DOI: 10.1002/adsc.201100102

Practical Synthesis of 2-Arylacetic Acid Esters *via* Palladium-Catalyzed Dealkoxycarbonylative Coupling of Malonates with Aryl Halides

Bingrui Song,[a] Felix Rudolphi,[a] Thomas Himmler,[b] and Lukas J. Gooßen[a,*]

[a] FB Chemie – Organische Chemie, TU Kaiserslautern, Erwin-Schrödinger-Straße, Geb. 54, D-67663 Kaiserslautern, Germany
Fax: (+49)-631-205-3921; e-mail: goossen@chemie.uni-kl.de
[b] Bayer CropScience AG, Alfred-Nobel-Str. 50, D-40789 Monheim, Germany

Received: February 10, 2011; Published online: May 23, 2011

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201100102.

Abstract: A new palladium-based system was developed that catalyzes the coupling of aryl halides with diethyl malonates in the presence of mild bases. In the course of the reaction, the intermediately formed diethyl arylmalonate is directly converted into the arylacetic acid ester *via* liberation of carbon dioxide and an alkanol. This cross-coupling/dealkoxycarbonylation process provides an efficient and high-yielding synthetic entry to diversely functionalized arylacetic acid esters. Two complementary protocols were developed, one of which is optimal for electron-rich, the other for electron-poor aryl halides. Both make use of low loadings of palladium(0) bis(dibenzylideneacetone) (0.5 mol%)/tri-*tert*-butylphosphonium tetrafluoroborate (1.1 mol%) as the catalyst and diethyl malonate as the reaction solvent. The new procedures are particularly effective for sterically hindered substrates.

Keywords: arylacetic acids; arylation; dealkoxycarbonylation; diethyl malonate; palladium

Introduction

Methylenecarboxyl groups are key functionalities in many biologically active compounds. Examples are auxins acting as phytohormonal growth regulators,[1] as well as analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) (Figure 1).[2,3] The development of mild and efficient synthetic methods for the introduction of methylenecarboxyl groups into functionalized molecules is thus of great interest.

Traditional methods for the preparation of arylacetic acids include the hydrolysis of benzyl cyanides (Scheme 1, **I**),[4] the carbonylation of benzyl halides with metal catalysts (**II**),[5] and the electrocatalytic carboxylation of benzyl chlorides (**III**).[6] However, these processes have inherent disadvantages. For example, neither benzyl cyanides nor benzyl halides are available in great structural variety.[7] Moreover, toxic carbon monoxide is required in carbonylation reactions, while electrocatalytic carboxylations require an elaborate reaction set-up.

As modern alternatives, transition metal-catalyzed cross-coupling reactions between aryl halides and Reformatsky reagents,[8] tin,[9] copper,[10] and other enolates (**IV**),[11] or ketene acetals (**V**) have been developed.[12] Among these reactions, the palladium-catalyzed couplings between aryl halides and enolates developed by Buchwald[13] and Hartwig[14] (**VI**) are particularly straightforward, but the deprotonation of acetic acid esters requires strong and expensive bases,

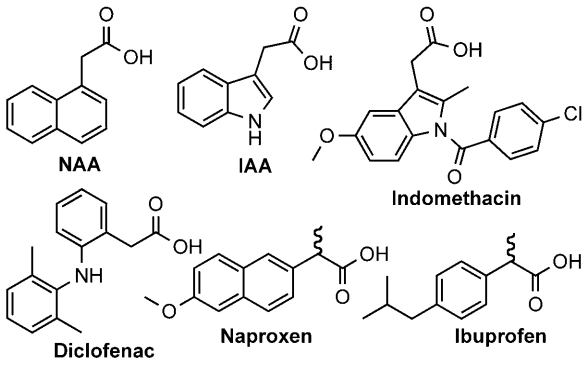
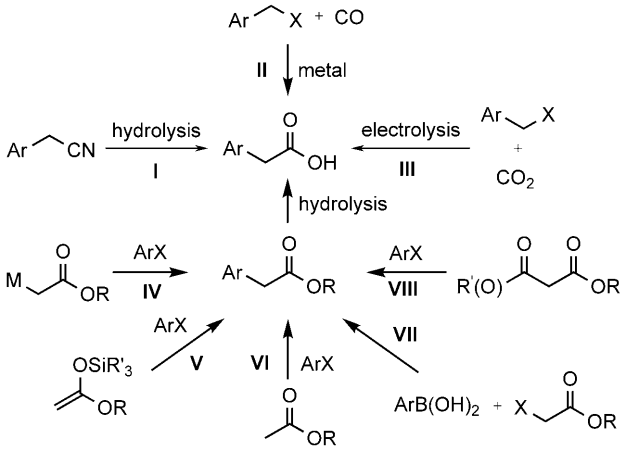
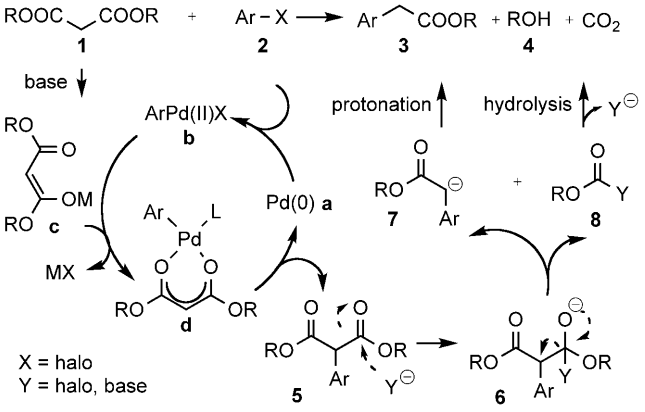


Figure 1. Examples of auxins and non-steroidal anti-inflammatory drugs.



Scheme 1. Traditional and modern syntheses of arylacetic acids.



Scheme 2. Proposed mechanism for the palladium-catalyzed dealkoxycarbonylative cross-coupling.

such as alkali metal hexamethyldisilazides or *tert*-butoxides. A broader range of functional groups is tolerated when using stabilized ketene derivatives or zinc enolates as the coupling partners.[15] The inverse approach, namely the coupling of α-bromoacetic acid derivatives with arylboronic acids (**VII**) is also compatible with many functional groups, but not effective for sterically demanding substrates, and requires the use of costly boron reagents.[16]

An interesting but less well-known alternative strategy to obtain 2-arylalkanoic acids consists in an initial cross-coupling of malonates or β-keto esters with aryl halides, followed by dealkoxycarbonylation or retro-Claisen condensation of the thermally labile intermediates (Scheme 1, **VIII**).[17] The coupling reaction is mediated by Pd[18] and Cu catalysts.[19] The advantage of this approach is that mild bases suffice to deprotonate the acidic β-dicarbonyl compounds. This synthetic pathway is particularly practical if the dealkoxycarbonylation takes place *in situ* under the conditions of the cross-coupling.

A plausible mechanism for the dealkoxycarbonylative cross-coupling of dialkyl malonates and aryl halides is depicted in Scheme 2.[20] Oxidative addition of the aryl halide (**2**) to the Pd(0) complex (**a**) gives rise to the arylpalladium(II) halide complex (**b**). The halide substituent is then replaced by an enolate nucleophile (**c**) formed *via* deprotonation of malonate (**1**). Reductive elimination of dialkyl α-arylmalonate (**5**) from the resulting palladium enolate complex (**d**) regenerates the Pd(0) complex, closing the catalytic circle for the palladium. At elevated temperatures, the dialkyl α-arylmalonate (**5**) directly undergoes dealkoxycarbonylation, presumably *via* a nucleophilic addition-elimination sequence. A base or halide nucleophile adds to one of the ester carbonyl groups with formation of the adduct **6**. In the subsequent elimination step, enolate **7**, which is resonance-stabilized by the newly introduced aryl group, is liberated together with the haloformate **8**.[20] On quenching the reaction mixture with water, hydrolysis of these intermediates leads to the desired arylacetic acid ester (**3**) along with an alcohol (**4**) and carbon dioxide.

Kondo reported that some aryl iodides and activated aryl bromides can be coupled this way with diethyl malonate in the presence of a Pd-catalyst and 10 equivalents of Cs_2CO_3.[21] However, it takes up to 76 h until the coupling and the subsequent dealkoxycarbonylation reach reasonable conversions. Çetinkaya et al. achieved higher yields within shorter reaction times for a range of aryl halides when employing specially synthesized palladium complexes with customized N-heterocyclic carbene ligands.[22] However, these ligands are not commercially available and accessible only *via* multistep syntheses. De Koning et al. investigated β-keto esters as alternative substrates and successively reported a palladium- and a copper-catalyzed protocol for the arylation of acetoacetate esters followed by *in situ* deacetylation.[23] However, these protocols have a rather narrow scope, and the deacetylation step often does not proceed to completion.

We evaluated all known protocols in the context of the synthesis of *ortho*-substituted aryl acetates, which are important precursors for active substances in crop protection.[24] However, only unsatisfactory yields were achieved in couplings of sterically demanding aryl halides, e.g., 2,6-dimethylphenyl bromide. We thus came to the conclusion that this appealing synthetic approach had not yet reached synthetic maturity. More effective catalyst systems involving commercially available components and inexpensive bases were clearly required to advance this reaction into a broadly applicable, practical synthetic entry to the important substrate class of arylacetic acids.

Results and Discussion

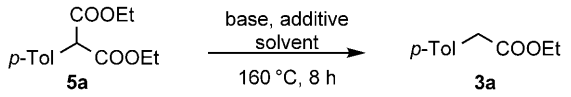
As a first step towards an effective reaction protocol for a dealkoxycarbonylative coupling of malonates, we investigated the dealkoxycarbonylation reaction of diethyl 4-tolylmalonate (**5a**) at 160 °C under various conditions (Table 1). We found that this compound, which would be the primary product of the desired cross-coupling between an aryl halide and diethyl malonate, is thermally rather unstable. In the presence of cesium carbonate and using polar solvents such as NMP, it rapidly decomposed with formation of multiple products. Only traces of the desired ethyl 4-tolyacetate were detected (entry 1). The selectivity of the dealkoxycarbonylation was substantially higher when using potassium phosphate as the base. However, the desired product was obtained in only 32% yield (entry 2). We next investigated less polar solvents, but did not achieve better results.

We finally tested the substrate for the desired coupling reaction, diethyl malonate (DEM), as the solvent. This inexpensive, high-boiling compound possesses a moderate polarity, so that it partially dissolves inorganic bases (entries 3–10). We were pleased to see that the selectivity of the dealkoxycarbonylation improved under these conditions (entry 3). Various bases were tested. Not only the expensive cesium carbonate (entry 4) but also the much less costly potassium phosphate effectively mediated the reaction (entry 3). In the presence of milder bases such as potassium carbonate (entry 5) or bicarbonate (entry 6), the dealkoxycarbonylation proceeds much more slowly. In an attempt to improve the solubility of potassium phosphate in the reaction solvent, we added catalytic quantities of 18-crown-6. This dramatically increased the efficiency of the dealkoxycarbonylation, and almost quantitative yields of the desired arylacetate **3a** were obtained (entry 8). Control experiments confirmed that the crown ether or DEM solvent alone do not promote the reaction (entries 9 and 10), and that under these conditions, diethyl malonate is a more effective reaction solvent than even NMP (entry 11).

Having thus found optimal conditions for the dealkoxycarbonylation, we next examined the cross-coupling step using the reaction of 4-bromotoluene (**2a**) and diethyl malonate as the model. We employed DEM as both substrate and solvent, and tested various palladium catalysts, ligand systems, and bases (Table 2).

As the initial palladium catalyst, we used a combination of $Pd(dba)_2$ and $P(t\text{-}Bu)_3$ in the form of its air-stable, easy-to-handle HBF_4 adduct. This catalyst is known to mediate the cross-coupling of aryl halides and malonates. Even at the elevated temperature of 160 °C, the arylmalonate **5a** remained the major product for most bases tested (Table 2, entries 1–6). Only cesium carbonate gave the dealkoxycarbonylated product **3a** as the main product, albeit in low yield (entry 3). The selectivity changed dramatically when 18-crown-6 was added to the reaction mixture (entry 7). In combination with potassium bases, this additive strongly facilitated the dealkoxycarbonylation, and the arylmalonate was no longer detected. The highest yields of the arylacetate were achieved with potassium phosphate (entries 8 and 9). Control experiments revealed that ammonium salts (entries 11–13) were inferior as phase-transfer catalysts, and that DMSO (entry 14), which is known to facilitate decarboxylation reactions,[25] is not effective in this context. The presence of stoichiometric quantities of water has a negative effect on the reaction outcome (entry 15). We next evaluated various palladium precursors and phosphine ligands (entries 16–20). These experiments revealed that several palladium precursors can be employed, but none of them possesses a higher activity than $Pd(dba)_2$. The choice of the phosphine is much more critical, and besides with $P(t\text{-}Bu)_3$, we achieved reasonable yields only with JohnPhos (38%). Under the optimal conditions using $Pd(dba)_2$ (0.5 mol%), $P(t\text{-}Bu)_3{\cdot}HBF_4$ (1.1 mol%), K_3PO_4 (2.8 equiv.), and 18-crown-6 (0.5 equiv.) in diethyl malonate (6.6 equiv.) at 160 °C, ethyl 4-tolylacetate **3a** was formed in 88% yield within only 8 h (entry 7). Not even traces of the malonate **5a** were detected in the reaction mixture.

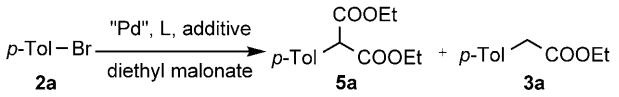
Table 1. Dealkoxycarbonylation of diethyl 4-tolylmalonate.[a]



Entry	Base	Additive	Solvent	Conv. [%]	Yield [%]
1	Cs_2CO_3	–	NMP	100	4
2	K_3PO_4	–	NMP	57	32
3	K_3PO_4	–	DEM[b]	50	40
4	Cs_2CO_3	–	DEM[b]	40	38
5	K_2CO_3	–	DEM[b]	14	12
6	$KHCO_3$	–	DEM[b]	16	11
7	$K_2CO_3/KHCO_3$[c]	–	DEM[b]	18	5
8	**K_3PO_4**	**18-C-6[d]**	DEM[b]	**99**	**97**
9	–	18-C-6[d]	DEM[b]	2	2
10	–	–	DEM[b]	1	1
11	K_3PO_4	18-C-6[d]	NMP	42	42

[a] *Reaction conditions:* **2a** (0.50 mmol), base (1.4 mmol), additive (0.25 mmol), solvent (1.0 mL), 160 °C, 8 h. Yields were determined by GC analysis, with *n*-tetradecane as internal standard.
[b] Diethyl malonate.
[c] K_2CO_3 (1.5 mmol), $KHCO_3$ (1.5 mmol).
[d] 18-Crown-6.

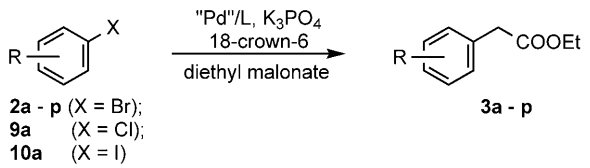
Table 2. Optimization of the dealkoxycarbonylative cross-coupling.[a]



Entry	"Pd"	Ligand	Base	Additive	Yield [%] 5a	3a
1[b]	$Pd(dba)_2$	$P(t\text{-}Bu)_3$[c]	$KHCO_3$	–	83	10
2[b]	$Pd(dba)_2$	$P(t\text{-}Bu)_3$[c]	K_2CO_3	–	82	18
3[b]	$Pd(dba)_2$	$P(t\text{-}Bu)_3$[c]	Cs_2CO_3	–	9	20
4[b]	$Pd(dba)_2$	$P(t\text{-}Bu)_3$[c]	Na_3PO_4	–	90	1
5[b]	$Pd(dba)_2$	$P(t\text{-}Bu)_3$[c]	K_3PO_4	–	47	38
6	$Pd(dba)_2$	$P(t\text{-}Bu)_3$[c]	K_3PO_4	–	50	46
7	**$Pd(dba)_2$**	**$P(t\text{-}Bu)_3$[c]**	**K_3PO_4**	**18-C-6[d]**	**0**	**88**
8	$Pd(dba)_2$	$P(t\text{-}Bu)_3$[c]	$KHCO_3$	18-C-6[d]	0	80
9	$Pd(dba)_2$	$P(t\text{-}Bu)_3$[c]	K_2CO_3	18-C-6[d]	0	75
10	$Pd(dba)_2$	$P(t\text{-}Bu)_3$[c]	Cs_2CO_3	18-C-6[d]	0	9
11	$Pd(dba)_2$	$P(t\text{-}Bu)_3$[c]	K_3PO_4	TBAB	29	45
12	$Pd(dba)_2$	$P(t\text{-}Bu)_3$[c]	K_3PO_4	TBAI	20	57
13	$Pd(dba)_2$	$P(t\text{-}Bu)_3$[c]	K_3PO_4	TBAF[e]	17	55
14	$Pd(dba)_2$	$P(t\text{-}Bu)_3$[c]	K_3PO_4	DMSO[f]	70	27
15	$Pd(dba)_2$	$P(t\text{-}Bu)_3$[c]	K_3PO_4	H_2O[f]	45	19
16	$Pd(OAc)_2$	$P(t\text{-}Bu)_3$[c]	K_3PO_4	18-C-6[d]	0	75
17	$[allylPdCl]_2$	$P(t\text{-}Bu)_3$[c]	K_3PO_4	18-C-6[d]	0	71
18	$Pd(PPh_3)_2Cl_2$	$P(t\text{-}Bu)_3$[c]	K_3PO_4	18-C-6[d]	0	60
19	$Pd(dba)_2$	$P(t\text{-}Bu)_3$	K_3PO_4	18-C-6[d]	0	76
20	$Pd(dba)_2$	JohnPhos	K_3PO_4	18-C-6[d]	2	38

[a] *Reaction conditions:* **1a** (1.00 mmol), diethyl malonate (6.6 mmol), Pd-source (0.5 mol%), ligand (1.1 mol%), base (2.8 mmol), additive (0.5 mmol); entries 1–6: 150 °C, 16 h; entries 6–20: 160 °C, 8 h. $[allylPdCl]_2$ = allylpalladium(II) chloride dimer; JohnPhos = (2-biphenylyl)di-*tert*-butylphosphine. Yields were determined by GC analysis, with *n*-tetradecane as internal standard.
[b] $Pd(dba)_2$ (1.0 mol%), $P(t\text{-}Bu)_3{\cdot}HBF_4$ (2.2 mol%), bases (2.3 mmol).
[c] $P(t\text{-}Bu)_3{\cdot}HBF_4$.
[d] 18-crown-6.
[e] Tetrabutylammonium fluoride hydrate.
[f] 1.00 mmol.

Table 3. Reaction scope of substituted aryl halides.[a]



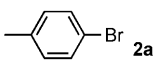
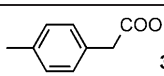
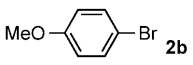
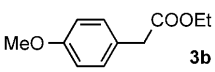
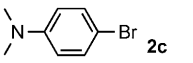
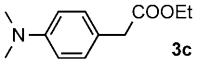
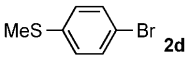
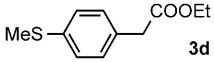
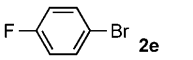
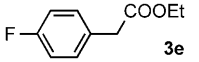
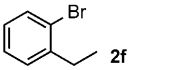
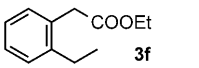
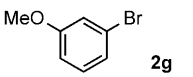
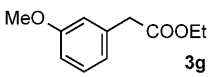
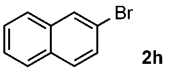
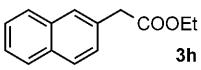
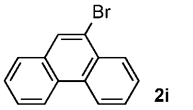
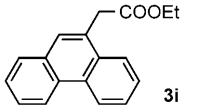
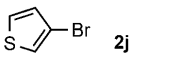
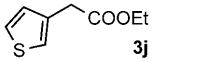
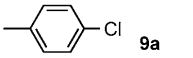
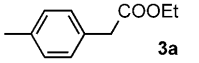
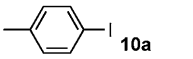
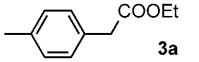
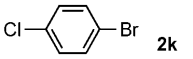
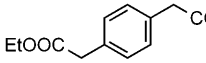
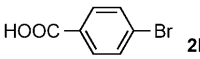
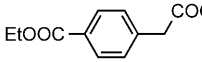
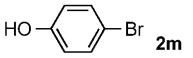
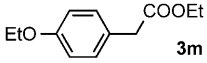
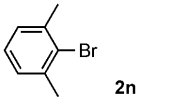
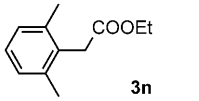
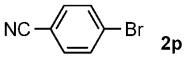
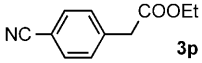
Substrate	Product	Yield [%]
 2a	 3a	87
 2b	 3b	94[b]

Table 3. (Continued)

Substrate	Product	Yield [%]
 2c	 3c	96[b]
 2d	 3d	95
 2e	 3e	86
 2f	 3f	88[c]
 2g	 3g	93
 2h	 3h	93
 2i	 3i	91
 2j	 3j	94
 9a	 3a	83[b]
 10a	 3a	89[b]
 2k	 3k	68
 2l	 3l	88
 2m	 3m	89
 2n	 3n	15[d,e]
 2p	 3p	15[d,f]

[a] *Reaction conditions* A: **1**, **9** or **10** (1.00 mmol), $Pd(dba)_2$ (0.5 mol%), $P(t\text{-}Bu)_3{\cdot}HBF_4$ (1.1 mol%), diethyl malonate (6.6 mmol), 18-crown-6 (0.5 mmol), K_3PO_4 (2.8 mmol), 160 °C, 8 h. Yield of isolated product.
[b] 12 h.
[c] 170 °C, 12 h.
[d] GC yields.
[e] 48% of the *m*-xylene was detected.
[f] 20% of benzonitrile was detected.

We also performed mechanistic studies to validate the proposed reaction pathway (Scheme 2). The detection of CO_2 with the help of lime water and of ethanol by ^1H NMR supports this mechanism. The obser-

vation that dimethyl malonate displays a similar reactivity to the diethyl derivative excludes an alternative pathway in which ethene is eliminated in the dealkoxycarbonylation step.

Having thus found an effective and practical protocol to prepare ethyl arylacetates, we next explored its scope by coupling a large variety of aryl halides with diethyl malonate under the previously optimized conditions. As shown in Table 3, the dealkoxycarbonylative cross-coupling reaction proceeded very well for electron-rich aryl halides. In all cases, the dealkoxycarbonylated products were exclusively obtained in high yields. Various functional groups were tolerated in *para* (**2b**–**e**), *ortho* (**2f**), and *meta* (**2g**) positions on the aryl ring. 2-Bromonaphthalene (**2h**) and 9-bromophenanthrene (**2i**), as well as 3-bromothiophene as an example of an electron-rich heteroaryl bromide (**2j**), were also converted in excellent yields. The new protocol can be applied also to the coupling of aryl chlorides and iodides (**9a** and **10a**). 4-Chlorophenyl bromide (**2k**) underwent coupling at both halides to give the corresponding diester in good yield within a short time. Due to the good ability of the catalyst to activate aryl chlorides, no differential reaction of the Cl and Br groups was observed. Under the reaction conditions, unprotected carboxylic acid groups (**2l**) are converted into the corresponding ethyl esters, presumably *via* transesterification with the diethyl malonate present in excess, or condensation with the ethanol liberated during the dealkoxycarbonylation step. In analogy, phenolic OH groups were converted into the ethyl ethers (**2m**).

However, the performance limit of this protocol was reached for sterically hindered substrates such as 2-bromo-*m*-xylene **2n**, and for electron-deficient aryl halides such as 4-bromobenzonitrile **2p**. In both cases, dehalogenation of the aryl halides was the major side reaction, and the products were obtained in unsatisfactory yields. When β-keto esters were subjected to the same reaction conditions, the phenylacetic acid derivatives were exclusively formed. This confirms the findings by de Koning that the retro-Claisen reaction is faster than the dealkoxycarbonylation.[23]

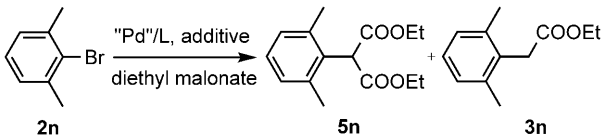
These results indicate that the reaction protocol is effective mainly for the coupling of electron-rich aryl halides. For these substrates, the dealkoxycarbonylation proceeds slowly compared to the cross-coupling, so that it needs to be facilitated by the most effective mediator, namely the combination of potassium phosphate and 18-crown-6. In contrast, the decarboxylation proceeds more rapidly than the cross-coupling for electron-deficient as well as sterically demanding aryl halides.[26] For these substrates, the bases and conditions must be adjusted such that the cross-coupling step proceeds with optimal selectivity, so as to avoid the undesired dehalogenation reactions.[27]

In order to find an alternative set of conditions which is optimal for sterically hindered substrates, we used the reaction of 2-bromo-*m*-xylene **2n** with diethyl malonate as a model to reevaluate various reaction conditions. The results are summarized in Table 4. Under none of the conditions tested was the malonate detected in significant quantities, confirming that in contrast to the previous model reaction of **2a**, the decarboxylation step is not critical for this sterically demanding substrate. Under the previous reaction conditions, the arylacetate **3n** was obtained in low yields, along with large amounts of *m*-xylene resulting from protodehalogenation (entry 1). Without 18-crown-6, the yield was similarly unsatisfactory (entry 2).

The yields improved substantially when employing carbonate bases (entries 3 and 4). A systematic study revealed that the optimal base consists of a 1:1 mixture of potassium carbonate and bicarbonate. The desired arylacetate **3n** was detected in 80% yield with the adapted conditions (entry 7). Control experiments confirmed that a 1:1 ratio between K_2CO_3 and $KHCO_3$ is crucial for the selectivity of cross-coupling *vs.* protodehalogenation (entries 9 and 10). The origin of the cooperative effect of these two bases is still unclear.

This second protocol was also effective in the coupling of the electron-deficient substrate **2p** (70% yield), which had given only 15% using the protocol

Table 4. Optimization for 2-bromo-*m*-xylene.[a]



Entry	Base [equiv.]	Additive	Yield [%]	
			5n	**3n**
1	K_3PO_4 (2.8)	18-C-6[b]	0	15[c]
2	K_3PO_4 (2.8)	–	1	12
3	K_2CO_3 (2.8)	–	1	54[d]
4	Cs_2CO_3 (2.8)	–	0	31
5	$KHCO_3$ (2.8)	–	0	14[e]
6	K_3PO_4 (1.5)/$KHCO_3$ (1.5)	–	0	51
7	**K_2CO_3 (1.5)/$KHCO_3$ (1.5)**	**–**	**0**	**80**
8	Na_2CO_3 (1.5)/$KHCO_3$ (1.5)	–	0	19
9	K_2CO_3 (2.0)/$KHCO_3$ (1.0)	–	0	65
10	K_2CO_2 (1.0)/$KHCO_3$ (2.0)	–	0	54

[a] *Reaction conditions:* **2n** (1.00 mmol), $Pd(dba)_2$ (0.5 mol%), $P(t\text{-}Bu)_3{\cdot}HBF_4$ (1.1 mol%), base (2.8–3.0 mmol), additive (0.5 mmol), diethyl malonate (6.6 mmol), 160 °C, 8 h. Yields were determined by GC analysis, with *n*-tetradecane as internal standard.
[b] 18-crown-6.
[c] 48% of *m*-xylene was detected.
[d] 32% of *m*-xylene was detected.
[e] 32% of **2n** and 17% of *m*-xylene were detected.

optimized for electron-rich compounds. Encouraged by these spot checks, we explored the scope of the new conditions for various aryl halides (Table 5).

The results confirm that the second set of conditions is superior for the coupling of sterically demanding and electron-deficient aryl bromides. The protodehalogenation was largely suppressed, and a good range of arylacetates was obtained in high yields. Common functionalities such as cyano, ester, benzoyl, trifluoromethyl, acetyl, and nitro groups were tolerated (**3p–w**). We were delighted to find that the conditions were also suitable for the conversion of aryl chlorides into the corresponding aryl acetates.

Test reactions confirmed that the protocols used in Table 3 and Table 5 are complementary to each other. The first, which involves potassium phosphate in combination with 18-crown-6 as the base, is highly effective for the coupling of electron-rich aryl halides but gives low yield for electron-deficient or sterically demanding substrates (Table 3, **3n** and **3p**). In contrast, the second, which is based on a potassium carbonate/bicarbonate mixture, allows the coupling of electron-poor and sterically demanding aryl halides, but is less effective for the coupling of electron-rich substrates (Table 5, **3a**).

Conclusions

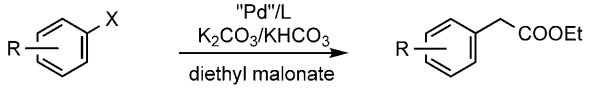
A new palladium catalyst system was developed that allows the convenient synthesis of diversely functionalized arylacetates from easily available aryl halides and diethyl malonate in the presence of mild bases. The reaction proceeds *via* the arylation of diethyl malonate with formation of diethyl 2-arylmalonates. These intermediates directly undergo a dealkoxycarbonylation to give arylacetic acid esters along with CO_2 and ethanol. The dealkoxycarbonylation step proceeds rapidly for electron-deficient and sterically demanding derivatives, but is much slower for electron-rich 2-arylmalonates.

Two complementary reaction protocols were necessary to provide a general synthetic entry to alkyl 2-arylacetates. The optimal conditions for the coupling of electron-rich aryl halides involve $Pd(dba)_2$ (0.5%)/P(*t*-Bu)$_3$·HBF_4 (1.1%) as the catalyst and 18-crown-6 (0.5 equiv.)/potassium phosphate (2.8 equiv.) as the base. This base/crown ether combination is essential for a quantitative dealkoxycarbonylation.

In contrast, electron-deficient and sterically demanding aryl halides are best coupled in the absence of crown ether, using a 1:1 potassium carbonate/bicarbonate mixture as the base. This way, the competing protodehalogenation of the aryl halides, otherwise a major side reaction, is effectively suppressed.

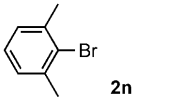
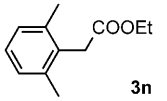
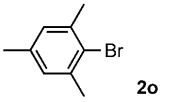
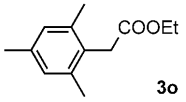
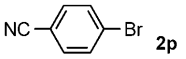
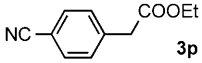
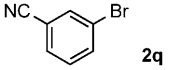
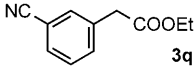
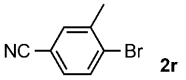
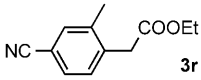
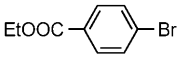
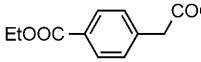
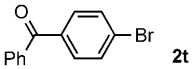
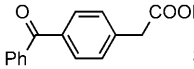
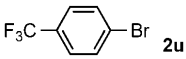
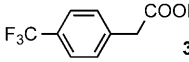
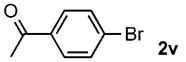
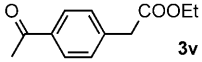
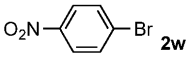
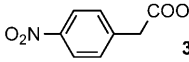
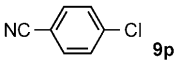
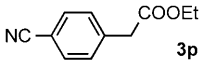
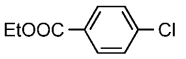
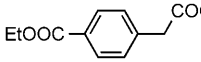
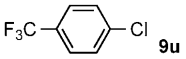
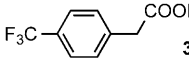
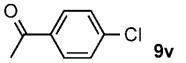
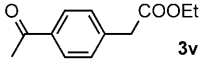
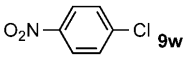
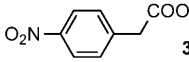
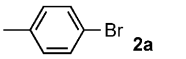
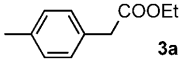
Overall, the new protocols, characterized by the use of commercially available, easy-to-handle catalysts

Table 5. Reaction scope for sterically hindered and electron-deficient substrates.[a]



2n - w (X = Br);
9p, 9s, 9u - w (X = Cl)

3n - w

Substrate	Product	Yield [%]
 **2n**	 **3n**	81
 **2o**	 **3o**	83
 **2p**	 **3p**	70
 **2q**	 **3q**	77
 **2r**	 **3r**	93
 **2s**	 **3l**	93
 **2t**	 **3t**	95
 **2u**	 **3u**	82
 **2v**	 **3v**	73
 **2w**	 **3w**	60
 **9p**	 **3p**	77
 **9s**	 **3l**	88
 **9u**	 **3u**	73
 **9v**	 **3v**	87
 **9w**	 **3w**	70
 **2a**	 **3a**	16[b,c]

[a] *Reaction conditions B:* **2** or **9** (1.00 mmol), $Pd(dba)_2$ (0.5 mol%), P(*t*-Bu)$_3$·HBF_4 (1.1 mol%), diethyl malonate (6.6 mmol), K_2CO_3 (1.5 mmol), $KHCO_3$ (1.5 mmol), 160 °C, 8 h. Yield of isolated product.

[b] GC yield.

[c] 82% of malonate product **5a** was detected by GC.

and mild bases as well as a high functional group tolerance, have decisively advanced the dealkoxycarbonylative cross-coupling of aryl halides and dialkyl malonates towards being a general and practical synthetic entry to the important substrate class of arylacetic acid derivatives.

Experimental Section

General Methods

Chemicals and solvents were either purchased (puriss p.A.) from commercial suppliers or purified by standard techniques. All reactions, if not stated otherwise, were performed in oven-dried glassware containing a teflon-coated stirrer bar and dry septum under a nitrogen atmosphere. All reactions were monitored by GC using tetradecane as an internal standard. Response factors of the products with regard to tetradecane were obtained experimentally by analyzing known quantities of the substances. GC analyses were carried out using an HP-5 capillary column (phenyl methyl siloxane, 30 m × 320 × 0.25, 100/2.3–30–300/3, 2 min at 60 °C, heating rate 30 °C min^{-1}, 3 min at 300 °C). Column chromatography was performed using a Combi Flash Companion-Chromatography-System (Isco-Systems) and Redi*Sep* packed columns (12 g). NMR spectra were obtained on Bruker AMX 400 (400 MHz) using $CDCl_3$ as solvent, 400 MHz and 101 MHz, respectively. Mass spectral data were acquired on a Varian GC-MS Saturn 2100 T. Melting points were measured on a Mettler FP 61 and infrared spectra on a Perkin–Elmer Spectrum BX, FT-IR System (HeNe 633 nm < 0.4 mW).

General Procedure A for the Preparation of Ethyl 2-Arylacetates 3a–m

In an oven-dried, 20-mL Schlenk tube equipped with a rubber cap and a stirrer bar were placed aryl halides **2a–m**, **9a** or **10a** (1.00 mmol), bis(dibenzylideneacetone)palladium(0) (0.005 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (0.011 mmol), potassium phosphate (2.8 mmol), 18-crown-6 (0.5 mmol) and diethyl malonate (6.6 mmol). The reaction vessel was evacuated and filled with nitrogen three times. The reaction mixture was stirred at 160 °C for 8–12 h. After the reaction was complete, the mixture was cooled to room temperature and diluted with ethyl acetate. The resulting solution was washed successively with water (20 mL), saturated sodium bicarbonate solution (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and the solvents were removed under vacuum. Purification of the residue by column chromatography (SiO_2, hexane/ethyl acetate gradient) gave the corresponding products **3a–m**.

General Procedure B for the Preparation of Ethyl 2-Arylacetates 3n–w

In an oven-dried, 20-mL Schlenk tube equipped with a rubber cap and a stirrer bar were placed aryl halides **2n–w**, **9p**, **9s**, or **9u–w** (1.00 mmol), bis(dibenzylideneacetone)palladium(0) (0.005 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (0.011 mmol), potassium carbonate (1.5 mmol), potassium bicarbonate (1.5 mmol) and diethyl malonate (6.6 mmol). The reaction vessel was evacuated and filled with nitrogen three times. The reaction mixture was stirred at 160 °C for 8 h. Upon completion, the reaction solution was cooled, diluted with ethyl acetate. The solution was washed successively with water (20 mL), saturated sodium bicarbonate solution (20 mL) and then with brine (20 mL), dried over $MgSO_4$, filtered, and the solvents removed under vacuum. Purification of the residue by column chromatography (SiO_2, hexane/ethyl acetate gradient) gave the corresponding products **3n–w**.

Ethyl 2-*p*-tolylacetate (3a): Compound **3a** was synthesized according to the general procedure A from diethyl malonate (1.0 mL, 6.6 mmol) and 4-bromotoluene (171 mg, 123 μL, 1.00 mmol) or 4-chlorotoluene (128 mg, 120 μL, 1.00 mmol) or 4-iodotoluene (218 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 5:95), **3a** was obtained as a colorless oil; yield: 155 mg (87%); 148 mg (83%); 159 mg (89%). The spectroscopic data (NMR) matched those reported in the literature for ethyl 2-*p*-tolylacetate [CAS-No. 14062-19-2].

Ethyl 2-(4-methoxyphenyl)acetate (3b): Compound **3b** was synthesized according to the general procedure A from diethyl malonate (1.0 mL, 6.6 mmol) and 4-bromoanisole (187 mg, 128 μL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 10:90), **3b** was obtained as a light yellow oil; yield: 183 mg (94%). The spectroscopic data (NMR) matched those reported in the literature for ethyl 2-(4-methoxyphenyl)acetate [CAS-No. 14062-18-1].

Ethyl 2-(4-(dimethylamino)phenyl)acetate (3c): Compound **3c** was synthesized according to the general procedure A from diethyl malonate (1.0 mL, 6.6 mmol) and 4-bromo-*N*,*N*-dimethylaniline (200 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 10:90), **3c** was obtained as a light green oil; yield: 199 mg (96%). The spectroscopic data (NMR) matched those reported in the literature for ethyl 2-(4-(dimethylamino)phenyl)acetate [CAS-No. 17078-29-4].

Ethyl 2-(4-(methylthio)phenyl)acetate (3d): Compound **3d** was synthesized according to the general procedure A from diethyl malonate (1.0 mL, 6.6 mmol) and 4-bromothioanisole (203 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 5:95), **3d** was obtained as a white solid; yield: 199 mg (95%); mp 57–58 °C. The spectroscopic data (NMR) matched those reported in the literature for ethyl 2-(4-(methylthio)phenyl)acetate [CAS-No. 14062-27-2].

Ethyl 2-(4-fluorophenyl)acetate (3e): Compound **3e** was synthesized according to the general procedure A from diethyl malonate (1.0 mL, 6.6 mmol) and 1-bromo-4-fluorobenzene (175 mg, 110 μL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 5:95), **3e** was obtained as a colorless oil; yield: 157 mg (86%). The spectroscopic data (NMR) matched those reported in the literature for ethyl 2-(4-fluorophenyl)acetate [CAS-No. 587-88-2].

Ethyl 2-(2-ethylphenyl)acetate (3f): Compound **3f** was synthesized according to the general procedure A from diethyl malonate (1.0 mL, 6.6 mmol) and 1-bromo-2-ethylbenzene (185 mg, 139 μL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane

5:95), **3f** was obtained as a light yellow oil; yield: 170 mg (88%). The spectroscopic data (NMR) matched those reported in the literature for ethyl 2-(2-ethylphenyl)acetate [CAS-No. 105337-78-8].

Ethyl 2-(3-methoxyphenyl)acetate (3g): Compound **3g** was synthesized according to the general procedure A from diethyl malonate (1.0 mL, 6.6 mmol) and 3-bromoanisole (187 mg, 128 μL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 10:90), **3g** was obtained as a light yellow oil; yield: 180 mg (93%). The spectroscopic data (NMR) matched those reported in the literature for ethyl 2-(3-methoxyphenyl)acetate [CAS-No. 35553-92-5].

Ethyl 2-(naphthalene-2-yl)acetate (3h): Compound **3h** was synthesized according to the general procedure A from diethyl malonate (1.0 mL, 6.6 mmol) and 2-bromonaphthaline (207 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 10:90), **3h** was obtained as a light yellow oil; yield: 200 mg (93%). The spectroscopic data (NMR) matched those reported in the literature for ethyl 2-(naphthalene-2-yl)acetate [CAS-No. 2122-70-5].

Ethyl 2-(phenanthren-9-yl)acetate (3i): Compound **3i** was synthesized according to the general procedure A from diethyl malonate (1.0 mL, 6.6 mmol) and 9-bromophenathrene (257 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 5:95), **3i** was obtained as a white solid; yield: 240 mg (91%); mp 83–84 °C. The spectroscopic data (NMR) matched those reported in the literature for ethyl 2-(phenanthren-9-yl)acetate [CAS-No. 101723-22-2].

Ethyl 2-(thiophen-3-yl)acetate (3j): Compound **3j** was synthesized according to the general procedure A from diethyl malonate (1.0 mL, 6.6 mmol) and 3-bromothiophene (163 mg, 94 μL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 5:95), **3j** was obtained as a light yellow oil; yield: 160 mg (94%). The spectroscopic data (NMR) matched those reported in the literature for ethyl 2-(thiophen-3-yl)acetate [CAS-No. 2122-70-5].

Diethyl 2,2′-(1,4-phenylene)diacetate (3k): Compound **3k** was synthesized according to the general procedure A from diethyl malonate (1.0 mL, 6.6 mmol) and 1-bromo-4-chlorobenzene (191 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 5:95), **3k** was obtained as a light yellow oil; yield: 171 mg (68%). The spectroscopic data (NMR) matched those reported in the literature for ethyl 2,2′-(1,4-phenylene)diacetate [CAS-No. 36076-26-3].

Ethyl 2-(4-(ethoxycarbonyl)phenyl)acetate (3l): Compound **3l** was synthesized through an *in situ* esterification of the dealkoxycarbonylative cross-coupling product according to the general procedure A from diethyl malonate (1.0 mL, 6.6 mmol) and 4-bromobenzoic acid (201 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 5:95), **3l** was obtained as a light yellow oil; yield: 208 mg (88%).

Compound **3l** was also synthesized according to the general procedure B from diethyl malonate (1.0 mL, 6.6 mmol) and ethyl 4-bromobenzoate (229 mg, 160 μL, 1.00 mmol) or ethyl 4-chlorobenzoate (185 mg, 156 μL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 5:95), **3l** was obtained as a light yellow oil; yield: 219 mg (93%); 208 mg (88%). The spectroscopic data (NMR) matched those reported in the literature for ethyl 2-(4-(ethoxycarbonyl)phenyl)acetate [CAS-No. 3516-89-0].

Ethyl 2-(4-ethoxyphenyl)acetate (3m): Compound **3m** was synthesized through an *in situ* etherification of the dealkoxycarbonylative cross-coupling product according to the general procedure A from diethyl malonate (1.0 mL, 6.6 mmol) and 4-bromophenol (173 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 5:95), **3m** was obtained as a light yellow oil; yield: 186 mg (89%). The spectroscopic data (NMR) matched those reported in the literature for ethyl 2-(4-ethoxyphenyl)acetate [CAS-No. 40784-88-1].

Ethyl 2-(2,6-dimethylphenyl)acetate (3n): Compound **3n** was synthesized according to the general procedure B from diethyl malonate (1.0 mL, 6.6 mmol) and 2-bromo-*m*-xylene (185 mg, 134 μL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 5:95), **3n** was obtained as a light yellow oil; yield: 156 mg (81%). The spectroscopic data (NMR) matched those reported in the literature for ethyl 2-(2,6-dimethylphenyl)acetate [CAS-No. 105337-15-3].

Ethyl 2-mesitylacetate (3o): Compound **3o** was synthesized according to the general procedure B from diethyl malonate (1.0 mL, 6.6 mmol) and 2-bromomesitylene (199 mg, 153 μL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 5:95), **3o** was obtained as a light yellow oil; yield: 172 mg (83%). The spectroscopic data (NMR) matched those reported in the literature for ethyl 2-mesitylacetate [CAS-No. 5460-08-2].

Ethyl 2-(4-cyanophenyl)acetate (3p): Compound **3p** was synthesized according to the general procedure B from diethyl malonate (1.0 mL, 6.6 mmol) and 4-bromobenzonitrile (182 mg, 1.00 mmol) or 4-chlorobenzonitrile (139 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 10:90), **3p** was obtained as a white solid; yield: 132 mg (70%); 145 mg (77%); mp 93 °C. The spectroscopic data (NMR) matched those reported in the literature for ethyl 2-(4-cyanophenyl)acetate [CAS-No. 1528-41-2].

Ethyl 2-(3-cyanophenyl)acetate (3q): Compound **3q** was synthesized according to the general procedure B from diethyl malonate (1.0 mL, 6.6 mmol) and 3-bromobenzonitrile (182 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 10:90), **3q** was obtained as a white solid; yield: 145 mg (77%); mp 50 °C. The spectroscopic data (NMR) matched those reported in the literature for ethyl 2-(3-cyanophenyl)acetate [CAS-No. 210113-91-0].

Ethyl 2-(4-cyano-2-methylphenyl)acetate (3r): Compound **3r** was synthesized according to the general procedure B from diethyl malonate (1.0 mL, 6.6 mmol) and 4-bromo-3-methylbenzonitrile (200 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 10:90), **3r** was obtained as a light yellow oil; yield: 190 mg (93%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.49$–7.41 (m, 2H), 7.28 (d, $J = 8.0$ Hz, 1H), 4.14 (q, $J = 8.0$ Hz, 2H), 3.65 (s, 2H), 2.33 (s, 3H), 1.23 (t, $J = 8.0$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 170.1$, 138.3, 133.6, 130.9, 129.8, 118.8, 111.1, 61.2, 39.2, 19.4, 14.1; MS (70 eV): m/z (%) =

204 (9), 203 (29) [M^+], 157 (19), 131 (40), 130 (100), 129 (20), 104 (16), 103 (37), 102 (12), 77 (23); IR (NaCl): $\tilde{\nu}$ = 2981 (vs), 2935 (s), 2229 (vs), 1731 (vs), 1607 (m), 1569 (w), 1499 (m), 1367 (s), 1334 (s), 1256 (s), 1234 (s), 1216 (s), 1174 (s), 1162 (s), 1030 (s), 886 (w), 838 (w), 808 (w), 788 cm^{-1} (w); anal. calcd. for $C_{12}H_{13}NO_2$: H 6.45, C 70.92, N 6.89; found: H 6.61, C 70.63, N 6.56.

Ethyl 2-(4-benzoylphenyl)acetate (3t): Compound **3t** was synthesized according to the general procedure B from diethyl malonate (1.0 mL, 6.6 mmol) and 4-bromobenzophenone (261 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 5:95), **3t** was obtained as a white solid; yield: 255 mg (95%); mp 61 °C. The spectroscopic data (NMR) matched those reported in the literature for ethyl 2-(4-benzoylphenyl)acetate [CAS-No. 24021-67-8].

Ethyl 2-[4-(trifluoromethyl)phenyl]acetate (3u): Compound **3u** was synthesized according to the general procedure B from diethyl malonate (1.0 mL, 6.6 mmol) and 4-bromobenzotrifluoride (227 mg, 142 μL, 1.00 mmol) or 4-chlorobenzotrifluoride (184 mg, 136 μL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 10:90), **3u** was obtained as a white solid; yield: 190 mg (82%); 170 mg (73%); mp 37 °C. The spectroscopic data (NMR) matched those reported in the literature for ethyl 2-[4-(trifluoromethyl)phenyl]acetate [CAS-No. 721-63-1].

Ethyl 2-(4-acetylphenyl)acetate (3v): Compound **3v** was synthesized according to the general procedure B from diethyl malonate (1.0 mL, 6.6 mmol) and 4-bromoacetophenone (199 mg, 1.00 mmol) or 4-chloroacetophenone (155 mg, 130 μL, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 15:85), **3v** was obtained as a white solid; yield: 150 mg (73%); 180 mg (87%); mp 61 °C. The spectroscopic data (NMR) matched those reported in the literature for 2-(4-acetylphenyl)acetate [CAS-No. 1528-42-3].

Ethyl 2-(4-nitrophenyl)acetate (3w): Compound **3w** was synthesized according to the general procedure B from diethyl malonate (1.0 mL, 6.6 mmol) and 1-bromo-4-nitrobenzene (202 mg, 1.00 mmol) or 1-chloro-4-nitrobenzene (158 mg, 1.00 mmol). After purification by flash column chromatography (SiO_2, ethyl acetate-hexane 15:85), **3w** was obtained as a yellow solid; yield: 125 mg (60%); 147 mg (70%); mp 61 °C. The spectroscopic data (NMR) matched those reported in the literature for ethyl 2-(4-nitrophenyl)acetate [CAS-No. 2122-70-5].

Acknowledgements

We thank the DFG and Bayer CropScience for financial support, and the Studienstiftung des Deutschen Volkes, the FCI for fellowships to Felix Rudolphi, and the DAAD and the Bayer Science & Education Foundation for fellowships to Bingrui Song.

References

[1] a) H. Kende, J. Zeevaart, *Plant Cell* **1997**, *9*, 1197–1210; b) M. Kutacek, R. S. Bandurski, J. H. Krekule, *Physiology and Biochemistry of Auxins in Plants*, Backhuys, Leiden, **1988**; c) F. Müller, *Agrochemicals*, Wiley-VCH, Weinheim, **2000**.

[2] a) D. Lednicer, L. A. Mitscher, *The Organic Chemistry of Drug Synthesis* John Wiley, New York, **1980**; b) J. D. Genders, D. Pletcher, *Chem. Ind.* **1996**, 682–686.

[3] a) S. H. Ferreira, S. Moncada, J. R. Vane, *Nat. New Biol.* **1971**, *231*, 237–239; b) A. R. Sallmann, *Am. J. Med.* **1986**, *80*, 29–33; c) P. J. Harrington, E. Lodewijk, *Org. Process Res. Dev.* **1997**, *1*, 72–76; d) G. Dannhardt, W. Kiefer, *Eur. J. Med. Chem.* **2001**, *36*, 109–126.

[4] a) R. Adams, A. F. Thal, *Org. Synth.* **1922**, *2*, 59–60; b) W. Wenner, *Org. Synth.* **1952**, *32*, 92–94.

[5] a) R. F. Heck, D. S. Breslow, *J. Am. Chem. Soc.* **1963**, *85*, 2779–2782; b) M. M. Taquikhan, S. B. Halligudi, S. H. R. Abdi, *J. Mol. Catal.* **1988**, *44*, 179–181.

[6] a) O. Sock, M. Troupel, J. Perichon, *Tetrahedron Lett.* **1985**, *26*, 1509–1512; b) J.-C. Folest, J.-M. Duprilot, J. Perichon, *Tetrahedron Lett.* **1985**, *26*, 2633–2636; c) A. A. Isse, A. Gennaro, *Chem. Commun.* **2002**, 2798–2799; d) M. D. Otero, B. Batanero, F. Barba, *Tetrahedron Lett.* **2006**, *47*, 2171–2173.

[7] a) R. Adams, A. F. Thal, *Org. Synth.* **1922**, *2*, 9–10; b) R. C. Fuson, N. Rabjohn, *Org. Synth.* **1945**, *25*, 69–71.

[8] a) W. W. Leake, R. Levine, *J. Am. Chem. Soc.* **1959**, *81*, 1627–1630; b) J. F. Fauvarque, A. Jutand, *J. Organomet. Chem.* **1979**, *177*, 273–281; c) F. Orsini, F. Pelizzoni, *Synth. Comm.* **1987**, *17*, 1389–1402; d) F. Orsini, F. Pelizzoni, L. M. Vallarino, *J. Organomet. Chem.* **1989**, *367*, 375–382.

[9] a) M. Kosugi, I. Hagiwara, T. Sumiya, T. Migita, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 242–246; b) M. Kosugi, Y. Negishi, M. Kameyama, T. Migita, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3383–3384.

[10] K. Okuro, M. Furuune, M. Miura, M. Nomura, *J. Org. Chem.* **1993**, *58*, 7606–7607.

[11] a) M. van Leeuwen, A. McKillop, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2433–2434; b) M. F. Semmelhack, R. D. Stauffer, T. D. Rogerson, *Tetrahedron Lett.* **1973**, *14*, 4519–4522; c) M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, L. D. Jones, *J. Am. Chem. Soc.* **1975**, *97*, 2507–2516; d) S. G. Lias, P. Ausloos, *J. Am. Chem. Soc.* **1977**, *99*, 4833–4835; e) M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 1473–1478.

[12] a) C. Carfagna, A. Musco, C. Sallese, *J. Org. chem.* **1991**, *56*, 261–263; b) R. Galarini, A. Musco, R. Pontellini, R. Santi, *J. Mol. Catal.*, **1992**, *72*, L11 L13; c) T. Sakamoto, Y. Kondo, K. Masumoto, H. Yamanaka, *Heterocycles* **1993**, *36*, 2509–2512; d) T. Sakamoto, Y. Kondo, K. Masumoto, H. Yamanaka, *J. Chem. Soc. Perkin Trans. 1* **1994**, 235–236; e) F. Agnelli, G. A. Sulikowski, *Tetrahedron Lett.* **1998**, *39*, 8807–8810.

[13] W. A. Moradi, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7996–8002.

[14] a) S. Lee, N. A. Beare, J. F. Hartwig, *J. Am. Chem. Soc.* **2001**, *123*, 8410–8411; b) M. Jørgensen, S. Lee, X. Liu, J. P. Wolkowski, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 12557–12565; c) D. A. Culkin, J. F. Hartwig, *Acc. Chem. Res.* **2003**, *36*, 234–245.

[15] a) T. Hama, X. Liu, D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 11176–11177; b) X. Liu, J. F. Hartwig, *J. Am. Chem. Soc.* **2004**, *126*, 5182–5191; c) T. Hama, D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 4976–4985.

[16] a) M. Sato, N. Miyaura, A. Suzuki, *Chem. Lett.* **1989**, *18*, 1405–1408; b) L. J. Gooβen, *Chem. Commun.* **2001**, 669–670; c) X.-X. Liu, M.-Z. Deng, *Chem. Commun.* **2002**, 622–623; d) A. Lei, X. Zhang, *Tetrahedron Lett.* **2002**, *43*, 2525–2528; e) C. Liu, C, He, W. Shi, M. Chen, A. Lei, *Org. Lett.* **2007**, *9*, 5601–5604; f) C. Guo, X. Yue, F.-L. Qing, *Synthesis* **2010**, 1837–1844; g) Z.-Y. Peng, J.-P. Wang, J. Cheng, X.-M. Xie, Z. Zhang, *Tetrahedron* **2010**, *66*, 8238–8241.

[17] a) J. T. Pinhey, B. A. Rowe, *Tetrahedron Lett.* **1980**, *21*, 965–968; b) J.-I. Setsune, K. Matsukawa, H. Wakemoto, T. Kitao, *Chem. Lett.* **1981**, 367–370; c) A. Osuka, T. Kobayashi, H. Suzuki, *Synthesis* **1983**, 67–68; d) R. Ugo, P. Nardi, P. Rinaldo, D. Roberto, *Gazz. Chim. Ital.* **1992**, *122*, 511–514.

[18] a) M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 1473–1478; b) J. M. Fox, X. Huang, A. Chieffi, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370; c) E. J. Hennessy, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 269–272; d) N. A. Beare, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 541–555; e) L. Djakovitch, K. Köhler, *J. Organomet. Chem.* **2000**, *606*, 101–107.

[19] a) K. Okuro, M. Furuune, M. Miura, M. Nomura, *J. Org. Chem.* **1993**, *58*, 7606–7607; b) J. P. Konopelski, J. M. Hottenroth, H. M. Oltra, E. A. Véliz, Z.-C. Yang, *Synlett* **1996**, 609–611; c) H. C. Hang, E. Drotleff, G. I. Elliott, T. A. Ritsema, J. P. Konopelski, *Synthesis* **1999**, 398–400; d) X. Xie, G. Cai, D. Ma. *Org. Lett.* **2005**, *7*, 4693–4695; e) S. F. Yip, H. Y. Cheung, Z. Zhou, F. Y. Kwong, *Org. Lett.* **2007**, *9*, 3469–3472.

[20] a) A. P. Krapcho, *Synthesis* **1982**, 805–822; b) A. P. Krapcho, *Arkivoc* **2007**, 1–53.

[21] Y. Kondo, K. Inamoto, M. Uchiyama, T. Sakamoto, *Chem. Commun.* **2001**, 2704–2705.

[22] I. Özdemir, M. Yiğit, E. Çetinkaya, B. Çetinkaya, *Tetrahedron Lett.* **2004**, *45*, 5823–5825.

[23] a) J. G. Zeevaart, C. J. Parkinson, C. B. de Koning, *Tetrahedron Lett.* **2004**, *45*, 4261–4264; b) J. G. Zeevaart, C. J. Parkinson, C. B. de Koning, *Tetrahedron Lett.* **2007**, *48*, 3289–3293.

[24] a) F. Lieb, H. Hagemann, A. Widdig, M. Ruther, R. Fischer, T. Bretschneider, C. Erdelen, U. Wachendorff-Neumann, A. Graff, U. Schneider, *PCT Int. Appl.* WO 97/36868, **1997**; b) T. Himmler, *PCT Int. Appl.* WO 05/075401, **2005**.

[25] a) A. P. Krapcho, G. A. Glynn, B. T. Grenon, *Tetrahedron Lett.* **1967**, 215–217; b) A. P. Krapcho, A. Lovey, *Tetrahedron Lett.* **1973**, 957–960; c) J. O. F. Melo, E. H. T. Pereira, C. L. Donnici, *Synth. Commun.* **1998**, *28*, 4179–4185.

[26] D. H. Miles, B.-S. Huang, *J. Org. Chem.* **1976**, *41*, 208–214.

[27] a) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2002**, *102*, 4009–4091; b) M. Murata, T. Sambommatsu, S. Watanabe, Y. Masuda, *Synlett* **2006**, 1867–1870; c) O. M. Demchuk, B. Yoruk, T. Blackburn, V. Snieckus, *Synlett* **2006**, 2908–2913.

