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Palladium-Catalyzed Cross-Coupling of Sterically Demanding Boronic Acids with α-Bromocarbonyl Compounds

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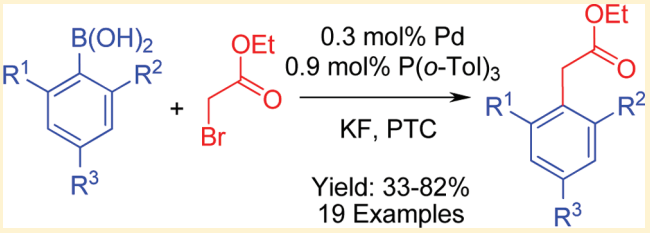
Supporting Information

ABSTRACT: A catalyst system generated in situ from $Pd(dba)_2$ and tri(*o*-tolyl)phosphine mediates the coupling of arylboronic acids with alkyl α-bromoacetates under formation of arylacetic acid esters at unprecedented low loadings. The new protocol, which involves potassium fluoride as the base and catalytic amounts of benzyltriethylammonium bromide as a phase transfer catalyst, is uniquely effective for the synthesis of sterically demanding arylacetic acid derivatives.



Many α-arylacetic acid derivatives display unique biological and pharmaceutical activities.[1] Examples include the anti-inflammatory and analgesic drugs Indomethacin or Diclofenac and the phytohormonal growth regulators indole-3-acetic acid (IAA) or phenylacetic acid (PAA).[2] Sterically demanding arylacetic acids are also valuable intermediates for the synthesis of modern agrochemicals with insecticidal (e.g., Spiromesifen, Spirotetramat) or herbicidal (e.g., Pinoxaden) activity (Figure 1).[3] Therefore, efficient procedures for the introduction of the methylenecarboxyl group into functionalized molecules are of considerable interest.[4]

Traditional syntheses of arylacetic acids involve multistep synthesis, harsh reaction conditions that are incompatible with sensitive functionalities, or toxic reagents. Examples are the hydrolysis of benzyl cyanides,[5] the transition-metal-catalyzed carbonylation of benzyl halides,[6] and the electrocatalytic carboxylation of benzyl halides.[7] Modern alternatives include the α-arylation of ester enolates,[8] coupling of malonates[9] or β-ketoesters[10] with aryl halides with in situ dealkoxycarbonylation or retro-Claisen condensation, and cross-coupling of α-halocarboxylic esters or amides with arylboronic acids.[11]

In the course of our research on highly potent insecticides and herbicides derived from sterically demanding arylacetic acids, we evaluated many of the synthetic strategies mentioned above. Unfortunately, all of these methods led to much lower yields for our target structures than for the sterically less demanding derivatives reported in the literature. Moreover, the tolerance of halide groups was essential as they are beneficial for the biologic activity of many of the target molecules.[3]

If any of the arylacetic acid syntheses discussed above was to fulfill these requirements, it would be the coupling of boronic acids with α-halocarboxylates. The reaction conditions of the initial protocol are very mild (3 mol % Pd(OAc), 9 mol % 1-naphthylphosphine, 5 equiv of K_3PO_4, 20 °C), and the reported examples include ortho-substituted and halogen-substituted arylacetates.[11a] However, when we applied them to the reaction of ethyl bromoacetate with the *o*,*o*-disubstituted 2,6-dimethylphenylboronic acid, we observed no formation to the desired ethyl 2-(2,6-dimethylphenyl)acetate (Scheme 1). The alternative nickel-based system[11c] also proved to be ineffective for such bulky substrates. The only catalyst system for which a successful coupling of an *o*,*o*-disubstituted arylboronic acid with an alkyl bromoacetate has been reported calls for taylor-made aminophosphine ligands,[11d] and we were reluctant to base our synthetic strategy on commercially unavailable catalysts.

We thus set out to develop a catalytic system that would use cheap and readily accessible ligands and be active enough to mediate the title reaction with catalyst loadings that are substantially lower than the 3 mol % required for the known protocols.

We systematically studied various combinations of palladium precursors, ligands, and bases for the reaction of ethyl bromoacetate with 2,6-dimethylphenylboronic acid (Table 1). Using 1 mol % palladium acetate as the palladium source and potassium phosphate as the base, predominantly protodeborylation was observed for most ligands including tri(1-naphthyl)phosphine, in situ generated NHC ligands, and bulky phosphines commonly used in cross-coupling chemistry. Solely with tris-*o*-tolylphosphine, the desired product was detected in encouraging yields (entries 1−6).

The yield could be improved by increasing the reaction temperature to 60 °C. At even higher temperatures, the catalyst decomposed with formation of palladium black, which resulted

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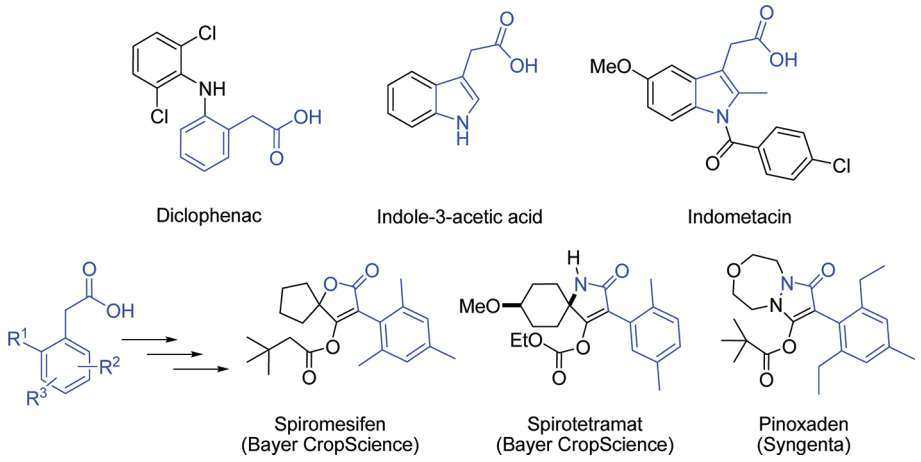
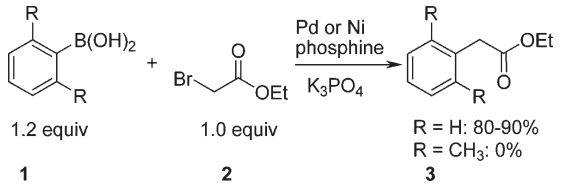


Figure 1. Examples of biologically active compounds derived from α-arylacetic acids.

Scheme 1. Cross-Coupling Reaction between Boronic Acids and Ethyl Bromoacetate



in a drop of activity and the formation of *o*-xylene as the major product (entries 7, 8). The choice of the palladium source also had a pronounced influence on the activity. Clearly better results were obtained with $Pd(dba)_2$ (entries 7 vs 10, 11). Further improvements of yield and selectivity were achieved when using the inexpensive ethyl bromoacetate in excess rather than the costly boronic acid (entry 11).

We next varied the base and found that for this combination of substrates, KF was more effective than K_2CO_3 or K_3PO_4 (entries 11−13). In contrast, phosphate bases were reported to give best results for sterically less demanding boronic acids.[11] The addition of small quantities of water, which had been beneficial in the previous protocols,[11a,d] led to increased conversion but also to a lower selectivity with regard to protodeborylation (entry 14).

The decisive progress was made by adding phase-transfer catalysts to increase the concentration of fluoride ions in solution and thus facilitate the transmetalation step. The presence of 10 mol % of quaternary ammonium salts sharply improved yields and selectivities (entries 15−18). Benzyltriethylammonium bromide was found to be particularly advantageous in that it has a comparatively low hygroscopicity and can easily be handled even in small quantities. In the presence of this phase-transfer catalyst, the desired product was obtained in 93% yield along with only 7% of the protodeborylation product **4a** (entry 18).

To permit the use of the reaction in an industrial synthesis, a further reduction of catalyst loading was imperative. We were thus delighted to find that in combination with benzyltriethylammonium bromide 0.3 mol % palladium is sufficient to ensure high yields. Even at 0.1 mol % catalyst loading, reasonable yields were obtained (entries 19−21).

Having thus found a simple but highly effective catalyst system for the coupling of sterically demanding arylboronic acids, we next investigated whether it would be generally applicable also to other substrates. As can be seen in Table 2, various arylboronic acids were coupled with α-bromocarbonyl compounds, giving the corresponding arylacetates in high yields using only 0.3 mol % palladium (Table 2). The protocol is uniquely effective for sterically demanding boronic acids **1a**−**i**. However, non-ortho-substituted boronic acids also gave yields that are comparable to those previously obtained using a 10-fold higher catalyst loading. Both electron-withdrawing and electron-donating functional groups were tolerated (**3j**−**o**). We were especially pleased to see that aromatic chloride groups did not give rise to any side reactions. The presence of bromide substuients is also tolerated as can be seen from the successful coupling of 4-bromobutyl bromoacetate (**2d**). Besides alkyl bromoacetates, bromoacetamides (**2b**) and even α-bromo ketones (**2c**), which gave no reaction with previous palladium systems,[11a,b,d] can be employed as coupling partners (**3p**−**q**).

In conclusion, the use of tetraalkylammonium salts as phase-transfer reagents together with potassium fluoride as the base allows coupling of various arylboronic acids with α-bromocarbonyl compounds in the presence of only 0.3 mol % of a catalyst generated in situ from $Pd(dba)_2$ and tri-*o*-tolylphosphine. The yields obtained with the new catalyst system, which exclusively comprises commercially available components, are comparable to the best ones previously obtained using at least 10-fold higher catalyst loadings. The new protocol is particularly effective for the synthesis of sterically demanding arylacetic esters, key intermediates en route to a new class of potent insecticides and herbicides.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Arylacetic Acid Derivatives. An oven-dried 20 mL flask was charged with the boronic acid **1a**−**o** (1.00 mmol), $Pd(dba)_2$ (1.73 mg, 3.00 μmol), tri(*o*-tolyl)-phosphine (2.74 mg, 9.00 μmol), benzyltriethylammonium bromide (27.8 mg, 0.10 mmol) and potassium fluoride (174 mg, 3.00 mmol). The reaction flask was closed, evacuated, and flushed with nitrogen. Subsequently, ethyl bromoacetate (**2a**) (167 mg, 1.50 mmol), the internal standard *n*-tetradecane (50 μL), and dry degassed THF (2 mL) were added via syringe. The resulting mixture was stirred at 60 °C for 24 h, diluted with ethyl acetate, and filtered through a pad of Celite and basic alumina (2:1). The filter cake was rinsed with ethyl acetate (20 mL).

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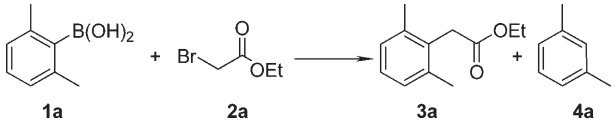
Table 1. Development of the Catalyst System[a]



1a 2a 3a 4a

no.	Pd	ligand	base	additive	T (°C)	**3a** (%)	**4a** (%)
1	1% $Pd(OAc)_2$	3% PPh_3	5 equiv K_3PO_4		20	0	26
2	1% $Pd(OAc)_2$	3% PCy_3	5 equiv K_3PO_4		20	0	23
3	1% $Pd(OAc)_2$	3% IMes·HCl	5 equiv K_3PO_4		20	0	48
4	1% $Pd(OAc)_2$	3% IPr·HCl	5 equiv K_3PO_4		20	4	18
5	1% $Pd(OAc)_2$	3% JohnPhos	5 equiv K_3PO_4		20	5	35
6	1% $Pd(OAc)_2$	3% P(*o*-Tol)$_3$	5 equiv K_3PO_4		20	12	20
7	1% $Pd(OAc)_2$	3% P(*o*-Tol)$_3$	5 equiv K_3PO_4		60	29	30
8	1% $Pd(OAc)_2$	3% P(*o*-Tol)$_3$	5 equiv K_3PO_4		80	18	34
9	1% $Pd(acac)_2$	3% P(*o*-Tol)$_3$	5 equiv K_3PO_4		60	5	13
10	1% $Pd(dba)_2$	3% P(*o*-Tol)$_3$	5 equiv K_3PO_4		60	41	30
11[b]	1% $Pd(dba)_2$	3% P(*o*-Tol)$_3$	5 equiv K_3PO_4		60	48	13
12[b]	1% $Pd(dba)_2$	3% P(*o*-Tol)$_3$	5 equiv K_2CO_3		60	47	12
13[b]	1% $Pd(dba)_2$	3% P(*o*-Tol)$_3$	5 equiv KF		60	53	8
14[b]	1% $Pd(dba)_2$	3% P(*o*-Tol)$_3$	5 equiv KF	1 equiv H_2O	60	86	14
15[b]	1% $Pd(dba)_2$	3% P(*o*-Tol)$_3$	3 equiv KF	TBAF·$3H_2O$	60	95	5
16[b]	1% $Pd(dba)_2$	3% P(*o*-Tol)$_3$	3 equiv KF	TBACl	60	92	8
17[b]	1% $Pd(dba)_2$	3% P(*o*-Tol)$_3$	3 equiv KF	Aliquat 336	60	94	6
18[b]	1% $Pd(dba)_2$	3% P(*o*-Tol)$_3$	3 equiv KF	$(PhCH_2)N^+(Et)_3Br^-$	60	93	7
19[b]	0.5% $Pd(dba)_2$	1.5% P(*o*-Tol)$_3$	3 equiv KF	$(PhCH_2)N^+(Et)_3Br^-$	60	82	8
20[b]	0.3 $Pd(dba)_2$	0.9% P(*o*-Tol)$_3$	3 equiv KF	$(PhCH_2)N^+(Et)_3Br^-$	60	79	10
21[b]	0.1 $Pd(dba)_2$	0.3% P(*o*-Tol)$_3$	3 equiv KF	$(PhCH_2)N^+(Et)_3Br^-$	60	45	15

[a] Reaction conditions: 1.10 mmol **1a**, 1.00 mmol **2a**, Pd-source, phosphine ligand, base, 0.10 mmol additive, 2 mL THF, 24 h. dba = dibenzylidenacetone, IMes·HCl = 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride, IPr·HCl = 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride. Yields were determined by GC analysis, with *n*-tetradecane as internal standard. [b] 1.00 mmol **1a**, 1.50 mmol **2a**.

The filtrate was dried over $MgSO_4$ and filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography yielding the corresponding arylacetic acid derivative.

Ethyl 2-(2,6-Dimethylphenyl)acetate (3a) [CAS: 105337-15-3]. Compound **3a** was synthesized following the general procedure starting from 2,6-dimethylphenylboronic acid (150 mg, 1.00 mmol) and ethyl bromoacetate (167 mg, 1.50 mmol). After column chromatography (SiO_2, hexane/ethyl acetate 5:1), **3a** was isolated as a colorless liquid (157 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04−7.12 (m, 3H), 4.14−4.20 (m, 2H), 3.71 (s, 2H), 2.36 (s, 6H), 1.24−1.30 (m, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 136.9, 131.6, 127.8, 126.7, 60.3, 35.2, 19.9, 13.9 ppm; MS (70 eV), m/z (%) 192 (21) [M^+], 146 (13), 119 (100), 91 (26), 77 (10); IR (NaCl) $\tilde{\nu}$ 2981 (w), 1712 (s), 16.38 (m), 1311 (m), 1202 (m), 1176 (m) cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_2$: C 74.97; H 8.39. Found: C 74.84; H 8.29.

Ethyl 2-Phenylacetate (3b) [CAS: 101-97-3]. Compound **3b** was prepared following the general procedure starting from phenylboronic acid (122 mg, 1.00 mmol) and ethyl bromoacetate (167 mg, 1.50 mmol). After column chromatography (SiO_2, hexane/ethyl acetate 5:1), **3b** was isolated as a colorless liquid (121 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.39 (m, 5H), 4.15−4.22 (m, 2H), 3.65 (s, 2H), 1.25−1.32 (m, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 134.3, 129.2, 128.5, 127.0, 60.8, 41.5, 14.2 ppm; MS (70 eV), m/z (%) 164 (12) [M^+], 136 (5), 91 (100), 65 (16), 40 (3); IR (NaCl) $\tilde{\nu}$ 2982 (w), 1736 (s), 1254 (w), 1158 (m), 1030 (m) cm^{-1}.

Ethyl 2-*o*-Tolylacetate (3c) [CAS: 40291-39-2]. Compound **3c** was prepared following the general procedure starting from 2-methylphenylboronic acid (136 mg, 1.00 mmol) and ethyl bromoacetate (167 mg, 1.50 mmol). After column chromatography (SiO_2, hexane/ethyl acetate 5:1), **3c** was isolated as a colorless liquid (99 mg, 56%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18 (s, 4H), 4.10−4.22 (m, 2H), 3.63 (s, 2H), 2.33 (s, 3H), 1.21−1.31 (m, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.9, 137.3, 133.4, 130.7, 130.6, 127.8, 126.5, 61.2, 39.7, 20.0, 14.6 ppm; MS (70 eV), m/z (%) 178 (15) [M^+], 132 (15), 105 (100), 78 (11), 51 (7); IR (NaCl) $\tilde{\nu}$ 2980 (s), 1735 (s), 1155 (m), 1031 (m), 746 (m) cm^{-1}.

Ethyl 2-(2-Ethylphenyl)acetate (3d) [CAS: 105337-78-8]. Compound **3d** was prepared following the general procedure starting from 2-ethylphenylboronic acid (150 mg, 1.00 mmol) and ethyl bromoacetate (167 mg, 1.50 mmol). After column chromatography (SiO_2, hexane/ethyl acetate 5:1), **3d** was isolated as a colorless liquid (127 mg, 61%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.17−7.32 (m, 4H), 4.15−4.28 (m, 2H), 3.71 (s, 2H), 2.73 (q, J = 7.6 Hz, 2H), 1.24−1.36 (m, 6H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.2, 143.0, 132.6, 130.8, 129.0, 127.9, 126.4, 61.2, 39.1, 26.2, 15.3, 14.6 ppm; MS (70 eV), m/z (%) 192 (9) [M^+],146 (36), 119 (100), 103 (14), 91 (42); IR (NaCl) $\tilde{\nu}$ 2968 (m), 2935 (w), 2875 (w), 1735 (s), 1153 (m), 1031 (m) cm^{-1}.

Ethyl 2-(2,4-Dimethylphenyl)acetate (3e) [CAS: 105337-16-4]. Compound **3e** was prepared following the general procedure from 2,4-dimethylphenylboronic acid (150 mg, 1.00 mmol) and ethyl bromoacetate (167 mg, 1.50 mmol). After column chromatography (SiO_2, hexane/ethyl

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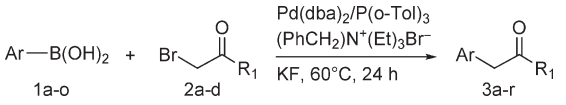
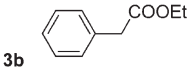
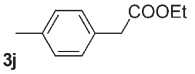
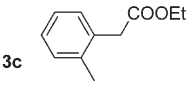
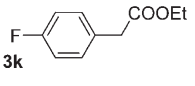
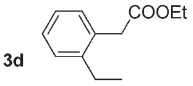
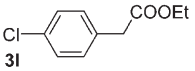
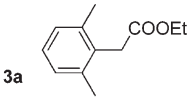
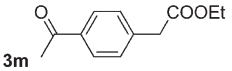
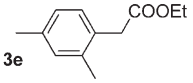
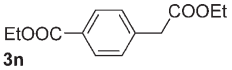
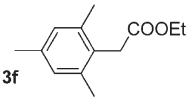
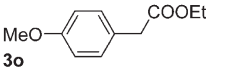
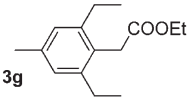
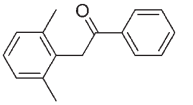
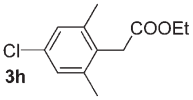
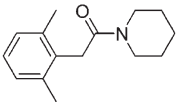
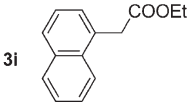
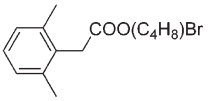
Table 2. Synthesis of Arylacetic Acid Derivatives[a]



Product	Yield(%)	Product	Yield(%)
 **3b**	74	 **3j**	69
 **3c**	56	 **3k**	33
 **3d**	61	 **3l**	58
 **3a**	82	 **3m**	60
 **3e**	55	 **3n**	71
 **3f**	62	 **3o**	77
 **3g**	54	 **3p**	47[b]
 **3h**	68	 **3q**	58[b]
 **3i**	77	 **3r**	48

[a] Reaction conditions: 1.00 mmol **1a**—**o**, 1.50 mmol **2a**—**d**, 3.00 mmol KF, 0.3 mol % $Pd(dba)_2$, 0.9 mol % P(*o*-Tol)$_3$, 10 mol % $(PhCH_2)N^+Et_3Br^-$, 2 mL THF, 60 °C, 24 h. [b] 5.00 mmol KF, 1 mol % $Pd(dba)_2$, 3 mol % P(*o*-Tol)$_3$.

acetate 5:1), **3e** was isolated as a colorless liquid (105 mg, 55%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.06—7.15 (m, 1H), 6.95—7.04 (m, 2H), 4.10—4.23 (m, 2H), 3.60 (s, 2H), 2.31 (d, J = 3.2 Hz, 6H), 1.21—1.32 (m, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.1, 137.3, 137.0, 131.6, 130.5, 130.3, 127.2, 61.1, 39.3, 21.4, 19.9, 14.6 ppm; MS (70 eV), m/z (%) 192 (27) [M^+], 146 (6), 119 (100), 91 (15), 65 (3); IR (NaCl) $\tilde{\nu}$ 2980 (m), 2923 (m), 1735 (s), 1154 (s), 1032 (m) cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_2$: C 74.97; H 8.39. Found: C 75.24, H 8.40.

Ethyl 2-Mesitylacetate (3f) [CAS: 5460-08-2]. Compound **3f** was synthesized following the general procedure from 2,4,6-trimethylphenylboronic acid (164 mg, 1.00 mmol) and ethyl bromoacetate (167 mg, 1.50 mmol). After column chromatography (SiO_2, hexane/ethyl acetate 5:1), **3f** was isolated as a colorless liquid (127 mg, 62%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.89 (s, 2H), 4.10—4.25 (m, 2H), 3.67 (s, 2H), 2.27—2.37 (m, 9H), 1.27 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.9, 137.4, 136.8, 129.3, 129.2, 61.1, 35.6, 21.3, 20.6, 14.7 ppm; MS (70 eV), m/z (%) 206 (23) [M^+], 160, (7), 133 (100), 105 (10) 91 (11); IR (NaCl) $\tilde{\nu}$ 2978 (m), 2867 (w), 1732 (s), 1157 (m), 1031 (m) cm^{-1}.

Ethyl 2-(2,6-Diethyl-4-methylphenyl)acetate (3g). Compound **3g** was synthesized following the general protocol starting from 2,6-diethyl-4-methylphenylboronic acid (186 mg, 1.00 mmol) and ethyl bromoacetate (167 mg, 1.50 mmol). After column chromatography (SiO_2, hexane/ethyl acetate 5:1), **3f** was isolated as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 4.16 (q, J = 7.2 Hz, 2H), 3.71 (s, 2H), 2.61—2.69 (m, 4H), 2.32 (s, 3H), 1.19—1.28 (m, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 143.0, 136.7, 127.2, 127.1, 60.6, 34.0, 26.4, 21.1, 15.1, 14.2 ppm; HRMS (EI-TOF) calcd for $C_{15}H_{22}O_2$, 234.1620, found 234.1635; MS (70 eV), m/z (%) 234 (37) [M^+], 161 (100), 147 (33), 133 (40), 119 (13); IR (NaCl) $\tilde{\nu}$ 2966 (s), 1739 (s), 1458 (w), 1156 (m), 1032 (m) cm^{-1}.

Ethyl 2-(4-Chloro-2,6-dimethylphenyl)acetate (3h). Compound **3h** was prepared according to the general protocol starting from 4-chloro-2,6-dimethylphenylboronic acid (186 mg, 1.00 mmol) and ethyl bromoacetate (167 mg, 1.50 mmol). After column chromatography (SiO_2, hexane/ethyl acetate 5:1), **3f** was isolated as a colorless oil that crystallized upon cooling; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 2H), 4.13 (q, J = 7.2 Hz, 2H), 3.62 (s, 2H), 2.29 (s, 6H), 1.23 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 139.0, 132.3, 130.3, 127.9, 60.8, 35.0, 20.1, 14.2 ppm; HRMS (EI-TOF) calcd for $C_{12}H_{15}O_2{}^{35}Cl$, 226.0761, found 226.0771; MS (70 eV), m/z (%) 226 (22) [M^+], 180 (9), 153 (100), 115 (17), 91 (11); IR (NaCl) $\tilde{\nu}$ 2980 (m), 1733 (s), 1328 (w), 1155 (m), 1030 (m) cm^{-1}; mp 26—27 °C.

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Anal. Calcd for $C_{12}H_{15}ClO_2$: C, 63.58; H, 6.67. Found: C, 63.30; H, 6.78.

Ethyl 2-(Naphthalen-1-yl)acetate (3i) [CAS: 2122-70-5]. Compound **3i** was prepared following the general procedure starting from 1-naphthalinboronic acid (172 mg, 1.00 mmol) and ethyl bromoacetate (167 mg, 1.50 mmol). After column chromatography (SiO_2, hexane/ethyl acetate 5:1), **3i** was isolated as a colorless liquid (166 mg, 77%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.80−7.84 (m, 1H), 7.55−7.58 (m, 1H), 7.50−7.54 (m, 1H), 7.43−7.47 (m, 2H), 4.16−4.20 (m, 2H), 4.09 (s, 2H), 1.23−1.27 (m, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.7, 133.9, 132.2, 130.8, 128.8, 128.1, 128.0, 126.4, 125.8, 125.6, 123.9, 61.0, 39.4, 14.3 ppm; MS (70 eV), m/z (%) 214 (100) [M^+], 141 (34), 115 (45), 89 (9), 63 (6); IR (NaCl) $\tilde{\nu}$ 3047 (w), 2981 (m), 1733 (s), 1173 (m), 1029 (m) cm^{-1}. Anal. Calcd for $C_{14}H_{14}O_2$: C 78.48; H 6.59. Found: C 78.35; H 6.86.

Ethyl 2-*p*-Tolylacetate (3j) [CAS: 2122-70-5]. Compound **3j** was prepared according to the general procedure from 4-methylphenylboronic acid (136 mg, 1.00 mmol) and ethyl bromoacetate (167 mg, 1.50 mmol). After column chromatography (SiO_2, hexane/ethyl acetate 5:1), **3j** was isolated as a colorless liquid (124 mg, 69%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.10−7.22 (m, 4H), 4.09−4.22 (m, 2H), 3.58 (s, 2H), 2.34 (s, 3H), 1.21−1.32 (m, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.2, 137.0, 131.6, 129.7, 129.5, 61.2, 41.5, 21.5, 14.6, ppm; MS (70 eV), m/z (%) 178 (24) [M^+], 105 (100), 77 (14), 91 (3), 50 (4); IR (NaCl) $\tilde{\nu}$ 2981 (m), 2926 (w), 1736 (s), 1515 (m), 1153 (m), 1032 (m) cm^{-1}.

Ethyl 2-(4-Fluorophenyl)acetate (3k) [CAS: 587-88-2]. Compound **3k** was prepared according to the general procedure from 4-fluorphenylboronic acid (140 mg, 1.00 mmol) and ethyl bromoacetate (167 mg, 1.50 mmol). After column chromatography (SiO_2, hexane/ethyl acetate 5:1), **3k** was isolated as a colorless liquid (60 mg, 33%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25−7.29 (m, 2H), 7.01−7.06 (m, 2H), 4.15−4.20 (m, 2H), 3.61 (s, 2H), 1.28 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.5, 162.8, 161.2, 130.0, 130.8, 129.9, 115.5, 115.4, 61.0, 40.6, 14.2 ppm; MS (70 eV), m/z (%) 182 (17) [M^+], 109 (100), 83 (15), 57 (5), 40 (2); IR (NaCl) $\tilde{\nu}$ 2984 (m), 1736 (s), 1510 (s), 1155 (m), 1031 (m) cm^{-1}.

Ethyl 2-(4-Chlorophenyl)acetate (3l) [CAS: 14062-24-9]. Compound **3l** was synthesized following the general procedure from 4-chlorophenylboronic acid (156 mg, 1.00 mmol) and ethyl bromoacetate (167 mg, 1.50 mmol). After column chromatography (SiO_2, hexane/ethyl acetate 5:1), **3l** was isolated as a colorless liquid (114 mg, 57%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30−7.33 (m, 2H), 7.23−7.26 (m, 2H), 4.15−4.19 (m, 2H), 3.60 (s, 2H), 1.25−1.29 (m, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.2, 133.0, 132.6, 130.7, 129.2, 129.0, 128.7, 61.1, 40.7, 14.2 ppm; MS (70 eV), m/z (%) 198 (25) [M^+], 125 (100), 89 (22), 73 (3), 63 (11); IR (NaCl) $\tilde{\nu}$ 2983 (m), 1735 (s), 1493 (s), 1158 (m), 1031 (m) cm^{-1}.

Ethyl 2-(4-Acetylphenyl)acetate (3m) [CAS: 1528-42-3]. Compound **3m** was prepared according to the general procedure starting from 4-acetylphenylboronic (164 mg, 1.00 mmol) and ethyl bromoacetate (167 mg, 1.50 mmol). After column chromatography (SiO_2, hexane/ethyl acetate 5:1), **3i** was isolated as a colorless solid (124 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 4.11−4.17 (m, 2H), 3.66 (s, 2H), 2.58 (s, 3H), 1.20−1.27 (m, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 197.7, 170.8, 139.5, 136.0, 129.6, 128.6, 61.1, 41.3, 26.6, 14.2 ppm; MS (70 eV), m/z (%) 192 (100),164 (16), 134 (14), 105 (19), 89 (11); IR (KBr) $\tilde{\nu}$ 2981 (w), 1735 (s), 1682 (m), 1274 (m), 1178 (m) cm^{-1}; mp 55−56 °C. Anal. Calcd for $C_{12}H_{14}O_3$: C 69.88; H 6.84. Found: C 69.95. H 6.99.

Synthesis of Ethyl 4-(2-Ethoxy-2-oxoethyl)benzoate (3n) [CAS: 3516-89-0]. Compound **3n** was prepared following the general procedure starting from 4-ethoxycarbonylphenylboronic acid (194 mg, 1.00 mmol) and ethyl bromoacetate (167 mg, 1.50 mmol). After column chromatography (SiO_2, hexane/ethyl acetate 5:1), **3n** was isolated as a yellow liquid (168 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.5 Hz, 1H), 4.36 (q, J = 8.2 Hz, 2H), 4.15 (q, J = 8.2 Hz, 2H), 3.65 (s, 2H), 1.38 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 166.4, 139.1, 129.8, 129.4, 129.3, 61.1, 60.9, 41.4, 14.3, 14.1 ppm; MS (70 eV), m/z (%) 237 (6) [M^+], 191 (39), 163 (100), 135 (39), 118 (13); IR (NaCl) $\tilde{\nu}$ 2982 (m), 2938 (w), 1735 (s), 1718 (s) 1277 (s) cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_4$: C 66.09; H 6.83. Found: C 65.98; H 7.05.

Ethyl 2-(4-Methoxyphenyl)acetate (3o) [CAS: 14062-18-1]. Compound **3o** was prepared according to the general procedure from 4-methoxyphenylboronic acid (152 mg, 1.00 mmol) and ethyl bromoacetate (167 mg, 1.50 mmol). After column chromatography (SiO_2, hexane/ethyl acetate 5:1), **3o** was isolated as a colorless liquid (155 mg, 77%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (d, J = 8.5 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 4.13−4.26 (m, 2H), 3.82 (s, 3H), 3.59 (s, 2H), 1.24−1.26 (m, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.3, 159.1, 130.7, 126.7, 114.4, 61.1, 55.6, 40.9, 14.6 ppm; MS (70 eV), m/z (%) 194 (24) [M^+], 121 (100), 91 (8), 77 (10), 51 (4); IR (NaCl) $\tilde{\nu}$ 2981 (m), 2836 (w), 1732 (s), 1513 (s), 1247 (m), 1032 (m) cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_3$: C 68.02; H 7.27. Found: C 67.91; H 7.18.

Synthesis of 2-(2,6-Dimethylphenyl)-1-phenylethanone (3p) [CAS: 23592-90-7]. Compound **3p** was prepared following the general procedure starting from 2,6-dimethylphenylboronic acid (150 mg, 1.00 mmol), 2-bromo-1-phenylethanone (299 mg, 1.50 mmol), $Pd(dba)_2$ (5.75 mg, 0.01 mmol), tri-*o*-tolylphosphine (10.0 mg, 0.03 mmol), benzyltriethylammonium bromide (27.8 mg, 0.10 mmol) and potassium fluoride (174 mg, 3.00 mmol). After column chromatography (SiO_2, hexane/ethyl acetate 5:1), **3i** was isolated as a light yellow solid (106 mg, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 7.2 Hz, 2H), 7.66 (d, J = 7.4 Hz, 1H), 7.54−7.61 (m, 2H), 7.12−7.21 (m, 3H), 4.45 (s, 2H), 2.30 (s, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.9, 137.4, 137.0, 133.1, 132.5, 128.7, 128.1, 128.0, 126.9, 39.7, 20.4 ppm; MS (70 eV), m/z (%) 223 (100) [M^+], 131 (3), 105 (49), 103 (38), 77 (47); IR (KBr) $\tilde{\nu}$ 1675 (s), 1654 (m), 1560 (w), 1449 (w), 1219 (s) cm^{-1}; mp 110 °C. Anal. Calcd for $C_{16}H_{16}O$: C 85.68; H 7.19. Found: C 85.39; H 7.22.

2-(2,6-Dimethylphenyl)-1-(piperidin-1-yl)ethanone (3q). Compound **3q** was prepared following the general procedure starting from 2,6-dimethylphenylboronic acid (150 mg, 1.00 mmol), *N*-(bromoacetyl)piperidine[12] (309 mg, 1.50 mmol), $Pd(dba)_2$ (5.75 mg, 0.01 mmol), tri-*o*-tolyphosphine (9.13 mg, 0.03 mmol) and potassium fluoride (290 mg, 5.00 mmol). After column chromatography (SiO_2, hexane/ethyl acetate 2:3), **3q** was isolated as a colorless solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.01−7.07 (m, 3H), 3.66 (s, 2H), 3.59 (s, 2H), 3.54 (s, 2H), 2.26(s, 6H), 1.67 (d, J = 5.3 Hz, 2H), 1.54−1.62 (m, 4H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.5, 136.9, 133.5, 128.0, 126.6, 46.8, 43.2, 34.0, 26.7, 25.8, 24.7, 20.4 ppm; HRMS (EI-TOF) calcd for $C_{15}H_{21}NO$, 231.1623, found 231.1607; MS (70 eV), m/z (%) 231 (48) [M^+], 217 (16), 119 (24), 112 (100), 84 (14), 69 (60); IR (KBr) $\tilde{\nu}$ 2935 (m), 2854 (w), 1636 (s), 1443 (m), 1219 (m), 771 (w) cm^{-1}; mp 72−73 °C.

4-Bromobutyl 2-(2,6-Dimethylphenyl)acetate (3r). Compound **3r** was synthesized following the general procedure starting from 2,6-dimethylphenylboronic acid (150 mg, 1.00 mmol) and 4-bromobutyl bromoacetate[13] (411 mg, 1.50 mmol). After column chromatography (SiO_2, hexane/ethyl acetate 5:1), **3r** was isolated as a colorless liquid (144 mg, 48%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.02−7.06 (m, 3H), 4.11 (t, J = 6.2 Hz, 2H), 3.68 (s, 2H), 3.35 (t, J = 6.2 Hz, 2H), 2.32 (s, 6H), 1.86 (m, 2H), 1.76 (m, 2H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 137.1, 131.6, 128.1, 127.1, 63.8, 35.4, 33, 29.2, 27.3, 20.3 ppm; HRMS (EI-TOF) calcd for $C_{14}H_{19}O_2{}^{80}Br$, 298.0568, found 298.0565; MS (70 eV), m/z (%) 300(4) [$^{82}BrM^+$], 298 (5) [^{80}Br M^+], 137 (44), 135 (54), 119 (100), 118 (35), 117 (18), 91 (24), 55 (20); IR ATR

$\tilde{\nu}$ 3021 (w), 2958 (w), 1729 (vs), 1590 (w), 1471 (w), 1444 (w), 1328 (w), 1244 (m), 1147 (vs), 1096 (w), 1032 (w), 1006 (w), 956 (w), 768 (s), 694 (w), 677 (w), 650 (w) cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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