Tetrahedron 70 (2014) 1508–1515

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A chemoselective Reformatsky–Negishi approach to α-haloaryl esters

Brian Wong [a], Xin Linghu [a], James J. Crawford [b], Joy Drobnick [b], Wendy Lee [b], Haiming Zhang [a,*]

[a] Small Molecule Process Chemistry, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, United States
[b] Discovery Chemistry, Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080, United States

ARTICLE INFO

Article history:
Received 6 November 2013
Received in revised form 18 December 2013
Accepted 19 December 2013
Available online 31 December 2013

Keywords:
Palladium
Catalysis
Chemoselective
Reformatsky reagent
Negishi coupling

ABSTRACT

A practical synthesis of α-haloaryl esters has been achieved via a chemoselective Negishi coupling of poly-halogenated aromatics and Reformatsky reagents in the presence of catalytic $Pd(dba)_2$ and Xantphos. This chemistry tolerates a variety of aryl halides and was successfully applied to the synthesis of Ibuprofen. The α-haloaryl ester products, exemplified by ethyl 2-(4-bromo-2-chlorophenyl)acetate (**3a**), can be further functionalized via palladium or copper catalysis to afford an array of α-aryl esters.

1. Introduction

α-Aryl esters and their carboxylic acid derivatives are the core structure for numerous biologically active compounds, such as Naproxen, Ibuprofen, Flurbiprofen, and Tolmetin, which are widely used to treat inflammatory diseases and to relieve pain (Fig. 1).[1] In the past decade, various transition metal-catalyzed methods have been developed for the synthesis of α-aryl esters and their derivatives.[2] There are four major catalytic strategies for the synthesis of α-aryl esters, namely, (1) Buchwald–Hartwig arylation of ester enolates (Scheme 1A);[3] (2) cross-coupling of Reformatsky reagents with aryl halides (Scheme 1B);[4] (3) coupling of α-haloesters with arylmetallic species, such as silanes,[5] Grignard reagents,[6] or boron compounds[7] catalyzed by nickel, iron or palladium (Scheme 1C); and (4) nickel-catalyzed coupling of aryl halides and α-haloesters (Scheme 1D).[8] Although each strategy has its own limitations, the combination of these four methods provides a powerful tool to effectively assemble a variety of highly functionalized α-aryl esters and their derivatives.

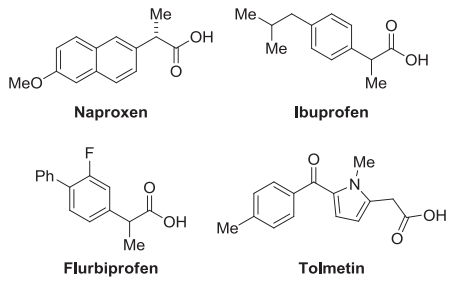
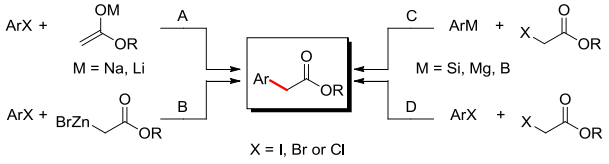


Fig. 1. Biologically active α-aryl carboxylic acids.



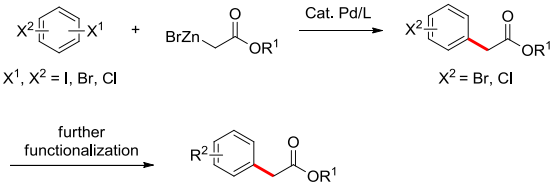
Scheme 1. Catalytic strategies to α-aryl esters.

To support an internal drug research program, we were faced with the need to develop a divergent synthesis of a wide spectrum of functionalized α-aryl esters for structure–activity relationship (SAR) studies. Our decision was to focus on a chemoselective Reformatsky–Negishi reaction[9] of poly-halogenated aromatics to generate α-haloaryl esters, which can potentially be further functionalized via palladium or copper catalysis (Scheme 2). Herein, we report a facile

* Corresponding author. Tel.: +1 650 467 8758; fax: +1 650 225 6238; e-mail address: zhang.haiming@gene.com (H. Zhang).

0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.12.053

chemoselective synthesis of α-haloaryl esters by a palladium-catalyzed Negishi coupling of multi-halogen substituted aromatics with Reformatsky reagents and preliminary results of further functionalization of a representative α-haloaryl ester product (Scheme 2).



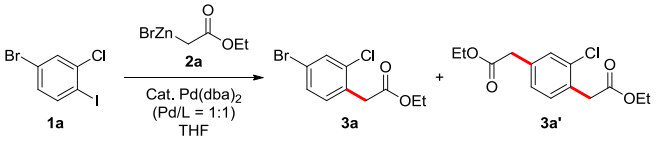
Scheme 2. Chemoselective Reformatsky–Negishi reaction.

2. Results and discussion

Hartwig reported that aryl bromides[4a,c] and chlorides[4b] underwent cross-coupling with Reformatsky reagents in the presence of $Pd(dba)_2$ and Qphos,[10] or $\{[P(^tBu)_3]PdBr\}_2$,[11] affording good to excellent yields of the desired α-aryl esters. However, only two dihalides, namely 1-bromo-4-chlorobenzene and 1-bromo-2-fluorobenzene, among nearly 30 halogenated aromatics were examined. In addition, more than half of the reactions employed the *tert*-butyl Reformatsky reagent. Other zinc reagents from non-*tert*-butyl esters typically required low temperature (−78 to −20 °C) and glove box technique to generate, thus making the reaction less practical, especially on scale. Our initial goal was to explore a catalytic system that may promote chemoselective Negishi coupling of multi-halogenated aromatics with the ethyl Reformatsky reagent.[12] The resulting products, α-haloaryl ethyl esters, could be further functionalized on the aromatic ring.

Our investigation commenced with the Negishi coupling of 4-bromo-2-chloro-1-iodobenzene (**1a**) with Reformatsky reagent ethyl 2-bromozincacetate (**2a**) to form ethyl 2-(4-bromo-2-chlorophenyl)acetate (**3a**). The coupling reaction of halide **1a** with 1.5 equiv of Reformatsky reagent **2a** under Hartwig's optimal conditions,[4a,c] which employed 1 mol % $Pd(dba)_2$ and 1 mol % Qphos in THF at 23 °C, was first examined (Table 1, entry 1). Unfortunately, the reaction was stalled at 67% conversion after 16 h and generated a 71:29 ratio of the desired ester **3a** and a major diester by-product **3a′** arising from Negishi reactions at both the iodo- and bromo- positions of halide **1a**. The relatively low conversion and formation of multiple impurities rendered the reaction impractical. Realizing that the combination of $Pd(dba)_2$ and Qphos was too active to distinguish C–I and C–Br bonds, we proceeded to screen various phosphine ligands in order to tune the reactivity and selectivity with higher initial catalyst/ligand loading (5 mol %) at an elevated temperature (65 °C). A screen of a subset of Buchwald ligands,[13] i.e., SPhos, RuPhos, JohnPhos and DavePhos, resulted in lower conversions (Table 1, entries 2–5), so did that of bidentate ligands DPPF, DPPM and BINAP (Table 1, entries 6–8). To our delight, when Xantphos[14,15] was employed, the reaction readily reached completion in 1.5 h with a 93:7 ratio of **3a** to **3a′** based on HPLC analysis, presumably because the unique combination of steric and electronic effects of Xantphos ligand facilitates both the oxidative addition and the transmetallation processes. The desired product **3a** was subsequently isolated in 80% yield (Table 1, entry 9). Further optimization including catalyst loading and stoichiometry of the Reformatsky reagent **2a** (Table 1, entries 10–12), reaction temperature (Table 1, entry 13) and solvent[16] led to the optimized conditions employing 2.5 mol % $Pd(dba)_2$, 2.5 mol % Xantphos, 1.2 equiv of **2a** in THF at 65 °C. Under this set of conditions, the reaction reached completion in 4 h with a 93:7 ratio of **3a** to **3a′** and ethyl ester **3a** was isolated in 80% yield (Table 1, entry 11).

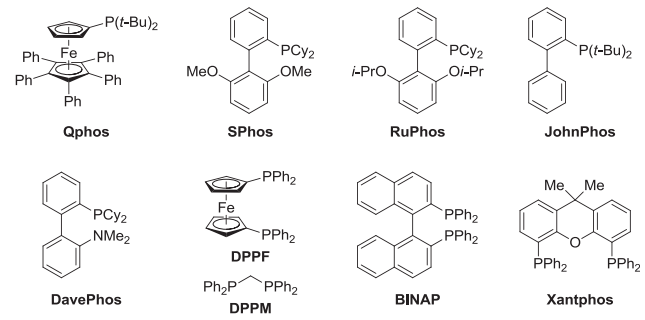
Table 1
Optimization of Reformatsky–Negishi coupling[a]



Entry	L, mol %	**2a** (equiv)	Temp (°C), time (h)	**3a**:**3a′**[b]	Conv'n (%)[b]
1	Qphos, 1	1.5	23, 16	71:29	67
2	SPhos, 5	1.5	65, 16	—	8
3	RuPhos, 5	1.5	65, 16	—	11
4	JohnPhos, 5	1.5	65, 16	29:71	51
5	DavePhos, 5	1.5	65, 16	30:70	58
6	DPPF, 5	1.5	65, 16	—	4
7	DPPM, 5	1.5	65, 16	—	18
8	BINAP, 5	1.5	65, 16	—	10
9	Xantphos, 5	1.5	65, 1.5	93:7	99(80)[c]
10	Xantphos, 2.5	1.5	65, 1.5	91:9	99(78)[c]
11	**Xantphos, 2.5**	**1.2**	**65, 4**	**93:7**	**99(80)**[c]
12	Xantphos, 1	1.2	65, 16	91:9	77
13	Xantphos, 2.5	1.2	40, 16	97:3	53

Bold emphasizes the optimized conditions.
[a] Reaction conditions: **1a** (0.63 g, 2.0 mmol), **2a** (0.40 M in THF, 1.2 or 1.5 equiv), $Pd(dba)_2$ (1–5 mol %), ligand (1–5 mol %), THF (6.0 mL).
[b] Determined by HPLC analysis at 220 nm.
[c] The numbers in parentheses are isolated yields of **3a**.

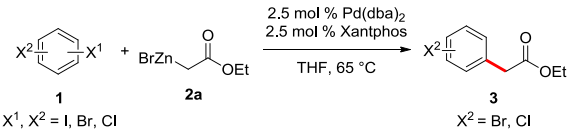
Phosphine ligands

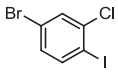
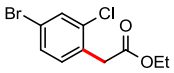
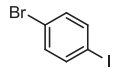
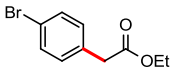
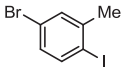
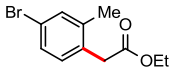
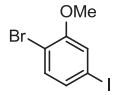
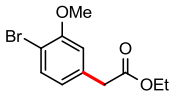
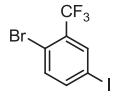
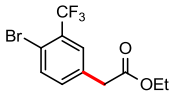
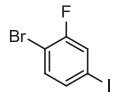
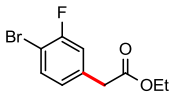
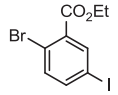
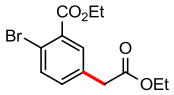
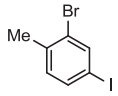
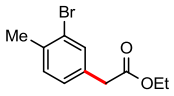
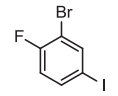
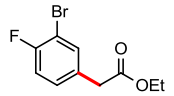
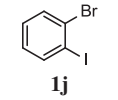
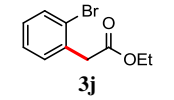
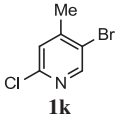
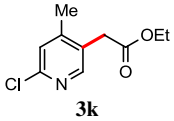


With optimal conditions available, we then set out to investigate the scope and limitations of this chemoselective Reformatsky–Negishi coupling reaction (Table 2). A scaled-up reaction using 10.0 g of halide **1a** (31.5 mmol) and reagent **2a** produced the same isolated yield of 80% as the smaller scale (2.0 mmol of **1a**), which attests the scalability of this chemistry (Table 2, entry 1). Moving to other halide substrates, a *para*-dihalide 1-bromo-4-iodobenzene (**1b**) readily afforded the desired ethyl ester in 81% in 1.5 h (Table 2, entry 2). When a substrate bearing an *ortho*-substituent to the iodide, namely 4-bromo-1-iodo-2-methylbenzene (**1c**) was employed, the coupling reaction not only required 1.5 equiv Reformatsky reagent **2a** to reach high conversion, but also produced lower isolated yield of 58%, presumably due to a steric effect caused by the *ortho*-methyl group (Table 2, entry 3). Substituents at *meta*-position to the iodide, whether electron donating (MeO) or electron withdrawing (CF_3, F, CO_2Et), all readily generated good yields of the desired ester products **3d**–**g** (Table 2, entries 4–7). Dihalides **1h** and **1i** with a *meta* bromo–iodo substitution pattern proceeded smoothly, affording 80% and 71% yields of ethyl esters **3h** and **3i**, respectively (Table 2, entries 8–9). Finally, simple *ortho*-dihalide 1-bromo-2-iodobenzene (**1j**) and heterocyclic dihalide 5-bromo-2-chloro-4-methylpyridine (**1k**) also gave good yields of the desired products **3j** and **3k** in 61% and 71%, albeit requiring 1.5 equiv of the Reformatsky reagent **2a** to reach high conversion (Table 2, entries 10–11).

Surprisingly, when α-methyl substituted Reformatsky reagent **2b** was subjected to the Negishi coupling reaction with halide **1a**, low

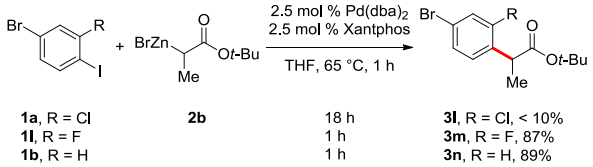
Table 2
Chemoselective Reformatsky–Negishi coupling of halides **1** with **2a**[a]



Entry	Halide	Product	Time (h)	Yield (%)[b]
1	 **1a**	 **3a**	4	80(80)[c]
2	 **1b**	 **3b**	1.5	81
3	 **1c**	 **3c**	4	58[d]
4	 **1d**	 **3d**	5	68
5	 **1e**	 **3e**	0.5	72
6	 **1f**	 **3f**	4	57
7	 **1g**	 **3g**	3	77
8	 **1h**	 **3h**	1.5	80
9	 **1i**	 **3i**	4	71
10	 **1j**	 **3j**	5	61[d]
11	 **1k**	 **3k**	3	71[d]

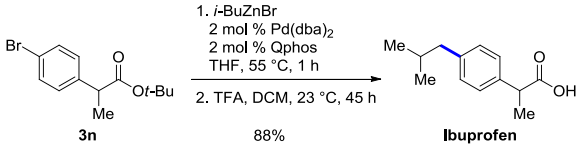
[a] Reaction conditions: **1a** (2.0 mmol), $Pd(dba)_2$ (2.5 mol %), Xantphos (2.5 mol %), **2a** (0.40 M in THF, 6.0 mL, 1.2 equiv), THF (6.0 mL), 65 °C.
[b] Isolated yield.
[c] Yield in parentheses is for reaction employing 10.0 g (31.5 mmol) of **1a**.
[d] 1.5 equiv of **2a** was employed.

conversion and multiple by-products were observed (Scheme 3). We reasoned that the increased steric hindrance brought by the α-methyl group in **2b** and the 2-chloro group in halide **1a** might hamper the transmetallation process, thus resulting in an inferior reaction. To confirm our hypothesis, halides **1l** and **1b** with smaller substituents, such as fluorine and hydrogen atom at the 2-position were reacted with **2b** under our standard conditions. To our satisfaction, both reactions afforded excellent yields of the desired esters **3m** and **3n** in 87% and 89%, respectively (Scheme 3). These results clearly indicate that steric effect plays an influential role in this coupling reaction.



Scheme 3. Negishi coupling using Reformatsky reagent **2b**.

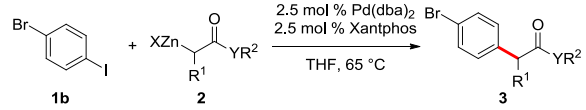
Ester **3n** could be readily converted to Ibuprofen without purifying any intermediate. In fact, ester **3n** was subjected to a Negishi coupling reaction with ^{i}BuZnBr in the presence of 2 mol % of $Pd(dba)_2$ and 2 mol % of Qphos, followed by TFA deprotection of *t*-Bu group to afford Ibuprofen in 88% isolated yield (Scheme 4). Overall, Ibuprofen was readily synthesized in three transformations featuring two Negishi couplings in 78% yield from 1-bromo-4-iodobenzene (**1b**).



Scheme 4. Synthesis of Ibuprofen from ester **3n**.

Next, we focused on using 1-bromo-4-iodobenzene (**1b**) to examine the scope of the Reformatsky reagents. The *tert*-butyl Reformatsky reagent **2c** generated the desired ester **3o** uneventfully in 73% yield in 1 h (Table 3, entry 1). However, when

Table 3
Negishi coupling of halide **1b** with zinc reagents



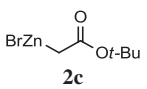
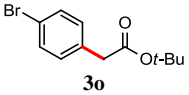
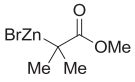
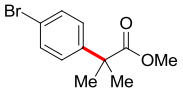
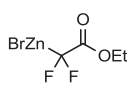
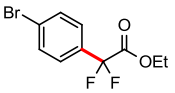
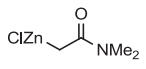
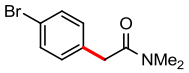
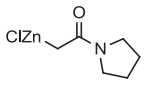
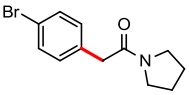
Entry	Zinc reagent	Product	Time (h)	Yield (%)[a]
1	 **2c**	 **3o**	1	73[b]
2	 **2d**	 **3p**	3	<10[b,c]
3	 **2e**	 **3q**	4	<10[b,d]

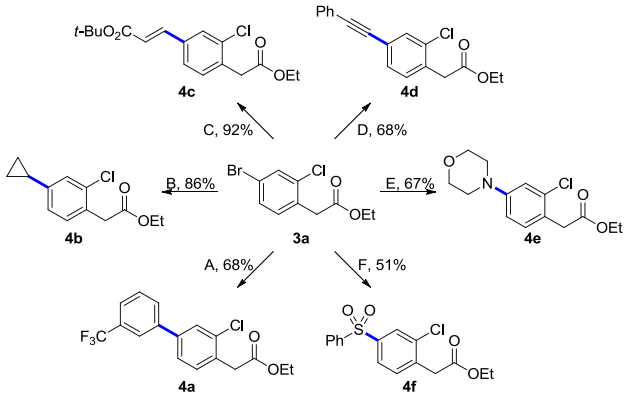
Table 3 (*continued*)

Entry	Zinc reagent	Product	Time (h)	Yield (%)[a]
4	 **2f**	 **3r**	16	71[e]
5	 **2g**	 **3s**	5	74[e]

[a] Isolated yield.
[b] Reaction conditions: **1b** (2.0 mmol), $Pd(dba)_2$ (2.5 mol %), Xantphos (2.5 mol %), **2** (1.2 equiv), THF (12 mL), 65 °C.
[c] Stalled at 65% conversion in 3 h with multiple products observed.
[d] Stalled at 25% conversion in 4 h with multiple products observed.
[e] Reaction conditions: **1b** (2.0 mmol), $Pd(dba)_2$ (2.5 mol %), Xantphos (2.5 mol %), amide precursor (1.2 equiv), NaHMDS (1.3 equiv), $ZnCl_2$ (2.6 equiv), THF (16 mL), PhMe (8 mL), 65 °C.

extra steric hindrance at the α-position was introduced to the Reformatsky reagent, for example, zinc reagent **2d** with a 2,2-dimethyl substituent, lower conversion and multiple products were observed (Table 3, entry 2). To our disappointment, the coupling reaction employing an electron-deficient Reformatsky reagent **2e** did not afford significant amount of product **3q**, presumably because the lessened nucleophilicity of the zinc reagent prevents an efficient transmetallation process (Table 3, entry 3). Therefore, we summarized that this chemistry is sensitive to the steric and electronic properties of the individual Reformatsky reagent under our conditions. Gratifyingly, although we were unable to prepare the Reformatsky reagents of amides by direct zinc insertion, zinc reagents **2f** and **2g** obtained by treating the corresponding amides with NaHMDS and $ZnCl_2$[4a,c] underwent the selective Negishi coupling, producing the desired α-haloaryl amides **3r** and **3s** in 71% and 74% yield, respectively (Table 3, entries 4–5).

To demonstrate the synthetic utility of this chemoselective Reformatsky–Negishi coupling chemistry, we converted compound **3a** to various functionalized α-aryl esters. For example, Suzuki–Miyaura[17] coupling of **3a** with 3-trifluoromethylphenylboronic acid or potassium cyclopropyltrifluoroborate[18] generated good yields of the coupling products in 68% and 86%, respectively (Scheme 5A and B); Mizoroki–Heck[19] and Sonogashira[20] coupling of **3a** with *tert*-butyl acrylate and phenylacetylene produced 92% and 68% yields



Scheme 5. Reagents and conditions: (A) **3a**, 3-$CF_3C_6H_4B(OH)_2$ (1.2 equiv), $Pd(PPh_3)_2Cl_2$ (12 mol %), Na_2CO_3 (3.0 equiv), MeCN/H_2O, μw, 110 °C, 0.5 h. (B) **3a**, *c*-$PrBF_3K$ (1.2 equiv), $Pd(OAc)_2$ (10 mol %), $^nBuAd_2P$ (15 mol %), Cs_2CO_3 (3.0 equiv), PhMe/H_2O, 80 °C, 16 h. (C) **3a**, $CH_2{=}CHCO_2{}^tBu$ (1.4 equiv), Pd(dtbpf)Cl_2 (2 mol %), TBAC (10 mol %), Cy_2NMe (1.5 equiv), DMA, 80 °C, 20 h. (D) **3a**, PhC≡CH (3.0 equiv), $Pd(PPh_3)_4$ (5 mol %), CuBr·Me_2S (10 mol %), Et_3N, DMF, 90 °C, 16 h. (E) **3a**, morpholine (1.2 equiv), $Pd(OAc)_2$ (10 mol %), Xantphos (10 mol %), Cs_2CO_3 (2.0 equiv), 1,4-dioxane, 110 °C, 20 h. (F) **3a**, $PhSO_2Na$ (2.0 equiv), $Cu(OTf)_2$ (20 mol %), $MeNHCH_2CH_2NHMe$ (50 mol %), DMSO, μw, 130 °C, 2 h.

of the corresponding products (Scheme 5C and D); Buchwald–Hartwig amination[13,21] of **3a** with morpholine also successfully afforded good yield (67%) of ethyl 2-(2-chloro-4-morpholinophenyl) acetate while copper catalyzed sulfonylation[22] of **3a** with sodium benzenesulfinate gave the desired sulfone compound in 51% yield (Scheme 5E and F).

3. Conclusion

In summary, we have developed an efficient protocol for the synthesis of α-haloaryl esters via a palladium-catalyzed chemoselective Reformatsky–Negishi coupling reaction. This coupling chemistry is scalable as demonstrated at 10-gram scale and tolerates a variety of aryl halides, but is sensitive to steric hindrance introduced by both the *ortho*-position of the halides and the α-position of the Reformatsky reagents. The reaction can also be extended to the synthesis of α-haloaryl amides using zinc reagents generated from the corresponding acetamides. The synthetic utility of this chemistry was demonstrated by a three-step synthesis of Ibuprofen from readily available starting materials. The product α-haloaryl esters can be further functionalized at the remaining halide position as exemplified by a diverse set of metal-catalyzed transformations using ethyl 2-(4-bromo-2-chlorophenyl)acetate (**3a**).

4. Experimental section

4.1. General

Unless stated otherwise, reactions were performed under an ambient atmosphere of nitrogen in 20 mL vials sealed by Teflon-lined caps. All solvents and commercially obtained reagents were used as received, unless specified otherwise. Zinc powder (median 6–9 micron, Alfa Aesar) was used for the preparation of Reformatsky reagents. Reformatsky reagent ethyl 2-bromozincacetate (**2a**) was prepared according to previously reported procedure and titrated to be 0.40 M.[12a] $Pd(dba)_2$ and Xantphos were purchased from Johnson Matthey and used directly. Microwave reactions were performed on a CEM Discover Explorer 48 reactor. Thin-layer chromatography (TLC) was conducted with EMD silica gel 60 F254 pre-coated plates and visualized using UV light (254 nm). Flash column chromatography was performed with pre-packed RediSep silica gel columns on a CombiFlash ISCO system using gradient EtOAc in hexanes (or heptane) as eluent and detected with both 220 and 254 nm wavelengths. Analytical HPLC analyses were performed with an Agilent 1290 Infinity Series HPLC instrument. ^1H NMR spectra were recorded on a Bruker 300 (at 300 MHz) or a Bruker 400 (at 400 MHz) and are reported relative to the residual solvent peak (δ 7.26 for $CDCl_3$, 2.50 for DMSO-d_6). ^{13}C NMR spectra were recorded on a Bruker 300 (at 75 MHz) or a Bruker 400 (at 101 MHz), and are reported relative to the residual solvent peak (δ 77.0 for $CDCl_3$, 39.5 for DMSO-d_6). Melting points are uncorrected and were recorded on a Büchi Melting Point B-540 apparatus. IR spectra were recorded on a Bruker Alpha Platinum-ATR spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS data were obtained on an LTQ Orbitrap Discovery (Thermo Fisher Scientific) at Genentech, Inc.

4.2. General procedure for the formation of Reformatsky reagents

To a 125 mL 3-neck round-bottom flask equipped with a condenser, a 60 mL addition funnel and a needle thermocouple under nitrogen was added zinc powder (2.45 g, 1.50 equiv), THF (15 mL) and the mixture was vacuumed and backfilled with nitrogen (3×). TMSCl (5 mol %, 0.16 mL) was added and the mixture was stirred for

15 min. A slight exotherm (ca. 2–3 °C) was observed. To the addition funnel was syringed in THF (35 mL) and 2-bromoester (25.0 mmol) and the well-mixed solution was added to the round-bottom flask in 1–2 min. Significant exotherm was usually observed after the addition. The mixture was then slowly cooled to room temperature and stirring was discontinued. A portion of the mixture was transferred into a 10 mL syringe through a Target® Nylon 0.45 μm filter (1.25-inch OD) and titrated using a solution of iodine (254 mg, 1.00 mmol) in 0.5 M THF solution of LiCl (3.0 mL) to determine the concentration.[23] The reagent was used right after the titration.[24]

*4.2.1. tert-Butyl 2-bromozincpropionate (**2b**).* Zinc powder (2.45 g, 1.5 equiv) and *tert*-butyl 2-bromopropionate (25.0 mmol, 5.23 g, 4.15 mL) were employed. Exotherm was observed right after the addition and the internal temperature rose to T_{max} at 57 °C without external cooling. The concentration was determined to be 0.23 M.

*4.2.2. tert-Butyl 2-bromozincacetate (**2c**).* Zinc powder (2.45 g, 1.5 equiv) and *tert*-butyl 2-bromoacetate (25.0 mmol, 4.88 g, 3.69 mL) were employed. Exotherm was not observed after the addition. The mixture was warmed up with a warm water bath (ca. 45 °C). When the internal temperature reached ca. 35 °C, the reaction was initiated and significant exotherm was observed with T_{max} reaching refluxing 65 °C without external cooling. The concentration was determined to be 0.22 M.

*4.2.3. Methyl 2-bromozinc-2-methylpropionate (**2d**).* Zinc powder (2.45 g, 1.5 equiv) and methyl 2-bromo-2-methylpropionate (25.0 mmol, 4.53 g, 3.24 mL) were employed. Exotherm was observed after the addition with T_{max} reaching 57 °C without external cooling. The concentration was determined to be 0.16 M.

*4.2.4. Ethyl 2-bromozinc-2,2-difluoroacetate (**2e**).* Zinc powder (2.45 g, 1.5 equiv) and ethyl 2-bromo-2,2-difluoroacetate (25.0 mmol, 5.07 g) were employed. Exotherm was observed after the addition with T_{max} reaching refluxing 65 °C without external cooling. The concentration was determined to be 0.16 M.[25]

4.3. General procedure for the Reformatsky–Negishi coupling employing ethyl 2-bromozincacetate (2a)

To a 20 mL vial with a stir bar was added aryl halide **1** (2.00 mmol), $Pd(dba)_2$ (28.8 mg, 2.5 mol %), Xantphos (28.9 mg, 2.5 mol %). The vial was sealed with a Teflon-lined cap and THF (6.0 mL) was added. The mixture was vacuumed and backfilled with nitrogen (3×). A solution of ethyl 2-bromozincacetate (**2a**) in THF (0.40 M, 6.0 mL, 1.2 equiv) filtered through a Target® Nylon 0.45 μm filter (1.25-inch OD) was syringed in and the reaction mixture was then heated to 65 °C and monitored by HPLC. Upon reaction completion based on HPLC analysis (≥95% conversion unless the reaction was stalled), the mixture was cooled to room temperature and quenched with 1 M aq HCl (5.0 mL), followed by addition of brine (5.0 mL). The organic layer was separated and concentrated in vacuum. The residue was purified by silica gel column chromatography using gradient EtOAc in hexanes.

*4.3.1. Ethyl 2-(4-bromo-2-chlorophenyl)acetate (**3a**).* 4-Bromo-2-chloro-1-iodobenzene (**1a**, 635 mg, 2.00 mmol) was employed. Compound **3a** was purified using EtOAc in hexanes (0–5%) and obtained as a pale yellow oil (444 mg, 80%). The 10-gram scale-up reaction was performed in a 250 mL 3-neck round-bottom flask using 4-bromo-2-chloro-1-iodobenzene (**1a**, 10.0 g, 31.5 mmol), $Pd(dba)_2$ (0.453 g, 2.5 mol %), Xantphos (0.456 g, 2.5 mol %) and ethyl 2-bromozincacetate (**2a**) in THF (0.40 M, 96 mL, 1.2 equiv). Compound **3a** was isolated as a yellow oil (7.03 g, 80%). FTIR (thin film, cm^{-1}) 2979, 1734, 1473, 1159; ^1H NMR (300 MHz, DMSO-d_6) δ 7.72 (d, J=1.8 Hz, 1H), 7.54 (dd, J=8.2, 2.0 Hz, 1H), 7.38 (d, J=8.2 Hz, 1H), 4.10 (q, J=7.1 Hz, 2H), 3.80 (s, 2H), 1.18 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.6, 134.9, 133.7, 132.3, 131.2, 130.2, 120.7, 60.5, 37.9, 14.0; HRMS (ESI+) calcd for $C_{10}H_{11}BrClO_2$ ($[M+H]^+$), 276.9625; found, 276.9615.

*4.3.2. Ethyl 2-(4-bromophenyl)acetate (**3b**).* 1-Bromo-4-iodobenzene (**1b**, 566 mg, 2.00 mmol) was employed. Compound **3b** was purified using EtOAc in hexanes (0–10%) and obtained as a pale yellow oil (392 mg, 81%). FTIR (thin film, cm^{-1}) 2981, 1730, 1488, 1153; ^1H NMR (300 MHz, DMSO-d_6) δ 7.61–7.41 (m, 2H), 7.23 (d, J=8.4 Hz, 2H), 4.08 (q, J=7.1 Hz, 2H), 3.66 (s, 2H), 1.18 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.7, 133.9, 131.6, 131.1, 120.0, 60.3, 14.0; HRMS (ESI+) calcd for $C_{10}H_{12}BrO_2$ ($[M+H]^+$), 243.0015; found, 243.0009.

*4.3.3. Ethyl 2-(4-bromo-2-methylphenyl)acetate (**3c**).* 4-Bromo-1-iodo-2-methylbenzene (**1c**, 594 mg, 2.00 mmol) and ethyl 2-bromozincacetate (**2a**) in THF (0.40 M, 7.5 mL, 1.5 equiv) were employed. Compound **3c** was purified using EtOAc in hexanes (0–10%) and obtained as a colorless oil (299 mg, 58%). FTIR (thin film, cm^{-1}) 2980, 1730, 1484, 1152; ^1H NMR (300 MHz, DMSO-d_6) δ 7.41 (d, J=1.8 Hz, 1H), 7.33 (dd, J=8.1, 2.0 Hz, 1H), 7.14 (d, J=8.1 Hz, 1H), 4.08 (q, J=7.1 Hz, 2H), 3.66 (s, 2H), 2.21 (s, 3H), 1.17 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.5, 139.6, 132.8, 132.30, 132.25, 128.6, 119.9, 60.3, 37.8, 18.7, 14.0; HRMS (ESI+) calcd for $C_{11}H_{14}BrO_2$ ($[M+H]^+$), 257.0172; found, 257.0163.

*4.3.4. Ethyl 2-(4-bromo-3-methoxyphenyl)acetate (**3d**).* 4-Bromo-3-methoxy-1-iodobenzene (**1d**, 616 mg, 2.00 mmol) was employed. Compound **3d** was purified using EtOAc in hexanes (0–10%) and obtained as a yellow oil (370 mg, 68%). FTIR (thin film, cm^{-1}) 2980, 1730, 1486, 1154; ^1H NMR (300 MHz, DMSO-d_6) δ 7.49 (d, J=8.0 Hz, 1H), 7.03 (d, J=1.7 Hz, 1H), 6.79 (dd, J=8.1, 1.8 Hz, 1H), 4.08 (q, J=7.1 Hz, 2H), 3.83 (s, 3H), 3.66 (s, 2H), 1.19 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.7, 155.1, 135.6, 132.5, 122.9, 113.9, 108.9, 60.3, 56.1, 39.9, 14.0; HRMS (ESI+) calcd for $C_{11}H_{14}BrO_3$ ($[M+H]^+$), 273.0121; found, 273.0111.

*4.3.5. Ethyl 2-(4-bromo-3-trifluoromethylphenyl)acetate (**3e**).* 4-Bromo-3-trifluoromethyl-1-iodobenzene (**1e**, 702 mg, 2.00 mmol) was employed. Compound **3e** was purified using EtOAc in hexanes (0–10%) and obtained as a yellow oil (450 mg, 72%). FTIR (thin film, cm^{-1}) 2985, 1732, 1317, 1126; ^1H NMR (300 MHz, DMSO-d_6) δ 7.84 (d, J=8.2 Hz, 1H), 7.78 (d, J=1.9 Hz, 1H), 7.50 (dd, J=8.2, 1.8 Hz, 1H), 4.09 (q, J=7.1 Hz, 2H), 3.81 (s, 2H), 1.19 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.4, 135.4, 135.1, 134.8, 129.1 (q, J=5.3 Hz), 128.1 (q, J=30.8 Hz), 122.9 (q, J=271.5 Hz), 117.2 (q, J=2.3 Hz), 67.0, 60.5, 38.9, 25.1, 14.0; HRMS (ESI+) calcd for $C_{11}H_9BrF_3O_2$ ($[M-H]^-$), 308.9744; found, 308.9745.

*4.3.6. Ethyl 2-(4-bromo-3-fluorophenyl)acetate (**3f**).* 4-Bromo-3-fluoro-1-iodobenzene (**1f**, 602 mg, 2.00 mmol) was employed. Compound **3f** was purified using EtOAc in hexanes (0–10%) and obtained as a pale yellow oil (298 mg, 57%). FTIR (thin film, cm^{-1}) 2983, 1731, 1486, 1150; ^1H NMR (300 MHz, DMSO-d_6) δ 7.65 (t, J=7.9 Hz, 1H), 7.32 (dd, J=10.0, 1.8 Hz, 1H), 7.09 (dd, J=8.2, 1.8 Hz, 1H), 4.09 (q, J=7.1 Hz, 2H), 3.72 (s, 2H), 1.19 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.4, 157.9 (d, J=243 Hz), 136.8 (d, J=7.4 Hz), 133.1, 127.3 (d, J=3.3 Hz), 117.8 (d, J=22.5 Hz), 106.2 (d, J=20.3 Hz), 60.4, 39.2 (d, J=1.5 Hz), 14.0; HRMS (ESI+) calcd for $C_{10}H_{11}BrFO_2$ ($[M+H]^+$), 260.9921; found, 260.9912.

*4.3.7. Ethyl 2-bromo-5-(2-ethoxy-2-oxoethyl)benzoate (**3g**).* Ethyl 2-bromo-5-iodobenzoate (**1g**, 710 mg, 2.00 mmol) was employed.

Compound **3g** was purified using EtOAc in hexanes (0–10%) and obtained as a yellow oil (485 mg, 77%). FTIR (thin film, cm^{-1}) 2982, 1726, 1250, 1027; ^1H NMR (300 MHz, DMSO-d_6) δ 7.74–7.62 (m, 2H), 7.38 (dd, J=8.2, 2.3 Hz, 1H), 4.33 (q, J=7.1 Hz, 2H), 4.09 (q, J=7.1 Hz, 2H), 3.75 (s, 2H), 1.32 (t, J=7.1 Hz, 3H), 1.19 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.5, 165.6, 134.5, 134.0, 133.7, 132.5, 131.6, 118.3, 61.4, 60.4, 39.0, 13.99, 13.96; HRMS (ESI+) calcd for $C_{13}H_{16}BrO_4$ ($[M+H]^+$), 315.0226; found, 315.0222.

*4.3.8. Ethyl 2-(3-bromo-4-methylphenyl)acetate (**3h**).* 2-Bromo-4-iodotoluene (**1h**, 594 mg, 2.00 mmol) was employed. Compound **3h** was purified using EtOAc in hexanes (0–10%) and obtained as a pale yellow oil (409 mg, 80%). FTIR (thin film, cm^{-1}) 2981, 1731, 1149, 1030; ^1H NMR (300 MHz, DMSO-d_6) δ 7.53–7.45 (m, 1H), 7.29 (d, J=7.8 Hz, 1H), 7.17 (dd, J=7.8, 1.4 Hz, 1H), 4.08 (q, J=7.1 Hz, 2H), 3.65 (s, 2H), 2.32 (s, 3H), 1.18 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.8, 135.6, 134.2, 132.8, 130.8, 128.7, 123.8, 60.3, 39.1, 21.9, 14.0; HRMS (ESI+) calcd for $C_{11}H_{14}BrO_2$ ($[M+H]^+$), 257.0172; found, 257.0172.

*4.3.9. Ethyl 2-(3-bromo-4-fluorophenyl)acetate (**3i**).* 2-Bromo-1-fluoro-4-iodobenzene (**1i**, 602 mg, 2.00 mmol) was employed. Compound **3i** was purified using EtOAc in hexanes (0–10%) and obtained as a pale yellow oil (370 mg, 71%). FTIR (thin film, cm^{-1}) 2983, 1730, 1494, 1244; ^1H NMR (300 MHz, DMSO-d_6) δ 7.64 (d, J=7.0 Hz, 1H), 7.36–7.29 (m, 2H), 4.10 (q, J=7.1 Hz, 2H), 3.71 (s, 2H), 1.19 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.7 (d, J=1.2 Hz), 158.7 (d, J=17.3 Hz), 134.2, 132.6 (d, J=3.7 Hz), 130.8 (d, J=7.4 Hz), 116.4 (d, J=21.8 Hz), 107.5 (d, J=21.0 Hz), 60.4, 38.6, 14.0; HRMS (ESI+) calcd for $C_{10}H_{11}BrFO_2$ ($[M+H]^+$), 260.9921; found, 260.9922.

*4.3.10. Ethyl 2-(2-bromophenyl)acetate (**3j**).* 2-Bromo-1-iodobenzene (**1j**, 566 mg, 2.00 mmol) and ethyl 2-bromozincacetate (**2a**) in THF (0.40 M, 7.5 mL, 1.5 equiv) were employed. Compound **3j** was purified using EtOAc in hexanes (0–10%) and obtained as a pale yellow oil (295 mg, 61%). FTIR (thin film, cm^{-1}) 2981, 1731, 1156, 1025; ^1H NMR (300 MHz, DMSO-d_6) δ 7.61 (dd, J=7.9, 1.1 Hz, 1H), 7.45–7.30 (m, 2H), 7.23 (dt, J=1.9, 7.6 Hz, 1H), 4.10 (q, J=7.1 Hz, 2H), 3.81 (s, 2H), 1.19 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.9, 134.5, 132.3, 132.2, 129.1, 127.7, 124.5, 60.4, 40.9, 14.0; HRMS (ESI+) calcd for $C_{10}H_{12}BrO_2$ ($[M+H]^+$), 243.0015; found, 243.0012.

*4.3.11. Ethyl 2-(6-chloro-4-methylpyridin-3-yl)acetate (**3k**).* 5-Bromo-2-chloro-4-methylpyridine (**1k**, 413 mg, 2.00 mmol) and ethyl 2-bromozincacetate (**2a**) in THF (0.40 M, 7.5 mL, 1.5 equiv) were employed. The reaction mixture was quenched with 1 M K_2HPO_4/KH_2PO_4 aq buffer solution (pH=7, 3.0 mL) and filtered. The mixture was added brine (5.0 mL) and the organic layer was separated and concentrated. Compound **3k** was purified using EtOAc in hexanes (0–25%) and obtained as a yellow oil (305 mg, 71%). FTIR (thin film, cm^{-1}) 2982, 1729, 1589, 1158; ^1H NMR (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.17 (s, 1H), 4.16 (q, J=9.0 Hz, 2H), 3.61 (s, 2H), 2.31 (s, 3H), 1.25 (t, J=9.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 150.5, 150.3, 149.6, 128.2, 125.3, 61.3, 35.8, 19.1, 14.1; HRMS (ESI+) calcd for $C_{10}H_{13}ClNO_2$ ($[M+H]^+$), 214.0629; found, 214.0625.

*4.3.12. tert-Butyl 2-(4-bromo-2-fluorophenyl)propionate (**3m**).* 4-Bromo-2-fluoro-1-iodobenzene (**1l**, 602 mg, 2.00 mmol), THF (1.5 mL) and *tert*-butyl 2-bromozincpropionate (**2b**) in THF (0.23 M, 10.5 mL, 1.2 equiv) were employed. Compound **3m** was purified using EtOAc in hexanes (0–8%) and obtained as a pale yellow oil (527 mg, 87%). FTIR (thin film, cm^{-1}) 2979, 1727, 1486, 1147; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.14 (m, 3H), 3.86 (q, J=9.0 Hz, 1H), 1.43 (d, J=9.0 Hz, 3H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 160.2 (d, J=249 Hz), 129.7 (d, J=5.3 Hz), 127.7 (d, J=7.5 Hz), 127.4 (d, J=3.8 Hz), 120.6 (d, J=9.8 Hz), 119.0 (d, J=25.5 Hz), 81.0, 39.1, 28.0, 17.3; HRMS (ESI+) calcd for $C_{13}H_{15}BrFO_2$ ($[M-H]^-$), 301.0245; found, 301.0246.

*4.3.13. tert-Butyl 2-(4-bromophenyl)propionate (**3n**).* 4-Bromo-1-iodobenzene (**1b**, 566 mg, 2.00 mmol), THF (1.5 mL) and *tert*-butyl 2-bromozincpropionate (**2b**) in THF (0.23 M, 10.5 mL, 1.2 equiv) were employed. Compound **3n** was purified using EtOAc in hexanes (0–8%) and obtained as a pale yellow oil (505 mg, 89%). FTIR (thin film, cm^{-1}) 2977, 1725, 1367, 1144; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J=9.0 Hz, 2H), 7.17 (d, J=9.0 Hz, 2H), 3.57 (q, J=6.0 Hz, 1H), 1.43 (d, J=6.0 Hz, 3H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 140.1, 131.5, 129.2, 120.7, 80.8, 46.0, 27.9, 18.4; HRMS (ESI+) calcd for $C_{13}H_{16}BrO_2$ ($[M-H]^-$), 283.0339; found, 283.0341.

*4.3.14. tert-Butyl 2-(4-bromophenyl)acetate (**3o**).* 4-Bromo-1-iodobenzene (**1b**, 566 mg, 2.00 mmol), THF (1.1 mL) and *tert*-butyl 2-bromozincacetate (**2c**) in THF (0.22 M, 10.9 mL, 1.2 equiv) were employed. Compound **3o** was purified using EtOAc in hexanes (0–8%) and obtained as a yellow oil (393 mg, 73%). FTIR (thin film, cm^{-1}) 2978, 1729, 1488, 1136; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J=9.0 Hz, 2H), 7.15 (d, J=9.0 Hz, 2H), 3.47 (s, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 133.7, 131.5, 130.9, 120.9, 81.1, 42.0, 28.0; HRMS (ESI+) calcd for $C_{12}H_{14}BrO_2$ ($[M-H]^-$), 269.0183; found, 269.0185.

*4.3.15. 2-(4-Bromophenyl)-N,N-dimethylacetamide (**3r**).* In a glove box, to a 50 mL round bottom flask with a stir bar was added NaHMDS (487 mg, 2.60 mmol), and toluene (8.0 mL). To a 20 mL vial with a stir bar was added anhydrous $ZnCl_2$ (709 mg, 2.6 equiv), THF (6.0 mL) and the mixture was agitated until $ZnCl_2$ dissolved. The flask and vial were sealed and removed from the glove box. The mixture in round bottom flask was cooled in an ice-water bath to 0–5 °C. Dimethylacetamide (209 mg, 2.40 mmol) was added. The mixture was stirred for 30 min, followed by the addition of $ZnCl_2$ in THF solution. The mixture was cooled to 0–5 °C and stirred for 30 min. To a 20 mL vial with a stir bar was added 1-bromo-4-iodo-benzene (**1b**, 556 mg, 2.00 mmol), $Pd(dba)_2$ (28.5 mg, 2.5 mol %), Xantphos (28.9 mg, 2.5 mol %), and toluene (10.0 mL). The mixture was agitated until all solids dissolved, vacuumed and backfilled with nitrogen (3×), and added to the 50 mL round bottom flask via syringe. The reaction mixture was then heated to 65 °C and monitored by HPLC. Upon reaction completion based on HPLC analysis, the mixture was cooled to room temperature and neutralized with 1 M aq HCl (2.5 mL) and brine (5.0 mL). The organic layer was separated and concentrated in vacuum. The residue was purified by silica gel column chromatography using EtOAc in hexanes (0–95%) to afford compound **3r** as a yellow amorphous solid (345 mg, 71%). FTIR (thin film, cm^{-1}) 2927, 1637, 1487, 1403; ^1H NMR (300 MHz, DMSO-d_6) δ 7.48 (d, J=8.3 Hz, 2H), 7.17 (d, J=8.3 Hz, 2H), 3.67 (s, 2H), 3.00 (s, 3H), 2.82 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.7, 135.5, 131.5, 130.9, 119.4, 38.8, 37.0, 35.0; HRMS (ESI+) calcd for $C_{10}H_{13}BrNO$ ($[M+H]^+$), 242.0175; found, 242.0172.

*4.3.16. 2-(4-Bromophenyl)-1-(pyrrolidin-1-yl)ethanone (**3s**).* Compound **3s** was prepared in a same fashion as **3r** but using 1-acetylpyrrolidine (272 mg, 2.40 mmol) as a yellow solid (396 mg, 74%). Mp 114.8–116.7 °C; FTIR (thin film, cm^{-1}) 2969, 2877, 1630, 1586; ^1H NMR (300 MHz, DMSO-d_6) δ 7.48 (d, J=8.3 Hz, 2H), 7.19 (d, J=8.3 Hz, 2H), 3.60 (s, 2H), 3.45 (t, J=6.7 Hz, 2H), 3.28 (t, J=6.8 Hz, 2H), 1.86 (d, J=6.4 Hz, 2H), 1.81–1.70 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.0, 135.3, 131.6, 130.9, 119.4, 46.2, 45.5, 40.1, 25.6, 23.9; HRMS (ESI+) calcd for $C_{12}H_{15}BrNO$ ($[M+H]^+$), 268.0332; found, 268.0326.

Ibuprofen. To a 5 mL vial was charged *tert*-butyl 2-(4-bromophenyl)propionate (**3n**, 180 mg, 0.631 mmol), $Pd(dba)_2$

(7.4 mg, 2 mol %) and Qphos (10.4 mg, 2 mol %) followed by ^{i}BuZnBr in THF (0.50 M, 2.0 mL, 1.4 equiv). The mixture was vacuumed and backfilled with nitrogen (3×) and then heated to 55 °C for 30 min. HPLC analysis showed >98% conversion. The mixture was cooled, diluted with EtOAc and quenched with 10 wt % aq NaH_2PO_4 with stirring. The mixture was filtered to remove solids and phases were separated. The organic layer was washed with water and brine, dried over Na_2SO_4 and filtered. The solution was concentrated and re-dissolved in DCM (2.0 mL). The mixture was charged TFA (0.14 mL, 3.0 equiv) and stirred at room temperature for 40 h. HPLC analysis showed ca. 85% conversion. The mixture was charged with TFA (0.10 mL, 2.0 equiv) and stirred at room temperature for 5 h. HPLC analysis showed 100% conversion. The reaction was cooled to 0 °C and quenched with 1 M aq NaOH and diluted with DCM (5.0 mL). Phases were separated and the aqueous layer was washed with EtOAc (5.0 mL). The aqueous layer was then adjusted its pH with concd HCl to pH 1–2 and extracted with EtOAc (5.0 mL, 2×). The combined organic layers were washed with water and concentrated under vacuum to give Ibuprofen as a thick yellow oil (115 mg, 88%). FTIR (thin film, cm^{-1}) 2954, 2925, 1702, 1229; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.80 (br s, 1H), 7.27 (d, J=8.1 Hz, 2H), 7.15 (d, J=8.1 Hz, 2H), 3.75 (q, J=7.2 Hz, 1H), 2.49 (d, J=7.2 Hz, 2H), 1.88 (m, 1H), 1.54 (d, J=3.6 Hz, 3H), 0.94 (d, J=7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.2, 140.9, 137.0, 129.4, 127.3, 45.1, 45.0, 30.2, 22.4, 18.1; HRMS (ESI+) calcd for $C_{13}H_{17}O_2$ ([M−H]$^-$), 205.1234; found, 205.1235. Data were in accordance with those previously reported in the literature.[26]

*4.3.17. Ethyl 2-(3-chloro-3′-(trifluoromethyl)-[1,1′-biphenyl]-4-yl) acetate (**4a**).* In a 5 mL microwave vial was added ethyl 2-(4-bromo-2-chlorophenyl)acetate (**3a**, 100 mg, 0.36 mmol), 3-(trifluoromethyl)phenylboronic acid (84 mg, 1.2 equiv), $PdCl_2(PPh_3)_2$ (30 mg, 12 mol %), MeCN (1.1 mL) and 1 M aq Na_2CO_3 solution (1.1 mL). The reaction mixture was microwaved at 110 °C for 30 min. The mixture was cooled and layers were separated. The aq layer was extracted with DCM (2×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography eluted with EtOAc in heptane to afford compound **4a** as a yellow oil (84 mg, 68%). FTIR (thin film, cm^{-1}) 2984, 1735, 1332, 1120; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.76 (m, 1H), 7.73–7.68 (m, 1H), 7.64–7.59 (m, 2H), 7.57–7.50 (m, 1H), 7.44 (dd, J=7.9, 1.9 Hz, 1H), 7.38 (d, J=8.1 Hz, 1H), 4.20 (q, J=7.1 Hz, 2H), 3.81 (s, 2H), 1.30–1.25 (t, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 140.4, 140.2, 135.2, 132.3, 132.0, 131.3 (q, J=32 Hz), 130.3, 129.4, 128.1, 125.6, 124.5 (q, J=3.8 Hz), 124.1 (q, J=272 Hz), 123.8 (q, J=3.8 Hz), 61.1, 38.9, 14.2; HRMS (ESI+) calcd for $C_{17}H_{15}ClF_3O_2$ ([M+H]$^+$), 343.0713; found, 343.0699.

*4.3.18. Ethyl 2-(2-chloro-4-cyclopropylphenyl)acetate (**4b**).* To a 5 mL vial was added ethyl 2-(4-bromo-2-chlorophenyl)acetate (**3a**, 100 mg, 0.36 mmol), potassium cyclopropyltrifluoroborate (66 mg, 1.2 equiv), $Pd(OAc)_2$ (8.1 mg, 10 mol %), butyl di-1-adamantylphosphine (20 mg, 15 mol %), Cs_2CO_3 (352 mg, 3.0 equiv), water (0.24 mL) and toluene (2.2 mL). The mixture was purged with nitrogen for 1 min and heated at 80 °C for 19 h. The reaction mixture was cooled, diluted with water and DCM and the layers were separated. The aqueous layer was extracted with DCM (2×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography to afford compound **4b** as a yellow oil (73 mg, 86%). FTIR (thin film, cm^{-1}) 3083, 2982, 1734, 1158; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J=7.9 Hz, 1H), 7.07 (d, J=1.9 Hz, 1H), 6.92 (dd, J=7.9, 1.9 Hz, 1H), 4.16 (q, J=7.1 Hz, 2H), 3.70 (s, 2H), 1.84 (dt, J=8.4, 5.1 Hz, 1H), 1.29–1.21 (t, J=7.1 Hz, 3H), 1.00–0.91 (m, 2H), 0.72–0.63 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 145.1, 134.4, 131.4, 131.1, 129.3, 126.7, 124.4, 60.9, 38.8, 14.9, 14.2, 9.3; HRMS (ESI+) calcd for $C_{13}H_{16}ClO_2$ ([M+H]$^+$), 239.0839; found, 239.0827.

*4.3.19. (E)-tert-Butyl 3-(3-chloro-4-(2-ethoxy-2-oxoethyl)phenyl) acrylate (**4c**).* To a 5 mL vial was added ethyl 2-(4-bromo-2-chlorophenyl)acetate (**3a**, 110 mg, 0.396 mmol), TBAC (11.0 mg, 10 mol %), 1,1′-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (5.2 mg, 2 mol %), DMA (1.5 mL), Cy_2NMe (0.127 mL, 1.5 equiv) and *tert*-butyl acrylate (71.1 mg, 0.082 mL, 1.4 equiv) and the mixture was degassed with nitrogen for 5 min. The reaction was then heated to 80 °C for 19 h. The cooled reaction mixture was filtered through Celite and the cake was washed with EtOAc (40 mL). The mixture was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by chromatography on silica eluted with 0–50% EtOAc in heptane. Compound **4c** was obtained as a colorless oil (119 mg, 92%). FTIR (thin film, cm^{-1}) 2979, 1735, 1704, 1638, 1144; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J=1.8 Hz, 1H), 7.49 (d, J=16.0 Hz, 1H), 7.36 (dd, J=8.0, 1.8 Hz, 1H), 7.29 (d, J=8.0 Hz, 1H), 6.35 (d, J=16.0 Hz, 1H), 4.18 (q, J=7.1 Hz, 2H), 3.77 (s, 2H), 1.53 (s, 9H), 1.26 (t, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 165.8, 141.5, 135.5, 135.1, 134.1, 131.8, 128.6, 126.3, 121.6, 80.8, 61.1, 39.1, 28.2, 14.1; HRMS (ESI+) calcd for $C_{17}H_{21}O_4ClNa$ ([M+Na]$^+$), 347.1026; found, 347.1021.

*4.3.20. Ethyl 2-(2-chloro-4-(phenylethynyl)phenyl)acetate (**4d**).* To a 5 mL vial was added ethyl 2-(4-bromo-2-chlorophenyl)acetate (**3a**, 122 mg, 0.440 mmol), $Pd(PPh_3)_4$ (25.4 mg, 5 mol %), $CuBr\cdot Me_2S$ (9.04 mg, 10 mol %), Et_3N (1.0 mL), and DMF (2.2 mL). The reaction mixture was degassed with nitrogen for 20 min, and phenylacetylene (0.14 mL, 1.30 mmol, 3.0 equiv) was added. The reaction mixture was stirred at 90 °C for 16 h and quenched with 5% aq ammonia in satd NH_4Cl solution, and then diluted with EtOAc (10 mL). The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography eluted with EtOAc/heptane to afford compound **4d** as a yellow solid (89.8 mg, 68%). Mp 57.2–59.0 °C; FTIR (thin film, cm^{-1}) 3063, 2988, 1736, 1330; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J=1.7 Hz, 1H), 7.52 (ddt, J=6.0, 5.2, 3.2 Hz, 2H), 7.41–7.33 (m, 4H), 7.27 (d, J=7.5 Hz, 1H), 4.19 (q, J=7.2 Hz, 2H), 3.77 (s, 2H), 1.27 (t, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 134.5, 132.7, 132.2, 131.7, 131.3, 130.0, 128.6, 128.4, 123.9, 122.7, 90.6, 87.7, 61.2, 39.2, 14.2; HRMS (ESI+) calcd for $C_{18}H_{16}O_2Cl$ ([M+H]$^+$), 299.0839; found, 299.0818.

*4.3.21. Ethyl 2-(2-chloro-4-morpholinophenyl)acetate (**4e**).* To a 5 mL vial was added ethyl 2-(4-bromo-2-chlorophenyl)acetate (**3a**, 112 mg, 0.404 mmol), morpholine (42.2 mg, 0.042 mL, 1.2 equiv), $Pd(OAc)_2$ (9.1 mg, 10 mol %), Xantphos (23.4 mg, 10 mol %), Cs_2CO_3 (263 mg, 2.0 equiv) and 1,4-dioxane (2.0 mL). The mixture was degassed with nitrogen for 5 min and heated at 110 °C for 19 h. The cooled reaction mixture was filtered through Celite and the cake was washed with EtOAc (40 mL). The mixture was washed with satd aq NH_4Cl and brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by chromatography on silica eluted with 0–100% EtOAc in heptane. Compound **4e** was obtained as a yellow solid (77 mg, 67%). Mp 61.8–63.1 °C; FTIR (thin film, cm^{-1}) 2971, 2841, 1723, 1505, 1172; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J=8.5 Hz, 1H), 6.90 (d, J=2.6 Hz, 1H), 6.76 (dd, J=8.5, 2.6 Hz, 1H), 4.17 (q, J=7.1 Hz, 2H), 3.89–3.78 (m, 4H), 3.67 (s, 2H), 3.17–3.09 (m, 4H), 1.25 (t, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 151.4, 135.2, 131.7, 123.3, 116.1, 114.1, 66.7, 60.9, 48.9, 38.3, 14.2; HRMS (ESI+) calcd for $C_{14}H_{19}ClNO_3$ ([M+H]$^+$), 284.1053; found, 284.1049.

*4.3.22. Ethyl 2-(2-chloro-4-(phenylsulfonyl)phenyl)acetate (**4f**).* To a 5 mL microwave vial was added ethyl 2-(4-bromo-2-

chlorophenyl)acetate (**3a**, 100 mg, 0.36 mmol), sodium benzenesulfinate (121.3 mg, 2.0 equiv), *N*,*N*′-dimethylethylenediamine (16 mg, 50 mol %), $Cu(OTf)_2$ (26.2 mg, 20 mol %) and degassed DMSO (3.6 mL). The reaction mixture was irradiated in the microwave at 130 °C for 2 h, diluted with EtOAc and filtered through a pad of Celite. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography eluted with EtOAc/heptane to afford compound **4f** as a yellow solid (62.3 mg, 51%). Mp 71.0–73.0 °C; FTIR (thin film, cm^{-1}) 2981, 1736, 1317, 1155; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97–7.94 (m, 2H), 7.93 (t, J=1.8 Hz, 1H), 7.81–7.77 (m, 1H), 7.62–7.56 (m, 1H), 7.56–7.49 (m, 2H), 7.44 (d, J=8.1 Hz, 1H), 4.17 (q, J=7.1 Hz, 2H), 3.79 (s, 2H), 1.25 (t, J=7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 142.1, 140.8, 138.1, 135.8, 133.6, 132.4, 129.5, 128.6, 127.8, 126.0, 61.5, 39.1, 14.1; HRMS (ESI+) calcd for $C_{16}H_{16}O_4ClS$ ($[M+H]^+$), 339.0458; found, 339.0428.

Acknowledgements

We thank Drs. Chong Han, Sushant Malhotra, Francis Gosselin, Greg Sowell, Chudi Ndubaku and Joachim Rudolph for helpful discussion, and Dr. Chunang Gu and Mr. Deven Wang for collecting HRMS data.

Supplementary data

Supplementary data associated with this article including copies of ^1H and ^{13}C NMR spectra for compounds **3a**–**k**, **3m**–**o**, **3r**–**s**, Ibuprofen, and **4a**–**f**. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tet.2013.12.053.

References and notes

1. Lednicer, D.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis*; Wiley: New York, 1980, Vol. 2.
2. For recent reviews of transition metal catalyzed α-arylation of carbonyl compounds see: (a) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676–707; (b) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082–1146; (c) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245.
3. (a) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996–8002; (b) Jørgensen, M.; Lee, S.; Liu, X.; Wolkowski, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 12557–12565.
4. (a) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176–11177; (b) Hama, T.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 1549–1552; (c) Hama, T.; Ge, S.; Hartwig, J. F. *J. Org. Chem.* **2013**, *78*, 8250–8266; (d) Duez, S.; Bernhardt, S.; Heppekausen, J.; Fleming, F. F.; Knochel, P. *Org. Lett.* **2011**, *13*, 1690–1693; (e) Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2007**, *26*, 4105–4108; (f) Orsini, F.; Pelizzoni, F.; Vallarino, L. M. *J. Organomet. Chem.* **1989**, *367*, 375–382.
5. Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302–3303.
6. Nakamura, M.; Jin, M. *Chem. Lett.* **2011**, *40*, 1012–1014.
7. Molander, G. A.; Traister, K. M.; Barcellos, T. *J. Org. Chem.* **2013**, *78*, 4123–4131.
8. Durandetti, M.; Gosmini, C.; Périchon, J. *Tetrahedron* **2007**, *63*, 1146–1153.
9. For reviews on Negishi coupling, see: (a) Negishi, E.-i.; Zeng, X.; Tan, Z.; Qian, M.; Hu, Q.; Huang, Z. In *Metal-catalyzed Cross-coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 815–889; (b) Negishi, E.-i. *Angew. Chem., Int. Ed.* **2011**, *50*, 6738–6764.
10. (a) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 10718–10719; (b) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553–5566.
11. Durà-Vilà, V.; Mingos, D. M. P.; Vilar, R.; White, A. J. P.; Williams, D. J. *J. Organomet. Chem.* **2000**, *600*, 198–205.
12. (a) Miki, S.; Nakamoto, K.; Kawakami, J.-i.; Handa, S.; Nuwa, S. *Synthesis* **2008**, *40*, 409–412; (b) Lombardo, M.; Trombini, C. In *The Chemistry of Organozinc Reagents*; Marek, I., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, 2006.
13. Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27–50.
14. Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081–3089.
15. Xantphos is a relatively inexpensive ligand. Strem price at largest package for Xantphos is $770/25 g ($18/mmol), for Qphos is $2135/10 g ($153/mmol), and for $\{[P(^tBu)_3]PdBr\}_2$ is $578/2 g ($222/mmol).
16. Reactions performed in PhMe (6.0 mL) and NMP (6.0 mL) under otherwise identical conditions were stalled in 2 h at 80% and 58% conversion with 94:6 and 91:9 ratio of **3a**/**3a**′, respectively.
17. For reviews on Suzuki–Miyaura coupling, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1470.
18. For a recent review on cross-coupling reactions of organotrifluoroborate salts, see: Molander, G. A.; Jean-Gerald, L. *Org. React.* **2013**, *79*, 1–316.
19. For a recent review on Mizoroki-Heck reactions, see: *The Mizoroki-Heck Reaction*; Oestreich, M., Ed.; Wiley: Chichester, UK, 2009.
20. For a recent review on Sonogashira coupling, see: Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922.
21. Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046–2067.
22. (a) Baskin, J. M.; Wang, Z. *Org. Lett.* **2002**, *4*, 4423–4425; (b) Suzuki, H.; Abe, H. *Tetrahedron Lett.* **1995**, *36*, 6239–6242.
23. Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *38*, 890–891.
24. All Reformatsky reagents should be used right after preparation and titration as they tend to decompose upon storage.
25. The quenching of this zinc reagent by iodine is slow due to its diminished nucleophilicity. The iodine solution was added 0.5 mL zinc solution and stirred for 3 min before addition of the next portion of 0.5 mL zinc solution. This process was repeated until a visible discoloration of the iodine solution was observed.
26. Greenhalgh, M. D.; Thomas, S. P. *J. Am. Chem. Soc.* **2012**, *134*, 11900–11903.