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Direct synthesis of 3-arylpropionic acids by tetraphosphine/palladium catalysed Heck reactions of aryl halides with acrolein ethylene acetal

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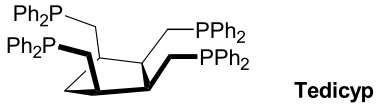
Abstract—Through the use of $[PdCl(C_3H_5)]_2$/*Cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane as a catalyst, a range of aryl bromides undergoes Heck reaction with acrolein ethylene acetal. With this acetal, the selective formation of 3-arylpropionic acids/esters was observed. The functional group tolerance on the aryl halide is remarkable; substituents such as fluoro, methyl, methoxy, acetyl, formyl, benzoyl, nitro or nitrile are tolerated. Furthermore, this catalyst can be used at low loading, even for reactions of sterically hindered aryl bromides.

1. Introduction

Arylpropionic acids are important building blocks in organic synthesis and their preparation is an important industrial goal.[1] Cacchi et al. have described recently that the palladium-catalysed Heck reaction[2] between aryl halides and acrolein acetals using $Pd(OAc)_2$ as catalyst is a very powerful method for the direct synthesis of 3-arylpropionic esters. However, this procedure needs a relatively high catalyst loading (3%) due to the absence of ligand on the palladium catalyst.[3] In recent years, several thermally stable palladium catalysts have been successfully used for Heck reactions,[4] but these catalysts have not been tested for the coupling of aryl halides with acrolein acetals. To our knowledge, only five phosphine ligands have been used for the reaction between aryl halides or vinyl halides and acrolein acetals: PPh_3, P(*o*-Me-$C_6H_4)_3$, P(*p*-Cl-$C_6H_4)_3$, P(2,4,6-triMeO-$C_6H_2)_3$ and dppf. In the presence of these phosphine ligands, the formation of the corresponding arylated or vinylated acrolein acetal (or aldehyde) derivatives[5a–c,e] or mixtures of products were generally obtained.[3,5d] We found only one example of a selective formation of a 3-arylpropionic acids using a Pd–phosphine catalyst.[6]

In order to find more efficient palladium catalysts, we have prepared the tetrapodal phosphine ligand, Tedicyp[7] (Fig. 1). We have reported recently several results obtained in allylic substitution,[7] Suzuki cross-coupling,[8] Sonogashira reactions[9] and Heck reaction[10] using Tedicyp as ligand. Here, in order to further establish the requirements for a successful Heck reaction, we wish to report on the reaction of aryl bromides with acrolein diethyl acetal or acrolein ethylene acetal using Tedicyp as the ligand.



Tedicyp

Figure 1.

2. Results and discussion

For this study, based on previous results,[10] DMF was chosen as the solvent for polarity reasons and potassium carbonate as the base. The reactions were performed at 110 °C under argon in the presence of a 1/2 ratio of $[Pd(C_3H_5)Cl]_2$/Tedicyp as catalyst.

First, we have investigated the Heck reactions of a few *para*- and *ortho*-substituted arylbromides with acrolein diethyl acetal. The results presented in the Table 1 disclose a low selectivity of the reaction. In all cases the formation of mixtures of cinnamaldehyde derivatives **1a–7a** and

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Table 1. Palladium–Tedicyp catalysed Heck reactions with acrolein diethyl acetal (Scheme 1)

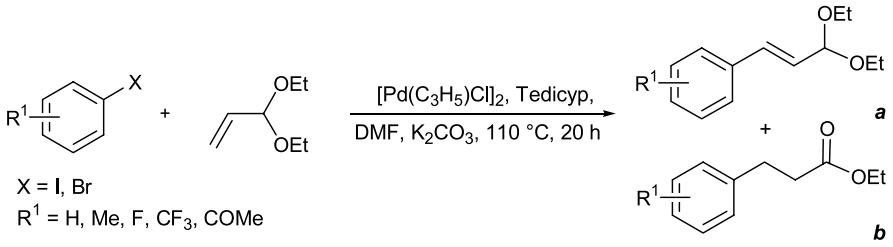
Entry	Aryl halide	Ratio substrate/catalyst	Ratio **a/b**	Products numbers	Yield (%)
1	Iodobenzene	1000	28/72	**1a**, **1b**	100
2	4-Bromoacetophenone	1000	21/79	**2a**, **2b**	100
3	4-Trifluoromethylbromobenzene	1000	27/73	**3a**, **3b**	95
4	4-Fluorobromobenzene	100	27/73	**4a**, **4b**	100
5	4-Methylbromobenzene	1000	28/72	**5a**, **5b**	100
6	2-Methylbromobenzene	250	40/60	**6a**, **6b**	80
7	2-Trifluoromethylbromobenzene	250	20/80	**7a**, **7b**	75

Conditions: Pd–Tedicyp catalyst, ArX (1 equiv), acrolein diethyl acetal (2 equiv), K_2CO_3 (2 equiv), DMF, 110 °C, 20 h, ratio **a/b** determined by NMR, yield in products **a**+**b**, GC and NMR yields.

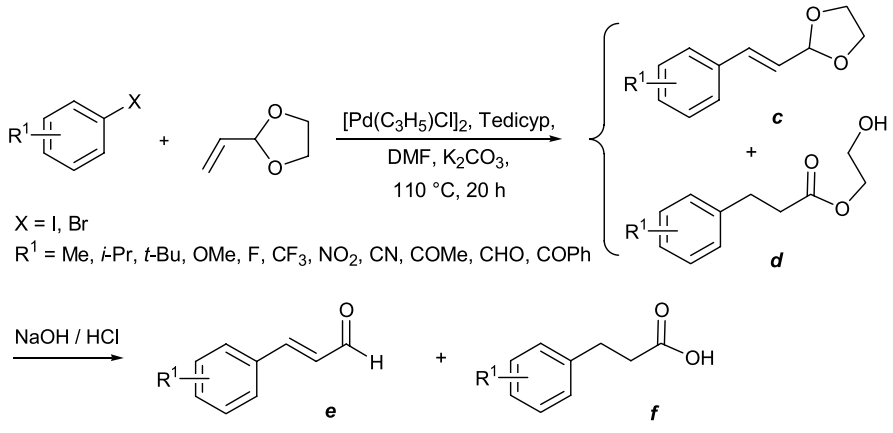
3-arylpropanoates **1b**–**7b** were observed (Table 1, entries 1–7). Similar mixtures of products had been obtained by Cacchi in the presence of PPh_3, P(*o*-Me-C_6H_4)$_3$, P(*p*-Cl-C_6H_4)$_3$ and P(2,4,6-triMeO-C_6H_2)$_3$ as ligands when acrolein diethyl acetal was used. The formation of these mixtures is due to the involvement of both the available β hydrogen atoms of the PdCH(CH_2Ar)[CH(OEt$_2$)] intermediate in the elimination step of the catalytic cycle (Scheme 1).

In order to improve the selectivity of this reaction, we studied several reactions conditions and we found that the use of acrolein ethylene acetal instead of acrolein diethyl acetal led to much higher selectivities in favour of the formation of 3-arylpropanoates (Scheme 2). For example, iodobenzene with acrolein diethyl acetal led to a mixture of phenylpropanoate and cinnamaldehyde in a ratio 72/28 (Table 1, entry 1). The same reaction performed with acrolein ethylene acetal gave the mixture of products in a ratio 97/3 (Table 2, entry 1). Moreover, the reaction using acrolein ethylene acetal can be performed with as little as 0.01% [Pd(C_3H_5)Cl]$_2$/Tedicyp catalyst.

Then, the reaction with acrolein ethylene acetal was applied to several aryl bromides (Table 2) and heteroaryl bromides (Table 3). We observed that in most cases the reaction performed with acrolein ethylene acetal proceeds very smoothly with high regioselectivity. First, we studied the reactivity of *para*-substituted aryl bromides. We observed that electron-withdrawing groups in the aryl bromide support the reaction, while electron-donation groups are unfavourable. Turnover numbers of 700–8400 can be achieved with this catalyst for activated substrates such as 4-bromoacetophenone, 4-bromobenzaldehyde, 4-bromobenzophenone, 4-bromobenzonitrile and 4-fluorobromobenzene (Table 2, entries 2–13). With the deactivated aryl bromides: 4-bromoanisole and 4-dimethylaminobromobenzene lower TONs of 100 and 45 were obtained respectively (Table 2, entries 16–19). A higher selectivity in favour of the formation of 3-arylpropanoates was observed with electron-poor aryl bromides than with electron-rich aryl bromides. For example, the reaction performed with 4-trifluoromethylbromobenzene led to 3-(4-trifluoro-methylphenyl)propionic acid in 99% selectivity. On the other hand, with 4-dimethylaminobromobenzene a lower selectivity of



Scheme 1.



Scheme 2.

Table 2. Palladium–Tedicyp catalysed Heck reactions with acrolein ethylene acetal (Scheme 2)

Entry	Aryl halide	Ratio substrate/catalyst	Ratio **c**/(**d**+**f**)[a]	Products numbers[b]	Yield in product **e** or **f** (%)[c]
1	4-Iodobenzene	10000	3/97	**8f**	92
2	4-Bromoacetophenone	1000	6/94	**9f**	88
3	4-Bromobenzophenone	1000	3/97	**10f**	91
4	4-Bromobenzophenone	10000	3/97	**10f**	(60)
5	4-Bromobenzaldehyde	1000	7/93	**11f**	(93)
6	4-Bromobenzaldehyde	10000	7/93	**11f**	84
7	4-Trifluoromethylbromobenzene	1000	1/99	**12f**	92
8	4-Trifluoromethylbromobenzene	10000	1/99	**12f**	(10)
9	4-Bromobenzonitrile	1000	3/97	**13f**	36[d]
10	3,5-Bis(trifluoromethyl)bromobenzene	1000	3/97	**14f**	89
11	4-Nitrobromobenzene	250	3/97	**15f**	83
12	4-Fluorobromobenzene	250	11/89	**16f**	79
13	4-Fluorobromobenzene	1000	10/90	**16f**	(70)
14	4-*t*-Butylbromobenzene	250	7/93	**17f**	(93)
15	4-*t*-Butylbromobenzene	1000	7/93	**17f**	84
16	4-Bromoanisole	100	13/87	**18f**	69
17	4-Bromoanisole	250	8/92	**18f**	(40)
18	4-Dimethylaminobromobenzene	25	14/86	**19f**	80
19	4-Dimethylaminobromobenzene	100	10/90	**19f**	(45)
20	3-Bromoacetophenone	1000	4/96	**20f**	87
21	3-Bromobenzaldehyde	1000	3/97	**21f**	89
22	3-Trifluoromethylbromobenzene	1000	1/99	**22f**	93
23	6-Methoxy-2-bromonaphthalene	1000	6/94	**23f**	90
24	2-Trifluoromethylbromobenzene	1000	2/98	**24f**	93
25	2-Fluorobromobenzene	100	10/90	**25f**	82
26	2-Fluorobromobenzene	250	8/92	**25f**	(30)
27	2-Bromotoluene	100	3/97	**26f**	87
28	2-Bromotoluene	250	3/97	**26f**	(82)
29	1-Bromonaphthalene	1000	2/98	**27f**	94
30	2-Bromoanisole	250	14/86	**28f**	60
31	2,6-Difluorobromobenzene	250	6/94	**29f**	78
32	9-Bromoanthracene	100	2/98	**30f**	82
33	2,4,6-Trimethylbromobenzene	25	75/25	**31e**	64
34	2,4,6-Trimethylbromobenzene	100	79/21	**31e**	(60)
35	2,6-Diethyl-4-methylbromobenzene	50	72/28	**32e**	62
36	2,4,6-Triisopropylbromobenzene	50	15/85	**33f**	78

Conditions: (1) Pd–Tedicyp catalyst, ArX (1 equiv), acrolein ethylene acetal (2 equiv), K_2CO_3 (2 equiv), DMF, 110 °C, 20 h; (2) NaOH, 50–80 °C, 1–4 h, isolated yields.
[a] Ratio of products **c**/(**d**+**f**) obtained before treatment by NaOH and HCl, calculated with ^{1}H NMR spectra of the crude mixture.
[b] Major product obtained after treatment by NaOH or HCl.
[c] Yield in the major product of the reaction, yields in parentheses are GC and NMR conversions.
[d] Product **13f** directly obtained without treatment by NaOH. The ester **13d** was also obtained in 43% yield.

86–90% in favour of the formation of 3-(4-dimethylaminophenyl)propionic acid was observed (Table 2, entries 7, 8, 18 and 19).

Then, we studied the influence of the presence of *meta* and *ortho* substituents on the aryl bromide on the reaction rate. As expected very similar TONs were obtained with *meta*-substituted aryl bromides than with the *para*-substituted (Table 2, entries 20–23). *Ortho*-substituents on the aryl bromides have a more important effect on the reactions rates. We observed that the coupling of 2-trifluoromethylbromobenzene or 1-bromonaphthalene with acrolein ethylene acetal proceeds in the presence of 0.1% catalyst, moreover a very high selectivity of 98% in favour of the formation of 3-arylpropanoates was observed (Table 2, entries 24 and 29). Next, we tried to evaluate the difference

Table 3. Palladium–Tedicyp catalysed Heck reactions with acrolein ethylene acetal and heteroaryl bromides (Scheme 3)

Entry	Aryl halide	Ratio substrate/catalyst	Ratio **c**/(**d**+**f**)[a]	Products number[b]	Yield in product **f** (%)
1	3-Bromopyridine	1000	6/94	**34f**	79
2	4-Bromopyridine	250	8/92	**35f**	84
3	3-Bromoquinoline	1000	6/94	**36f**	80
4	4-Bromoisoquinoline	250	5/95	**37f**	87
5	2-Bromothiophene	50	6/94	**38f**	75
6	2-Bromothiophene	100	6/94	**38f**	80[c]
7	3-Bromothiophene	100	7/93	**39f**	70
8	3-Bromofurane	100	5/95	**40f**	81[d]

Conditions: (1) Pd–Tedicyp catalyst, ArX (1 equiv), acrolein ethylene acetal (2 equiv), K_2CO_3 (2 equiv), DMF, 110 °C, 20 h; (2) NaOH, 50–80 °C, 1–4 h, isolated yields.
[a] Ratio of products **c**/(**d**+**f**) obtained before treatment by NaOH and HCl, calculated by ^{1}H NMR of the crude mixture.
[b] Major product obtained after treatment by NaOH.
[c] GC and NMR conversion.
[d] Reaction temp.: 90 °C.

of reaction rate between mono- and di-*ortho*-substituted aryl bromides, and we observed that even very hindered aryl bromides could be coupled efficiently with acrolein ethylene acetal,. For example, with 9-bromoanthracene and 1-bromo-2,4,6-triisopropylbenzene the 3-arylpropanoates were also obtained in 98% and 85% selectivities respectively in the presence of 1–2% catalyst (Table 2, entries 32 and 36). The coupling reactions also proceeds in the presence of 2,4,6-trimethylbromobenzene and 2,6-diethyl-4-methylbromobenzene, but with these substrates the selectivity of the reaction was completely reversed and the cinnamaldehyde derivatives were reproducibly obtained in 72–79% selectivity (Table 2, entries 33–35). Presumably, the steric demand of the two *ortho* alkyl groups disfavours one of the two possible β-hydride eliminations to generate either the cinnamaldehyde derivatives or the 3-arylpropanoates.

In most cases, mixtures of 3-arylpropanoates esters **d** and 3-arylpropionic acids **f** were obtained after the Pd catalysed reaction due to partial K_2CO_3-catalysed hydrolysis of the esters. In order to obtain selectively the 3-arylpropionic acids **f**, the hydrolysis of the esters **d** was performed with a NaOH solution. Aldehydes **31e** and **32e** were obtained by deprotection of acetals **31c** and **32c** using an HCl (1 M) solution.

Finally, we have investigated the Heck reaction of seven heteroaryl bromides. The results are summarized in Table 3. Pyridines or quinolines are π-electron deficient. Thiophenes or furanes are π-electron excessive. If the oxidative addition of the aryl halides to the palladium complex is the rate-limiting step of the reaction with this catalyst, the reactions should be slower with thiophenes or furanes than with pyridines or quinolines. In the presence of 3-bromopyridine, 4-bromopyridine, 3-bromoquinoline and 4-bromoisoquinoline the reactions were performed with 0.4–0.1% catalyst (Table 3, entries 1–4). Slower reactions were observed with 2-bromothiophene and 3-bromothiophene and 1% catalyst were necessary in order to obtain high conversions (Table 3, entries 5–7). The reaction in the presence of 3-bromofurane also led to the corresponding adduct (Table 3, entry 8). With all these heteroaryl bromides high selectivities in favor of the formation of 3-heteroaryl propionic acids were observed. These results seems also to indicate that the oxidative addition of the heteroaryl bromides to palladium is the rate-limiting step of this reaction.

The synthesis of 1,4-phenylenedipropionic acid **41f** from 1,4-dibromobenzene using 4 equiv of acrolein ethylene acetal in the presence of 1% catalyst also proceeds in good yield.

In summary, we have established that the Tedicyp–palladium system provides an efficient catalyst for the selective synthesis of 3-arylpropionic acids from acrolein ethylene acetal and aryl bromides. The use of acrolein ethylene acetal led to much higher selectivities in favour of the formation of 3-arylpropanoates (up to 99% selectivity) than the reactions performed with acrolein diethyl acetal. Moreover the uses of this Pd-tetraphosphine catalyst allow the use of low-catalyst loading. This reaction can be performed with as little as 0.01% catalyst with some of the aryl bromides. Due to the high price of palladium, the practical advantage of such low catalyst loadings can become increasingly important for industrial processes. In all cases, the formation of homocoupling products from aryl halides was not observed. A wide range of functions such as methoxy, fluoro, acetyl, formyl, benzoyl, nitro or nitrile on the aryl bromide are tolerated. The steric hindrance of the aryl bromide has an important effect on the reaction rates and on the selectivity of the reactions. Lower TONs were obtained for the coupling with sterically hindered aryl bromides such as 9-bromoanthracene. Several heteroaromatic substrates have also been used successfully. Moreover, acrolein acetals are commercially available and this is a practical advantage of this reaction.

3. Experimental

General remarks. All reactions were run under argon in Schlenk tubes using vacuum lines. DMF analytical grade was not distilled before use. Some of the aryl halides were distilled before use. Potassium carbonate (99+) was used without drying. Commercial acrolein diethyl acetal (95%) and acrolein ethylene acetal (99%) were used without purification. The reactions were followed by GC and NMR for high boiling point substrates and by GC for low boiling point substrates. ^1H and ^{13}C spectrum were recorded with a Bruker 300 MHz spectrometer in $CDCl_3$ solutions. Chemical shift are reported in ppm relative to $CDCl_3$ (7.25 for ^1H NMR and 77.0 for ^{13}C NMR). Flash chromatography were performed on silica gel (230–400 mesh) GC and NMR yields in the tables are conversions of the aryl halides into the product calculated with GC and ^1H NMR spectrum of the crude mixtures.

3.1. Preparation of the Pd–Tedicyp catalyst

An oven-dried 40-mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (30 mg, 81 μmol) and Tedicyp (140 mg, 162 μmol). 10 mL of anhydrous DMF were added, then the solution was stirred at room temperature for ten minutes. The appropriate catalyst concentration was obtained by successive dilutions. ^{31}P NMR (162 MHz, $CDCl_3$) δ 25 (w=80 Hz), 19.4 (w=110 Hz).

3.2. General procedure

In a typical experiment, the aryl halide (1 mmol), acrolein ethylene acetal (0.200 g, 2 mmol) and K_2CO_3 (0.276 g, 2 mmol) were dissolved in DMF (3 mL) under an argon atmosphere. The prepared Pd–Tedicyp catalyst complex (see tables) was then transferred to the reaction flask via cannula. The reaction mixture was stirred at 110 °C for 20 h. The solution was diluted with H_2O (2 ml) and NaOH was added (0.200 g). The reaction mixture was stirred at 50–80 °C for 1–4 h. The mixture was acidified with an HCl solution (pH 2–4) then the product was extracted three times with CH_2Cl_2. For compounds **19**, **35**–**38**, the mixture was acidified with an HCl solution (pH 6–7) then the product was extracted three times with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography.

3.2.1. 3-Phenylpropionic acid 8f. From iodobenzene (0.204 g, 1 mmol), product **8f** was obtained in 92% (0.138 g) yield. Before hydrolysis **8d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (t, 2H, J=7.6 Hz), 7.23–7.18 (m, 3H), 4.18 (t, 2H, J=4.6 Hz), 3.75 (t, 2H, J=4.6 Hz), 2.96 (t, 2H, J=7.6 Hz), 2.68 (t, 2H, J=7.6 Hz).

3.2.2. 3-(4-Acetylphenyl)propionic acid 9f. From 4-bromoacetophenone (0.199 g, 1 mmol), product **9f** was obtained in 88% (0.169 g) yield. Before hydrolysis **9d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, 2H, J=8.2 Hz), 7.29 (d, 2H, J=8.2 Hz), 4.20 (t, 2H, J=4.6 Hz), 3.79 (t, 2H, J=4.6 Hz), 3.02 (t, 2H, J=7.6 Hz), 2.70 (t, 2H, J=7.6 Hz), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 172.7, 146.0, 135.5, 128.7, 128.5, 66.2, 61.1, 35.1, 30.8, 26.5.

3.2.3. 3-(4-Benzoylphenyl)propionic acid 10f. From 4-bromobenzophenone (0.261 g, 1 mmol), product **10f** was obtained in 91% (0.231 g) yield. Before hydrolysis **10d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, 2H, J=7.5 Hz), 7.73 (d, 2H, J=8.2 Hz), 7.57 (t, 1H, J=7.5 Hz), 7.46 (t, 2H, J=7.5 Hz), 7.31 (d, 2H, J=8.3 Hz), 4.21 (t, 2H, J=4.6 Hz), 3.79 (t, 2H, J=4.6 Hz), 3.05 (t, 2H, J=7.6 Hz), 2.73 (t, 2H, J=7.6 Hz).

3.2.4. 3-(4-Formylphenyl)propionic acid 11f. From 4-bromobenzaldehyde (0.185 g, 1 mmol), product **11f** was obtained in 84% (0.150 g) yield. Before hydrolysis **11d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.78 (d, 2H, J=8.2 Hz), 7.34 (d, 2H, J=8.2 Hz), 4.18 (t, 2H, J=4.6 Hz), 3.76 (t, 2H, J=4.6 Hz), 3.02 (t, 2H, J=7.6 Hz), 2.69 (t, 2H, J=7.6 Hz).

3.2.5. 3-(4-Trifluoromethylphenyl)propionic acid 12f. From 4-trifluoromethylbromobenzene (0.225 g, 1 mmol), product **12f** was obtained in 92% (0.201 g) yield. Before hydrolysis **12d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, 2H, J=8.1 Hz), 7.30 (d, 2H, J=8.1 Hz), 4.19 (t, 2H, J=4.6 Hz), 3.77 (t, 2H, J=4.6 Hz), 3.01 (t, 2H, J=7.6 Hz), 2.68 (t, 2H, J=7.6 Hz).

3.2.6. 3-(4-Cyanophenyl)propionic acid 13f. From 4-bromobenzonitrile (0.182 g, 1 mmol), product **13f** was obtained in 36% (0.063 g) yield. This compound was not treated with an NaOH solution, and ester **13d** was also isolated in 43% (0.094 g) yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, 2H, J=8.5 Hz), 7.29 (d, 2H, J=8.5 Hz), 4.17 (t, 2H, J=4.6 Hz), 3.76 (t, 2H, J=4.6 Hz), 2.99 (t, 2H, J=7.6 Hz), 2.67 (t, 2H, J=7.6 Hz).

3.2.7. 3-[3,5-Bis(trifluoromethyl)phenyl]propionic acid 14f. From 3,5-bis(trifluoromethyl)bromobenzene (0.293 g, 1 mmol), product **14f** was obtained in 89% (0.255 g) yield. Before hydrolysis **14d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.67 (s, 2H), 4.21 (t, 2H, J=4.6 Hz), 3.80 (t, 2H, J=4.6 Hz), 3.09 (t, 2H, J=7.6 Hz), 2.73 (t, 2H, J=7.6 Hz).

3.2.8. 3-(4-Nitrophenyl)propionic acid 15f. From 4-bromonitrobenzene (0.202 g, 1 mmol), product **15f** was obtained in 83% (0.162 g) yield. Before hydrolysis **15d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, 2H, J=8.7 Hz), 7.36 (d, 2H, J=8.7 Hz), 4.21 (t, 2H, J=4.6 Hz), 3.80 (t, 2H, J=4.6 Hz), 3.07 (t, 2H, J=7.6 Hz), 2.72 (t, 2H, J=7.6 Hz).

3.2.9. 3-(4-Fluorophenyl)propionic acid 16f. From 4-fluorobromobenzene (0.175 g, 1 mmol), product **16f** was obtained in 79% (0.133 g) yield. Before hydrolysis **16d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (m, 2H), 6.85 (t, 2H, J=8.5 Hz), 4.09 (t, 2H, J=4.6 Hz), 3.67 (t, 2H, J=4.6 Hz), 2.83 (t, 2H, J=7.6 Hz), 2.55 (t, 2H, J=7.6 Hz).

3.2.10. 3-(4-*tert*-Butylphenyl)propionic acid 17f. From 4-*tert*-butylbromobenzene (0.213 g, 1 mmol), product **17f** was obtained in 84% (0.173 g) yield. Before hydrolysis **17d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, 2H, J=8.3 Hz), 7.13 (d, 2H, J=8.3 Hz), 4.19 (t, 2H, J=4.6 Hz), 3.75 (t, 2H, J=4.6 Hz), 2.94 (t, 2H, J=7.6 Hz), 2.67 (t, 2H, J=7.6 Hz), 1.30 (s, 9H).

3.2.11. 3-(4-Methoxyphenyl)propionic acid 18f. From 4-bromoanisole (0.187 g, 1 mmol), product **18f** was obtained in 69% (0.124 g) yield. Before hydrolysis **18d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, 2H, J=8.5 Hz), 6.80 (d, 2H, J=8.5 Hz), 4.15 (t, 2H, J=4.6 Hz), 3.75 (t, 2H, J=4.6 Hz), 3.74 (s, 3H), 2.87 (t, 2H, J=7.6 Hz), 2.61 (t, 2H, J=7.6 Hz).

3.2.12. 3-(4-Dimethylaminophenyl)propionic acid 19f. From 4-bromo-*N*,*N*-dimethylaniline (0.200 g, 1 mmol), product **19f** was obtained in 80% (0.155 g) yield. Before hydrolysis **19d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, 2H, J=8.1 Hz), 6.67 (d, 2H, J=8.1 Hz), 4.16 (t, 2H, J=4.6 Hz), 3.74 (t, 2H, J=4.6 Hz), 2.90 (s, 6H), 2.87 (t, 2H, J=7.6 Hz), 2.62 (t, 2H, J=7.6 Hz).

3.2.13. 3-(3-Acetylphenyl)propionic acid 20f. From 3-bromoacetophenone (0.199 g, 1 mmol), product **20f** was obtained in 87% (0.167 g) yield. Colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (m, 2H), 7.40 (m, 2H), 2.99 (t, 2H, J=7.6 Hz), 2.65 (t, 2H, J=7.6 Hz), 2.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 172.3, 140.7, 137.3, 133.1, 128.7, 128.0, 126.6, 35.3, 30.4, 26.6; $C_{11}H_{12}O_3$: Calcd C 68.74, H 6.29; Found C 68.58, H 6.34. Before hydrolysis **20d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (m, 2H), 7.40 (m, 2H), 4.20 (t, 2H, J=4.6 Hz), 3.78 (t, 2H, J=4.6 Hz), 3.02 (t, 2H, J=7.6 Hz), 2.70 (t, 2H, J=7.6 Hz), 2.57 (s, 3H).

3.2.14. 3-(3-Formylphenyl)propionic acid 21f. From 3-bromobenzaldehyde (0.185 g, 1 mmol), product **21f** was obtained in 89% (0.159 g) yield. Before hydrolysis **21d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.73 (m, 2H), 7.48 (m, 2H), 4.20 (t, 2H, J=4.6 Hz), 3.78 (t, 2H, J=4.6 Hz), 3.05 (t, 2H, J=7.6 Hz), 2.72 (t, 2H, J=7.6 Hz).

3.2.15. 3-(3-Trifluoromethylphenyl)propionic acid 22f. From 3-trifluoromethylbromobenzene (0.225 g, 1 mmol), product **22f** was obtained in 93% (0.203 g) yield. Before hydrolysis **22d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (m, 2H), 7.39 (m, 2H), 4.20 (t, 2H, J=4.6 Hz), 3.79 (t, 2H, J=4.6 Hz), 3.02 (t, 2H, J=7.6 Hz), 2.70 (t, 2H, J=7.6 Hz).

3.2.16. 3-(6-Methoxynaphthalen-2-yl)propionic acid 23f. From 1-bromo-6-methoxynaphthalene (0.237 g, 1 mmol), product **23f** was obtained in 90% (0.207 g) yield. Before hydrolysis **23d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, 2H, J=8.3 Hz), 7.56 (s, 1H), 7.29 (d, 1H, J=8.5 Hz), 7.12 (d, 1H, J=8.3 Hz), 7.10 (s, 1H), 4.19 (t, 2H, J=4.6 Hz), 3.90 (s, 3H), 3.74 (t, 2H, J=4.6 Hz), 3.09 (t, 2H, J=7.6 Hz), 2.75 (t, 2H, J=7.6 Hz).

3.2.17. 3-(2-Trifluoromethylphenyl)propionic acid 24f. From 2-trifluoromethylbromobenzene (0.225 g, 1 mmol), product **24f** was obtained in 93% (0.203 g) yield. Before hydrolysis **24d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, 1H, J=7.8 Hz), 7.47 (t, 1H, J=7.2 Hz), 7.35 (d, 1H, J=7.8 Hz), 7.31 (t, 1H, J=7.2 Hz), 4.22 (t, 2H, J=4.6 Hz), 3.80 (m, 2H), 3.14 (t, 2H, J=7.6 Hz), 2.67 (t, 2H, J=7.6 Hz).

3.2.18. 3-(2-Fluorophenyl)propionic acid 25f. From 2-fluorobromobenzene (0.175 g, 1 mmol), product **25f** was obtained in 82% (0.138 g) yield. Before hydrolysis **25d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.15 (m, 2H), 7.07–6.97 (m, 2H), 4.19 (t, 2H, J=4.6 Hz), 3.77 (m, 2H), 2.98 (t, 2H, J=7.6 Hz), 2.68 (t, 2H, J=7.6 Hz).

3.2.19. 3-(2-Methylphenyl)propionic acid 26f. From 2-bromotoluene (0.171 g, 1 mmol), product **26f** was obtained in 87% (0.143 g) yield. Before hydrolysis **26d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.05 (s, 4H), 4.20 (t, 2H, J=4.6 Hz), 3.79 (t, 2H, J=4.6 Hz), 2.95 (t, 2H, J=7.6 Hz), 2.64 (t, 2H, J=7.6 Hz), 2.32 (s, 3H).

3.2.20. 3-(Naphthalen-1-yl)propionic acid 27f. From 1-bromonaphthalene (0.207 g, 1 mmol), product **27f** was obtained in 94% (0.188 g) yield. Before hydrolysis **27d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, 1H, J=8.3 Hz), 7.86 (d, 1H, J=8.3 Hz), 7.73 (d, 1H, J=8.3 Hz), 7.54 (t, 1H, J=7.8 Hz), 7.48 (t, 1H, J=7.8 Hz), 7.40 (t, 1H, J=7.8 Hz), 7.35 (d, 1H, J=7.0 Hz), 4.20 (t, 2H, J=4.6 Hz), 3.75 (t, 2H, J=4.6 Hz), 3.44 (t, 2H, J=7.6 Hz), 2.81 (t, 2H, J=7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 136.2, 133.8, 131.5, 128.9, 127.2, 126.1, 125.9, 125.6, 125.5, 123.3, 66.1, 61.1, 35.0, 28.0.

3.2.21. 3-(2-Methoxyphenyl)propionic acid 28f. From 2-bromoanisole (0.187 g, 1 mmol), product **28f** was obtained in 60% (0.108 g) yield. Before hydrolysis **28d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (t, 1H, J=7.5 Hz), 7.14 (d, 1H, J=7.1 Hz), 6.87 (t, 1H, J=7.5 Hz), 6.84 (d, 1H, J=7.9 Hz), 4.18 (t, 2H, J=4.6 Hz), 3.82 (s, 3H), 3.76 (t, 2H, J=4.6 Hz), 2.95 (t, 2H, J=7.6 Hz), 2.66 (t, 2H, J=7.6 Hz).

3.2.22. 3-(2,6-Difluorophenyl)propionic acid 29f. From 2,6-difluorobromobenzene (0.193 g, 1 mmol), product **29f** was obtained in 78% (0.145 g) yield. Before hydrolysis **29d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (m, 1H), 6.85 (t, 2H, J=7.8 Hz), 4.21 (t, 2H, J=4.6 Hz), 3.80 (t, 2H, J=4.6 Hz), 3.02 (t, 2H, J=7.6 Hz), 2.65 (t, 2H, J=7.6 Hz).

3.2.23. 3-(Anthracen-9-yl)propionic acid 30f. From 9-bromoanthracene (0.257 g, 1 mmol), product **30f** was obtained in 82% (0.205 g) yield. Before hydrolysis **30d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.25 (d, 1H, J=8.5 Hz), 8.01 (d, 1H, J=8.3 Hz), 7.53 (t, 1H, J=6.8 Hz), 7.47 (t, 1H, J=6.8 Hz), 4.23 (t, 2H, J=4.6 Hz), 3.98 (t, 2H, J=7.6 Hz), 3.77 (t, 2H, J=4.6 Hz), 2.84 (t, 2H, J=7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 132.1, 131.6, 129.5, 129.3, 126.5, 126.0, 125.0, 123.8, 66.3, 61.2, 35.2, 23.2.

3.2.24. *E*-3-(2,4,6-Trimethylphenyl)propenal 31e. From bromomesitylene (0.199 g, 1 mmol) and after HCl hydrolysis aldehyde **31e** was obtained in 64% (0.111 g) yield. Product **31d** was also observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 2H), 4.23 (t, 2H, J=4.6 Hz), 3.81 (t, 2H, J=4.6 Hz), 2.95 (t, 2H, J=7.6 Hz), 2.48 (t, 2H, J=7.6 Hz), 2.34 (s, 6H), 2.29 (s, 3H).

3.2.25. *E*-3-(2,6-Diethyl-4-methylphenyl)propenal 32e. From 2,6-diethyl-4-methylbromobenzene (0.227 g, 1 mmol) and after HCl hydrolysis aldehyde **32e** was obtained in 62% (0.125 g) yield. Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (d, 1H, J=7.8 Hz), 7.72 (d, 1H, J=16.5 Hz), 6.94 (s, 2H), 6.36 (dd, 1H, J=16.5, 7.8 Hz), 2.65 (q, 4H, J=7.6 Hz), 2.33 (s, 3H), 1.19 (t, 6H, J=7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.1, 152.0, 142.7, 139.5, 134.3, 129.4, 127.6, 26.9, 21.3, 15.5; $C_{14}H_{18}O$: Calcd C 83.12, H 8.97; Found C 82.96, H 9.07. Product **32d** was also observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 2H), 4.24 (t, 2H, J=4.6 Hz), 3.82 (t, 2H, J=4.6 Hz), 2.61 (q, 4H, J=7.6 Hz), 2.96 (t, 2H, J=7.6 Hz), 2.50 (t, 2H, J=7.6 Hz), 2.28 (s, 3H), 1.21 (t, 6H, J=7.6 Hz).

3.2.26. 3-(2,4,6-Triisopropylphenyl)propionic acid 33f. From 2,4,6-triisopropylbromobenzene (0.283 g, 1 mmol), product **33f** was obtained in 78% (0.215 g) yield. White solid mp 106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (s, 2H), 3.13 (sept, 2H, J=6.8 Hz), 3.01 (t, 2H, J=8.6 Hz), 2.85 (sept, 1H, J=6.8 Hz), 2.49 (t, 2H, J=8.6 Hz), 1.24 (d, 18H, J=6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 146.9, 146.6, 131.1, 35.8, 34.1, 29.2, 24.5, 24.0, 22.9; $C_{18}H_{28}O_2$: Calcd C 78.21, H 10.21; Found C 78.00, H 10.31. Before hydrolysis **33d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (s, 2H), 4.25 (t, 2H, J=4.6 Hz), 3.84 (t, 2H, J=4.6 Hz), 3.12 (sept, 2H, J=6.8 Hz), 2.97 (t, 2H, J=7.6 Hz), 2.85 (sept, 1H, J=6.8 Hz), 2.50 (t, 2H, J=7.6 Hz), 1.25 (m, 18H).

3.2.27. 3-(Pyridin-3-yl)propionic acid 34f. From 3-bromopyridine (0.158 g, 1 mmol), product **34f** was obtained in 79% (0.119 g) yield. Before hydrolysis **34d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (m, 2H), 7.54 (d, 1H, J=7.7 Hz), 7.24 (dd, 1H, J=7.7 and 5.1 Hz), 4.20 (t, 2H, J=4.6 Hz), 3.79 (t, 2H, J=4.6 Hz), 2.97 (t, 2H, J=7.6 Hz), 2.80 (t, 2H, J=7.6 Hz).

3.2.28. 3-(Pyridin-4-yl)propionic acid 35f. From 4-bromopyridine (0.158 g, 1 mmol), product **35f** was obtained in 84% (0.127 g) yield. Before hydrolysis **35d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, 2H, J=5.8 Hz), 7.09 (d, 2H, J=5.8 Hz), 4.17 (t, 2H, J=4.6 Hz), 3.76 (t, 2H, J=4.6 Hz), 2.91 (t, 2H, J=7.6 Hz), 2.64 (t, 2H, J=7.6 Hz).

3.2.29. 3-(Quinolin-3-yl)propionic acid 36f. From 3-bromoquinoline (0.208 g, 1 mmol), product **36f** was obtained in 80% (0.161 g) yield. Before hydrolysis **36d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.02 (d, 1H, J=8.5 Hz), 7.95 (s, 1H), 7.71 (d, 1H, J=8.3 Hz), 7.60 (t, 1H, J=7.5 Hz), 7.48 (t, 1H, J=7.5 Hz), 4.20 (t, 2H, J=4.6 Hz), 3.78 (t, 2H, J=4.6 Hz), 3.05 (t, 2H, J=7.6 Hz), 2.70 (t, 2H, J=7.6 Hz).

3.2.30. 3-(Isoquinolin-4-yl)propionic acid 37f. From 4-bromoisoquinoline (0.208 g, 1 mmol), product **37f** was obtained in 87% (0.175 g) yield. White solid mp 145 °C; ^{1}H NMR (300 MHz, DMSO) δ 9.18 (s, 1H), 8.38 (s, 1H), 8.12 (d, 1H, J=8.5 Hz), 8.09 (d, 1H, J=8.5 Hz), 7.82 (t, 1H, J=7.5 Hz), 7.68 (t, 1H, J=7.5 Hz), 3.27 (t, 2H, J=7.6 Hz), 2.66 (t, 2H, J=7.6 Hz); ^{13}C NMR (75 MHz, DMSO) δ 173.7, 151.5, 142.5, 134.0, 130.9, 130.0, 128.4, 128.1, 127.3, 122.9, 34.5, 24.8. $C_{12}H_{11}NO_2$: Calcd C 71.63, H 6.96; Found C 71.24, H 7.01. Before hydrolysis **37d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.33 (s, 1H), 7.95 (d, 1H, J=8.5 Hz), 7.89 (d, 1H, J=8.5 Hz), 7.66 (t, 1H, J=7.7 Hz), 7.54 (t, 1H, J=7.7 Hz), 4.20 (t, 2H, J=4.6 Hz), 3.78 (t, 2H, J=4.6 Hz), 3.30 (t, 2H, J=7.6 Hz), 2.72 (t, 2H, J=7.6 Hz).

3.2.31. 3-(Thiophen-2-yl)propionic acid 38f. From 2-bromothiophene (0.163 g, 1 mmol), product **38f** was obtained in 75% (0.117 g) yield. Before hydrolysis **38d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, 1H, J=5.1 Hz), 6.87 (dd, 1H, J=5.1, 3.4 Hz), 6.77 (m, 1H), 4.19 (t, 2H, J=4.6 Hz), 3.76 (t, 2H, J=4.6 Hz), 3.15 (t, 2H, J=7.6 Hz), 2.70 (t, 2H, J=7.6 Hz).

3.2.32. 3-(Thiophen-3-yl)propionic acid 39f. From 3-bromothiophene (0.163 g, 1 mmol), product **39f** was obtained in 70% (0.109 g) yield. Before hydrolysis **39d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00–6.96 (m, 2H), 6.95 (dd, 1H, J=5.1, 1.1 Hz), 4.20 (t, 2H, J=4.6 Hz), 3.78 (t, 2H, J=4.6 Hz), 2.99 (t, 2H, J=7.6 Hz), 2.68 (t, 2H, J=7.6 Hz).

3.2.33. 3-(Furan-3-yl)propionic acid 40f. From 3-bromofurane (0.147 g, 1 mmol), product **40f** was obtained in 81% (0.113 g) yield. Before hydrolysis **40d** was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.23 (s, 1H), 6.26 (s, 1H), 4.20 (t, 2H, J=4.6 Hz), 3.79 (t, 2H, J=4.6 Hz), 2.76 (t, 2H, J=7.6 Hz), 2.59 (t, 2H, J=7.6 Hz).

3.2.34. 1,4-Phenylenedipropionic acid 41f. From 1,4-dibromobenzene (0.236 g, 1 mmol), acrolein ethyene acetal (0.400 g, 4 mmol) and K_2CO_3 (0.552 g, 4 mmol), Pd–Tedicyp (0.01 mmol) dissolved in DMF (3 mL) under an argon atmosphere. Product **41f** was obtained in 74% (0.164 g) yield. Before hydrolysis the diester was observed: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (s, 4H), 4.11 (t, 4H, J=4.6 Hz), 3.69 (t, 4H, J=4.6 Hz), 2.83 (t, 4H, J=7.6 Hz), 2.58 (t, 4H, J=7.6 Hz).

Registry No.: **8f**, 114-84-1; **9f**, 39105-51-6; **10f**, 71388-83-5; **11f**, 34961-64-3; **12f**, 53473-36-2; **13f**, 42287-94-5; **14f**, 181772-16-7; **15f**, 16642-79-8; **16f**, 459-31-4; **17f**, 1208-64-6; **18f**, 1929-29-9; **19f**, 73718-09-9; **21f**, 56030-19-4; **22f**, 585-50-2; **23f**, 3453-40-5; **24f**, 94022-99-8; **25f**, 1643-26-1; **26f**, 22084-89-5; **27f**, 3243-42-3; **28f**, 6342-77-4; **29f**, 167683-63-8; **30f**, 41034-83-7; **31e**, 131534-70-8; **34f**, 3724-19-4; **35f**, 6318-43-0; **36f**, 67752-28-7; **38f**, 5928-51-8; **39f**, 16378-06-6; **40f**, 90048-04-7; **41f**, 4251-21-2.

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