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Palladium Catalysis

Access to β-Keto Esters by Palladium-Catalyzed Carbonylative Coupling of Aryl Halides with Monoester Potassium Malonates**

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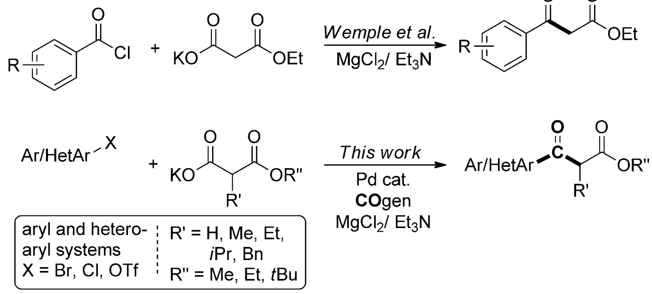
Over the past 150 years since the discovery of the acetoacetic ester condensation by Geuther in 1863,[1] and the subsequent extensive research into the reaction by Claisen,[2] β-keto esters have played a prominent role in organic synthesis. Such compounds serve as key building blocks in the synthesis of many pharmaceuticals and natural products, providing direct access to a wide variety of heterocycles.[3,4] A direct procedure for accessing β-keto esters involves the acylation of diethyl malonate, followed by partial hydrolysis and subsequent decarboxylation of only one of the two ester groups. The disadvantage of this method is the possibility of diacylation, hydrolysis of both ester groups and retro-condensation, leading to the carboxylic acid starting material.[3] On the other hand, Wemple and co-workers reported a modified route to β-keto esters,[5] through the acylation of monoethyl potassium malonate with acid chlorides using a combination of $MgCl_2$ and Et_3N,[6,7] followed by decarboxylation. Nevertheless, both methods rely on the use of reactive carboxylic acid chlorides as reagents for these reactions, requiring their synthesis from the carboxylic acid precursor.

An alternative and complementary approach would involve the Pd-catalyzed carbonylative α-arylation of monoethyl potassium malonate with carbon monoxide and aryl halides (Scheme 1).[8–10] In this way, no reactive intermediates would be required, thus simplifying the storage of the reagents. Because of the mild reaction conditions generally associated with Pd-catalyzed couplings, a wide scope of both nucleophilic and electrophilic coupling partners would be allowed. Furthermore, this method would be ideal for the isotope labeling of the ketone group with carbon-13 and carbon-14 arising from an isotopically labeled CO, thus providing easy access to isotopically labeled heterocycles that are accessible from β-keto esters.

Previously, Tanaka and Kobayashi reported a few examples of the intermolecular carbonylative arylation of malonate derivatives under high CO pressure (20 atm) and at elevated temperatures (120 °C).[11] This method was only

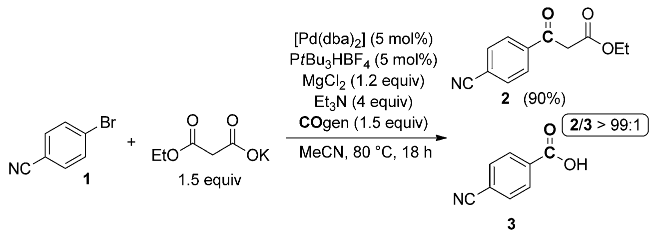


Scheme 1. Synthesis of β-keto esters by a Pd-carbonylative coupling strategy with aryl halides. Bn = benzyl, Tf = trifluoromethanesulfonyl.

applied with aryl iodides, and their results were generally unpredictable in product distribution and gave variable yields.

Herein, we report an effective catalytic system based on palladium, which promotes the carbonylative arylation of potassium malonate monoesters with aryl bromides, aryl triflates, and electron-deficient aryl chlorides for the mild and selective preparation of β-keto esters. Notably, the method relies on the use of only stoichiometric amounts of carbon monoxide applied from an solid precursor (COgen)[12] and delivered ex situ, thereby allowing this approach to be highly adaptable for carbon-isotope labeling of the keto group.[9,13]

To identify an effective catalytic system for the carbonylative arylation of malonates, we initially examined the coupling of 4-bromobenzonitrile (**1**) with monoethyl potassium malonate. In a small optimization study, we quickly discovered that a combination of $[Pd(dba)_2]$ (dba = dibenzylideneacetone) and $PtBu_3$ promoted the carbonylative coupling, allowing the isolation of β-keto ester **2** in high yield and selectivity over carboxylic acid **3** (Scheme 2).[14,15] Moreover, for successful coupling, this reaction required both the addition of $MgCl_2$ (1.2 equiv) and triethylamine (4 equiv). The use of other magnesium salts, including $MgBr_2$, $MgSO_4$, $Mg(OEt)_2$ and $Mg(OtBu_2)$, provided less interesting results. Exchanging $MgCl_2$ with $ZnCl_2$ led to a reversal in the product distribution, exclusively generating **3**. Substituting the mono-



Scheme 2. Preliminary optimization studies for the carbonylative coupling of 4-bromobenzonitrile (**1**) with the malonate monoester.

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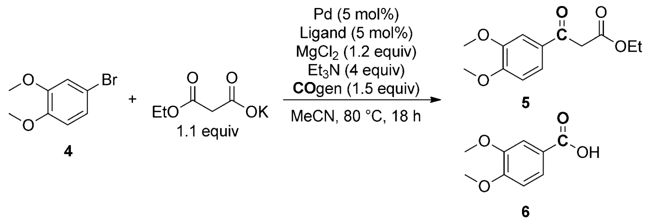
ethyl potassium malonate with its corresponding sodium salt or the free acid also led only to the formation of **3**.

Unfortunately, the suitability of the coupling conditions was short lived, as attempts with an electron-rich aryl bromide, represented by **4**, resulted only in a 20 % conversion. Further optimization was therefore undertaken with this substrate, as shown in Table 1. Other Pd sources were first tested and $[Pd(cod)Cl_2]$ (cod = 1,5-cyclooctadiene) led to a small increase in conversion (entry 1), whereas $[Pd_2(cinnamyl)_2Cl_2]$ and $[Pd_2(allyl)_2Cl_2]$ were less effective (results not shown). Screening different ligands revealed that 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) was superior, giving full conversion into the desired product (entry 7). The use of $Pd(OAc)_2$ as the metal source also gave comparable results (entry 12). Finally, different solvents were tested to identify a higher-boiling solvent than acetonitrile. Switching to butyronitrile and dioxane furnished excellent results, with β-keto ester **5** in both cases isolated in a satisfactory 99 % yield.

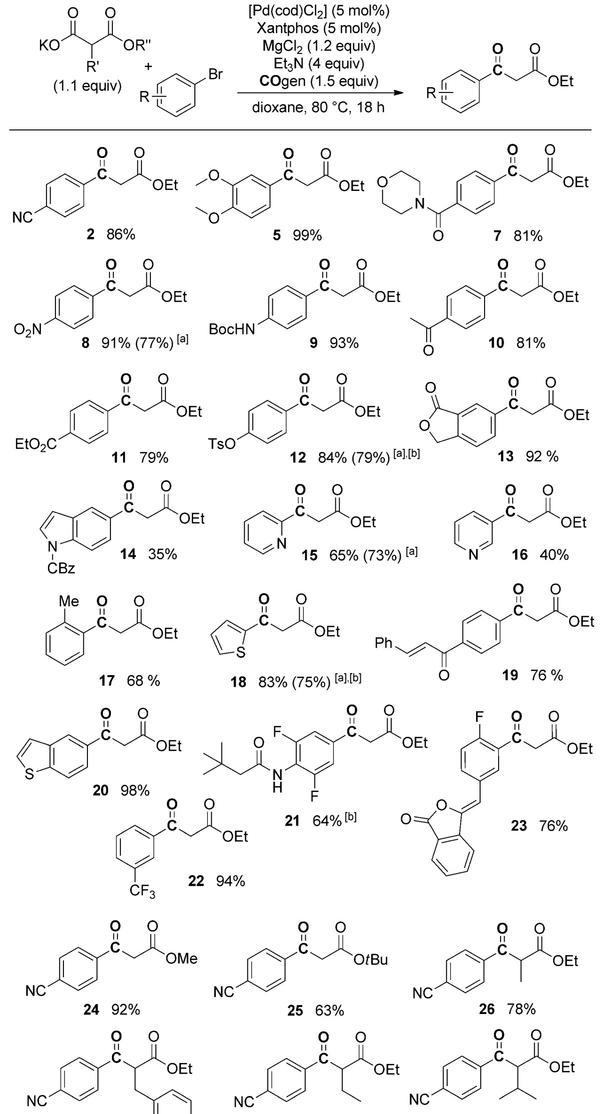
Table 1: Optimization of the carbonylative arylation of monoethyl potassium malonates with aryl bromide **4**.[a]



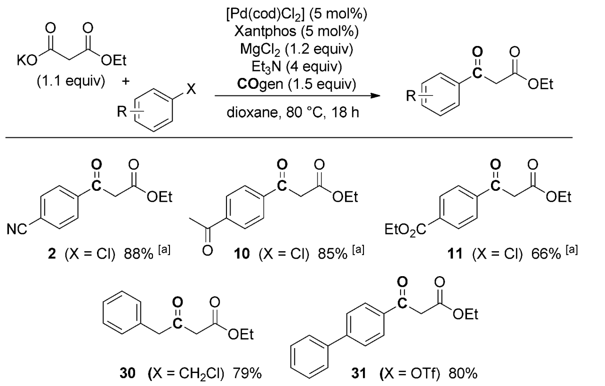
Entry	Ligand	Solvent	Conv. of **4**[b] [%] (ratio of **5**/**6**)
1	$P(tBu_3)HBF_4$	MeCN	24 (> 99:1)
2	$P(o\text{-tol})_3$	MeCN	< 5
3	PCy_3HBF_4	MeCN	< 5
4	PPh_3	MeCN	16 (> 99:1)
5	CatA	MeCN	26 (> 99:1)
6	dppf	MeCN	31 (> 99:1)
7	Xantphos	MeCN	> 95 (> 99:1)
8	*t*Bu-Josiphos	MeCN	< 5
9	d*t*bpf	MeCN	< 5
10	dppb	MeCN	< 5
11[c]	Xantphos	MeCN	90 (> 99:1)
12[d]	Xantphos	MeCN	> 95 (> 99:1)
13	Xantphos	*n*PrCN	> 95 (> 99:1)[e]
14	Xantphos	dioxane	> 95 (> 99:1)[e]
15	Xantphos	toluene	52 (> 99:1)
16	Xantphos	Me-THF	> 95 (60:40)
17	Xantphos	DMA	< 5
18	Xantphos	DME	72 (> 99:1)

[a] All reactions were run in a two-chamber system, as reported earlier.[13] Chamber A: aryl bromide (0.5 mmol), $[Pd(cod)Cl_2]$ (0.025 mmol), ligand (0.025 mmol), monoethyl potassium malonate (0.55 mmol), $MgCl_2$ (0.6 mmol), Et_3N (2 mmol), and MeCN (3 mL) at 80 °C. Chamber B: COgen (0.75 mmol), Cy_2NMe (1.5 mmol), $[Pd(cod)Cl_2]$ (0.038 mmol), $P(tBu)_3HBF_4$ (0.038 mmol), MeCN (3 mL) at 80 °C for 18 h. [b] Determined by ^1H NMR analysis. [c] $PdCl_2$ was used instead of $[Pd(cod)Cl_2]$. [d] $Pd(OAc)_2$ was used instead of $[Pd(cod)Cl_2]$. [e] 99 % yield of isolated β-ketoester **5**. CatA = di(1-adamantyl)-*n*-butylphosphine, DMA = dimethylacetamide, DME = 1,2-dimethoxyethane, dppb = 1,4-bis(diphenylphosphino)butane, dppf = 1,1′-bis(diphenylphosphino)ferrocene, d*t*bpf = 1,1′-bis(di-*tert*-butylphosphino)ferrocene, *t*Bu-Josiphos (2R)-1-{(1R)-1-[bis(1,1-dimethylethyl)phosphino]ethyl}-2-(diphenylphosphino)-ferrocene.

With these optimized reaction conditions in hand, we set out to test the generality of this reaction. Gratifyingly, a variety of aryl bromides successfully coupled to monoethyl potassium malonate, as shown in Scheme 3. Not only electron-rich, but also electron-poor aryl bromides proved to work well, leading to high carbonylative-coupling yields.[16] *Ortho*-substituents on the aromatic ring, such as fluorine or methyl, were also tolerated (compounds **17** and **23**). Furthermore, heterocyclic compounds were adaptable to the applied reaction conditions, as illustrated with β-keto esters **15**, **16**, and **18**. For the reactions leading to the products **12** and **21**, it was necessary to heat to 100 °C to obtain good coupling yields.



Scheme 3. Carbonylative arylation of monoethyl potassium malonate with aryl halides. Reaction conditions: Chamber A: Aryl bromide (0.3 mmol), $[Pd(cod)Cl_2]$ (0.015 mmol), Xantphos (0.015 mmol), monoethyl potassium malonate (0.33 mmol), $MgCl_2$ (0.36 mmol), Et_3N (1.2 mmol), and dioxane (3 mL) at 80 °C. Chamber B: COgen (0.45 mmol), Cy_2NMe (0.9 mmol), $[Pd(cod)Cl_2]$ (0.023 mmol), $P(tBu)_3HBF_4$ (0.023 mmol), and dioxane (3 mL) at 80 °C for 18 h. [a] Yields in parentheses were obtained from reactions run with $Pd(OAc)_2$. [b] Reaction run at 100 °C in butyronitrile with Cy_2NMe as the base.



Scheme 4. Carbonylative arylation of monoethyl potassium malonate with aryl halides. Reaction conditions: Chamber A: aryl halide (0.5 mmol), [Pd(cod)Cl_2] (0.025 mmol), Xantphos (0.025 mmol), monoethyl potassium malonate (0.55 mmol), $MgCl_2$ (0.6 mmol), Et_3N (2 mmol), and dioxane (3 mL) at 80 °C. Chamber B: COgen (0.75 mmol), Cy_2NMe (1.5 mmol), [Pd(cod)Cl_2] (0.0375 mmol), P(*t*Bu)$_3$HBF_4 (0.0375 mmol), dioxane (3 mL) at 80 °C for 18 h. [a] Reaction run at 120 °C in diglyme with Cy_2NMe as the base.

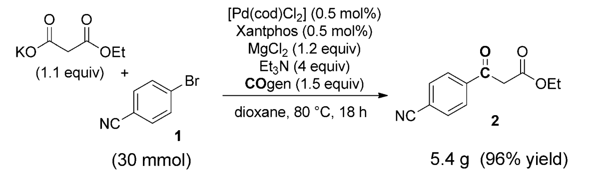
In these cases, triethylamine was substituted for Cy_2NMe (Cy = cyclohexyl), and butyronitrile was used as a higher-boiling solvent. It should be noted in examples **24–29** that the developed procedure can be adapted to other monoester potassium malonates, including those with substituents in the α-position.

As demonstrated in Scheme 4, electron-deficient aryl chlorides can likewise be transformed into the corresponding β-ketoesters (**2**, **10** and **11**) in good yields. For full conversion, it is necessary to run these reactions at elevated temperatures (120 °C), and hence diglyme was used as the solvent.[17] On the other hand, both a benzyl chloride and an aryl triflate functioned well under the standard conditions, as shown with the β-keto esters **30** and **31**, respectively.

The pressure was measured over the course of the carbonylative coupling of aryl bromide **1** with monoethyl potassium malonate (0.3 mmol scale); it showed a rapid increase to approximately 1.9 bar, as a result of CO release.[14] As the carbon monoxide is consumed, the reaction pressure decreases by 0.72 bar, which corresponds to 0.3 mmol of CO (1 equiv). Hence, decarboxylation does not take place during the reaction; if this was the case, the reaction pressure should remain constant at ca. 1.9 bar throughout the reaction course (one CO provides one CO_2). Instead, decarboxylation must occur upon quenching of the reaction mixture with formic acid.[18]

The efficiency of accessing β-keto esters on a larger scale was next investigated. The carbonylative coupling was applied to the synthesis of ethyl 3-(4-cyanophenyl)-3-oxopropanoate **2** on a 30 mmol scale (Scheme 5). To our delight, the catalyst loading could be reduced to 0.5 mol% with no reduction in the product yield. Hence, 5.4 g of β-keto ester **2** could be isolated in 96% yield.

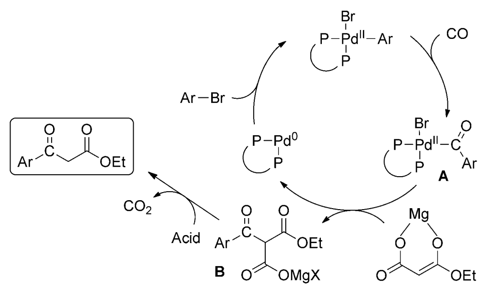
In Scheme 6, we provide a possible mechanism for this Pd-catalyzed transformation. Oxidative addition into the aryl–halide bond followed by CO insertion provides Pd–acyl complex **A**. At this point three scenarios could explain the



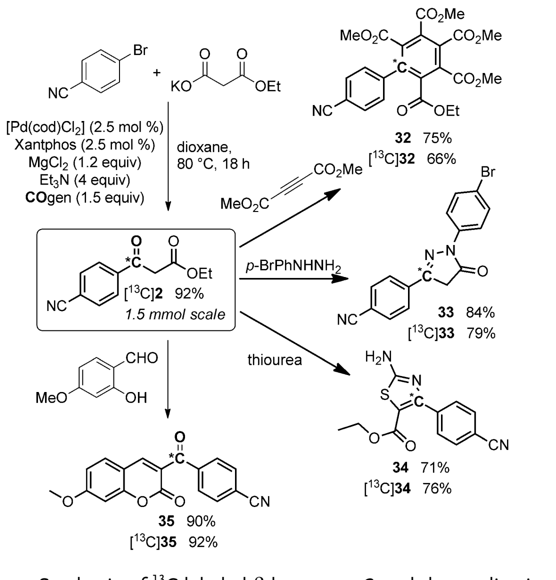
Scheme 5. Example of the gram-scale synthesis of β-keto ester **2** (30 mmol scale) with low catalyst loading.

formation of the acylated malonate **B**: 1) direct nucleophilic acyl substitution on the acyl complex **A**; 2) a transmetalation step, involving the magnesium malonate followed by reductive elimination; 3) reductive elimination of complex **A** to generate the acyl bromide, followed by a nucleophilic acyl-substitution step. Acid-promoted decarboxylation would then lead to the desired product.

Finally, we examined the usefulness of this method for the synthesis of isotopically labeled aryl and heteroaryl systems (Scheme 7). The introduction of a single site-specific carbon-13 label into β-keto esters was shown for the synthesis of [13C]**2** by replacing COgen with ^{13}COgen. In this way, 300 mg of [13C]**2** could be secured on a 1.5 mmol scale (92% yield). Both β-keto ester **2** and [13C]**2** were easily transformed into a benzene ring by reaction with dimethyl acetylenedicarboxylate, yielding compounds **32** and [13C]**32**. Reaction with (4-bromophenyl)hydrazine led to the pyrazoles **33** and [13C]**33**



Scheme 6. Possible mechanistic scenario.



Scheme 7. Synthesis of ^{13}C-labeled β-keto ester **2** and the application of **2** and [13C]**2** in cyclization reactions.

and reaction with thiourea yielded thiazoles **34** and [^{13}C]**34**. In all three examples, the C-13 labeling is incorporated in the ring. Finally, the keto-coumarins **35** and [^{13}C]**35** were synthesized in high yield by coupling the β-keto ester with 2-hydroxy-4-methoxybenzaldehyde.

In summary, the Pd-catalyzed carbonylative arylation of potassium malonate monoesters provides a rapid route to β-keto esters, which serve as direct precursors to important heterocyclic compounds. The method is adaptable to a number of aryl bromides and other substrates, including aryl chlorides possessing electron-poor substitutents. Furthermore, this technique proves effective for carbon-isotope labeling of biologically relevant structures, such as coumarins, pyrazoles, thiazole, and benzene derivatives. Further work is in progress to examine other carbonylative couplings using the $MgCl_2/Et_3N$ system for the preparation of dicarbonyl systems such as β-ketoamides and related systems.

Experimental Section

Ethyl 3-(4-cyanophenyl)-3-oxopropanoate (**2**, Scheme 2): Chamber A: In an argon-filled glovebox, 4-bromobenzonitrile (54 mg, 0.3 mmol), [Pd(cod)Cl_2] (4.3 mg, 0.015 mmol), Xantphos (8.7 mg, 0.015 mmol), monoethyl potassium malonate (56.4 mg, 0.33 mmol), $MgCl_2$ (34 mg, 0.36 mmol), Et_3N (168 μL, 1.2 mmol), and dioxane (3.0 mL), in that order, were added to chamber A of the two-chamber COware system.[12] The chamber was sealed with a screwcap fitted with a Teflon seal. Chamber B (1.5 equiv CO): In an argon-filled glovebox, $HBF_4{\cdot}P(t\mathrm{Bu})_3$ (6.5 mg, 0.023 mmol), [Pd(cod)Cl_2] (6.4 mg, 0.023 mmol), 9-methyl-9*H*-fluorene-9-carbonyl chloride (109 mg, 0.45 mmol), dioxane (3.0 mL), and Cy_2NMe (192 μL, 0.9 mmol), in that order, were added to chamber B of the two-chamber system. The chamber was sealed with a screwcap fitted with a Teflon seal. The loaded two-chamber system was removed from the glovebox and heated to 80°C for 18 h. The reaction was quenched with HCO_2H, and the product was purified by flash chromatography using pentane/CH_2Cl_2 (1:1→100% CH_2Cl_2) as eluent. This provided the titled compound as a mixture of the enol- and keto forms as a colorless solid (57 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 12.55$ (s, 1H), 7.86 (d, $J = 8.6$ Hz, 2H), 7.70 (d, $J = 8.6$ Hz, 2H), 5.71 (s, 1H), 4.28 (q, $J = 7.1$ Hz, 2H), 3.99 (s, 1H), 1.33 (t, $J = 6.9$ Hz, 3H) minor enol tautomer (characteristic peaks) 8.05 (d, $J = 8.6$ Hz, 2H), 7.80 (d, $J = 8.6$ Hz, 2H), 4.21 ppm (q, $J = 7.1$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.7$, 168.6, 137.6, 132.3, 126.5, 118.2, 114.4, 89.7, 60.8, 14.2 ppm. HRMS $C_{12}H_{11}NO_3$ [M+H$^+$]; calculated 218.0817, found 218.0813.

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[14] See the Supporting Information.
[15] The carboxylic acid **3** is possibly formed from the initial halide displacement of the acyl Pd^{II} halide intermediate by the magnesium enolate, which is produced from the deprotonation of monoethyl potassium malonate. Subsequent reductive elimination of the *O*-bound enolate to generate a mixed acid anhydride and hydrolysis upon workup would lead to the benzoic acid product.
[16] The CO insertion step into the Pd–aryl bond can be slow with aromatic ring systems possessing electron-deficient substituents, for example, in the carbonylative Suzuki–Miyaura coupling; see: T. Ishiyama, H. Kizaki, T. Hayashi, A. Suzuki, N. Miyaura, *J. Org. Chem.* **1998**, *63*, 4726. The good yields obtained for our reaction suggest that the CO insertion step is effective for both types of aryl bromides and that this step is not rate determining. Nevertheless, we do not have a clear explanation for this observation.
[17] Aryl chlorides with electron donating groups were unreactive to these reaction conditions at 120°C.
[18] Upon quenching of the reaction mixture with formic acid, considerable gas evolution was observed.

