, 139.70, 133.09, 132.61, 129.20, 127.61, 127.10, 123.99, 122.67, 80.84, 30.18, 28.27, 28.23, 23.90, 23.84.

HRMS (DART): *m*/*z* [M + NH_4] calcd for $C_{16}H_{25}ClNO_2$: 298.15738; found: 298.15752.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380198. Included are ^1H and ^{13}C NMR spectra of the coupling products.

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