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Palladium-Catalysed Carbonylative α-Arylation of Acetone and Acetophenones to 1,3-Diketones

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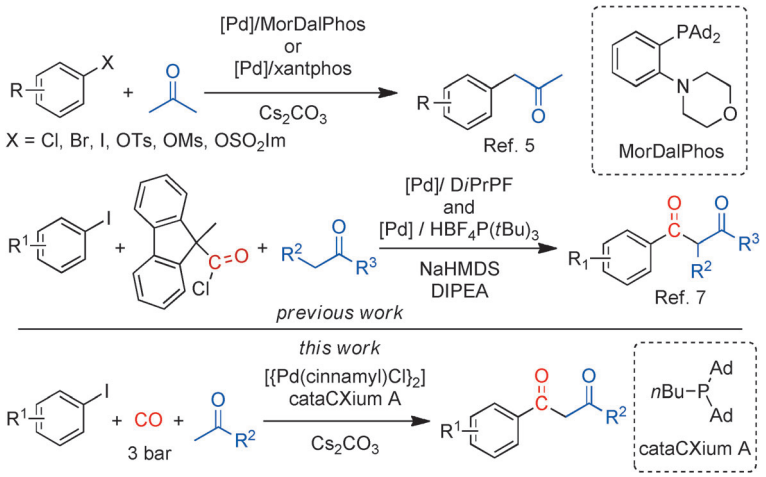
The coupling of activated carbon nucleophiles has served as a key platform for the development of palladium-catalysed (hetero)arylation reactions of esters, ketones and related α-CH acidic substrates in the past few decades.[1] Stemming from the pioneering work of Miura, Buchwald, Hartwig and others, catalytic α-arylation procedures have found multiple synthetic applications.[2] Mechanistic studies have led to the development of efficient catalyst systems for α-arylation reactions, which in turn have been utilised in the formation of allylic and benzylic carbonyl compounds by way of $C(sp^2)$–$C(sp^3)$ bond formation starting from various α-CH acidic compounds (i.e., ketones, esters, malonates, amides, aldehydes and nitriles).[3,4] As a result, the α-arylation of more demanding, less CH acidic compounds such as acetone have also been developed, initially by some of us, and later by Ackermann and co-workers.[5]

An important extension of such methodologies would be the carbonylative version of the α-arylation reaction and various efforts have been made to achieve this goal. However, the scope has mostly been limited to the use of malonate derivatives as starting materials.[6] Recently, Skrydstrup and co-workers reported the first system that allows for the intermolecular carbonylative α-arylation of ketones, thereby preventing the alkoxycarbonylation of the enolate derivative to an acylated enol.[7] Although an intricate CO surrogate is required, their system nicely demonstrates the direct synthesis of 1,3-diketones from aryl iodides and simple ketones. Unfortunately, the protocol was not suitable for the most simple and abundant ketones, such as acetone and acetophenone, and exhibits a lack of selectivity in the presence of gaseous CO.

Clearly, the carbonylative α-arylation of acetone and other easily available ketones is important since the resulting 1,3-diketones are common in numerous biologically relevant compounds and are therefore valuable building blocks. Convenient access to 1,3-diketones is of particular interest especially with regard to the synthesis of heterocyclic compounds.[8] Traditionally, these frameworks are synthesised from enolates and carbonyl compounds through aldol condensation and subsequent oxidation of the resulting β-hydroxy ketones. Hence, the direct synthesis of 1,3-diketones from aryl halides, carbon monoxide and acetone as a simple and abundant carbon feedstock would represent a desirable alternative. Herein, we report the first examples of such carbonylative α-arylation reactions. A readily available catalyst system is employed ([{Pd(cinnamyl)Cl}$_2$]/*n*BuPAd$_2$) that allows for the selective formation of 1,3-diketones under a low pressure of gaseous CO and with the use of Cs_2CO_3 as base (Scheme 1).



Scheme 1. (Carbonylative) α-arylation of ketones (xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, D*i*PrPF = 1,1′-bis(diisopropylphosphino)ferrocene, DIPEA = *N*,*N*-diisopropylethylamine, Im = imidazolyl, Ad = 1-adamantyl).

Initial attempts to perform carbonylative coupling of iodobenzene and α-CH acidic carbonyl compounds were con-

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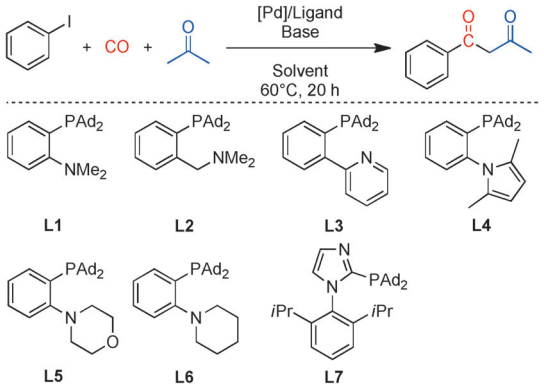
ducted with the [{Pd(cinnamyl)Cl}$_2$]/*n*BuPAd$_2$ catalyst system, which has been used to promote a diverse array of carbonylation reactions.[9] We have previously shown that applying deoxybenzoin, as a comparatively acidic substrate, under these conditions led to the formation of the corresponding vinylbenzoate compound.[10] However, to our surprise, the same catalyst system enabled the selective formation of the corresponding 1,3-diketone when acetone was employed. Thus, when iodobenzene was reacted with acetone under 10 bar of CO in the presence of [{Pd(cinnamyl)Cl}$_2$]/*n*BuPAd$_2$ and Cs_2CO_3 as base, 1-phenylbutane-1,3-dione was obtained in a promising 19% yield (Table 1, entry 1). At a reduced CO pressure of 5 bar, improved product formation, resulting in a 27% yield, was observed (Table 1, entry 2). Decreasing the reaction temperature to 60°C had only a minor effect on the yield (24%) but enhanced the selectivity (Table 1, entry 3). After an increased reaction time of 20 h was found to be beneficial to the yield, testing of different solvents did not show any positive effect (Table 1, entries 3–7). Nevertheless, the use of 2 mL of acetone improved the yield dramatically to 52%; thus the use of additional solvent could be omitted (Table 1, entry 8). Under these conditions several other inorganic (K_2CO_3, K_3PO_4, KOH, CsF), as well as organic (KHMDS, NaO*t*Bu, KO*t*Bu), bases were applied in the model system but in all cases the desired 1,3-diketone was formed in only 12 to 25% yields (for further details, see the Supporting Information). Other palladium precursors such as [Pd_2dba_3] (dba = dibenzylideneacetone), $PdCl_2$ or Pd(acac)$_2$ (acac = acetylacetonate) afforded 10 to 20% less product formation than the [{Pd(cinnamyl)Cl}$_2$] complex (for further details, see the Supporting Information). Although the origins of the beneficial reactivity achieved when using [{Pd(cinnamyl)Cl}$_2$] in this chemistry have not been evaluated in detail, previous observations suggest that such precursors are effective in providing access to the requisite Pd^0 species.[11]

Table 1. Optimisation of the model system.[a]



Entry	Ligand	Solvent	p_{CO} [bar]	T [°C]	Conv. [%][b]	Yield [%][b]
1	*n*BuPAd$_2$	dioxane	10	100	>99	19
2	*n*BuPAd$_2$	dioxane	5	100	>99	27
3	*n*BuPAd$_2$	dioxane	5	60	i) 75 ii) 79[c]	24 35[c]
4	*n*BuPAd$_2$	DMF	5	60	>99	11[c]
5	*n*BuPAd$_2$	toluene	5	60	36	15[c]
6	*n*BuPAd$_2$	DMSO	5	60	>99	9[c]
7	*n*BuPAd$_2$	MeCN	5	60	87	11[c]
8	*n*BuPAd$_2$	acetone	5	60	87	66[c]
9	*n*BuPAd$_2$	acetone	3	60	80	67[c]
10	*n*BuPAd$_2$	acetone	1	60	65	62[c]
11	*n*BuPAd$_2$	acetone	3	60	95	71[d]
12	PPh_3	acetone	3	60	>99	53[d]
13	PCy_3	acetone	3	60	87	36[d]
14	P(*t*Bu)$_3$·HBF$_4$	acetone	3	60	79	0[d]
15	**L1**	acetone	3	60	97	24[d]
16	**L2**	acetone	3	60	53	13[d]
17	**L3**	acetone	3	60	95	11[d]
18	**L4**	acetone	3	60	70	13[d]
19	**L5**	acetone	3	60	48	10[d]
20	**L6**	acetone	3	60	51	11[d]
21	**L7**	acetone	3	60	76	14[d]

[a] General reaction conditions: iodobenzene (1 mmol), acetone (10 mmol; 2 mL in cases for which acetone is used as the solvent), [{Pd(cinnamyl)Cl}$_2$] (1 mol%), ligand (4 mol%), Cs_2CO_3 (2 mmol), solvent (2 mL), 100°C, 16 h. [b] Conversions and yields determined on the basis of calibrated GC data by using hexadecane as an internal standard. [c] 20 h. [d] 36 h.

Although 3 bar of carbon monoxide was found to be the optimal pressure for the transformation (67% yield), it was shown that even an atmospheric pressure of CO enables the formation of the desired product in 62% yield (Table 1, entries 9 and 10).

By extending the reaction time to 36 h, nearly full conversion and a 71% yield of the desired diketone was achieved. We then turned our attention to determining the influence of different ligands on our model system (Table 1, entry 11). The use of triphenylphosphine and tricyclohexylphosphine, simple monodentate phosphines, afforded 53 and 36% yields of the corresponding product, but tri-*tert*-butylphosphonium tetrafluoroborate did not promote the formation of the product (Table 1, entries 12–14).

Since MorDalPhos (**L5**) had shown favourable activity in noncarbonylative α-arylation protocols,[5a,b] this and several structurally related di(1-adamanyl)phosphines (**L1**–**L7**) were also tested; however, rather low yields (10–24%; Table 1, entries 15–21) of the target 1,3-diketone product were obtained. Considering that as electronically different ligands as PPh_3 and *n*BuPAd$_2$ gave similar yields but sterically rather different RPAd$_2$ ligands were significantly less successful, a very specific steric demand seems to be crucial for a selective reaction, especially since the majority of the tested ligands are known to enable oxidative addition and CO insertion of aryl iodides.

Thus, [{Pd(cinnamyl)Cl}$_2$]/*n*BuPAd$_2$ at 60°C by using 3 bar of CO and Cs_2CO_3 as base proved to be the optimal reaction conditions for enabling this transformation (Table 1, entry 11). Notably, in all optimisation reactions, no side products derived either from the noncarbonylative α-arylation or multiple arylation reactions of acetone were detected. However, varying amounts of benzoic acid and benzaldehyde were observed, especially in cases of high conversion but low yield, showing that side reactions involving iodoben-

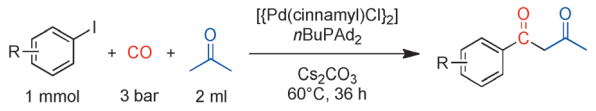
zene are the primary competing pathways that interfere with the formation of the desired 1,3-diketone product.

With optimised reaction conditions established, we turned our focus to the scope of the reaction towards the aryl iodide coupling partner (Table 2). The model reaction with iodobenzene led to the isolation of 1-phenylbutane-1,3-dione in 69% yield (Table 2, entry 1). Similarly, 3- and 4-iodotoluene were converted into the corresponding products in good yields of 68 and 71%, respectively (Table 2, entries 2 and 3). 3,5-Dimethyliodobenzene and 4-*tert*-butyliodobenzene gave slightly lower yields of 54 and 62% (Table 2, entries 4 and 5). The presence of alkoxy substituents on the aryl iodide substrates proved to be detrimental to the coupling process and resulted in decreased yields ranging from 41 to 47% (Table 2, entries 6–9). However, the use of 4-fluoroiodobenzene gave a good yield of 74%, whereas the product of the reaction of 4-chloroiodobenzene was obtained in only 47% yield (Table 2, entries 10 and 11). Hence, the relationship between the nature of the substituent on the aryl ring and the yield is unclear. Additionally, we demonstrated that bicyclic (naphthyl) and heterocyclic (pyridyl, thiophenyl) aryl iodides afforded the desired 1,3-diketone by use of this protocol, albeit in modest yields (41–56%; Table 2, entries 12–15). Attempts to apply other aryl halides under very similar conditions resulted in consistently low (in the case of ArBr) or no (in the case of ArCl) product formation, thus requiring independent comprehensive investigations.

Next, we examined the scope of the reaction towards the ketone coupling partner (Table 3). By using 2-butanone, the corresponding product was isolated in 73% yield (Table 3, entry 1). Acetophenone was also tolerated under these conditions, affording the 1,3-diketone in high yield (Table 3, entry 2). In addition, benzoylation of fluoro- and chloro-substituted acetophenone substrates proceeded smoothly and gave the corresponding products in 71 and 81% yield, respectively (Table 3, entries 3 and 4). Examples containing stronger electron-withdrawing groups, as well as *ortho*-substitution, on the acetophenone moiety proved more challenging in this system, resulting in lower yields of the 1,3-diketones (Table 3, entries 5–7). To our delight, 2-acetylthiophene, a representative heterocyclic substrate, was also converted into the corresponding 1,3-diketone (Table 3, entry 8). As is typically the case for this class of 1,3-diketones, the products were isolated as the ketoenol tautomer, as observed by ^{1}H NMR spectroscopy, although in certain instances the diketone is visible in small amounts.

We were then able to extend this methodology to a one-pot synthesis of aryl-substituted pyrazoles, which are known to have a broad spectrum of biological activities.[12] Several protocols for their synthesis have previously been reported, including the cyclo-condensation of hydrazines with 1,3-dicarbonyl compounds or ethynyl ketones.[13] In addition, we recently described the synthesis of 1,3-substituted pyrazoles by the in situ formation of 1-aryl-3-alkoxy propenones by employing a carbonylative Heck-coupling reaction.[14]

Table 2. Pd-catalysed carbonylative α-arylation of acetone.[a]



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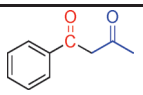
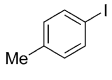
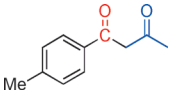
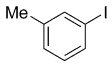
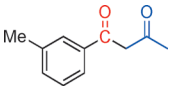
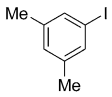
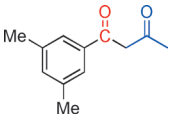
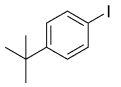
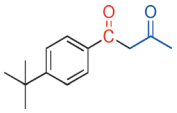
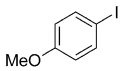
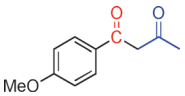
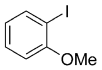
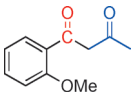
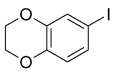
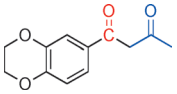
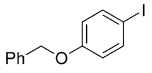
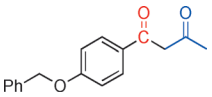
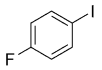
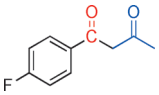
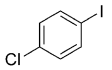
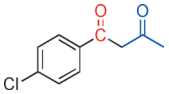
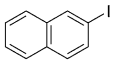
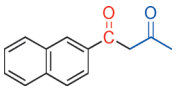
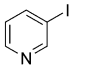
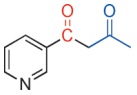
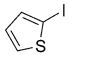
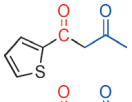
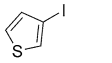
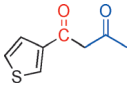
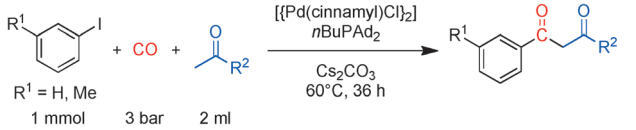
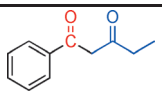
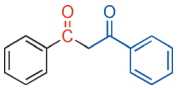
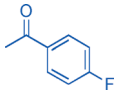
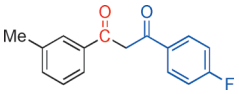
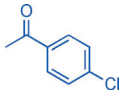
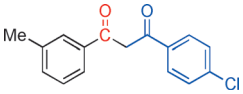
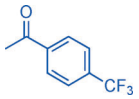
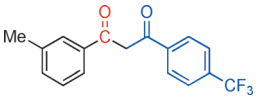
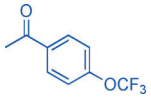
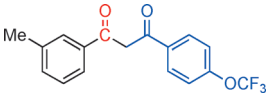
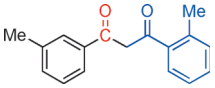
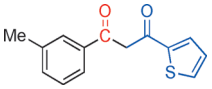
1			69
2			71
3			68
4			54
5			62
6			41
7			45
8			47
9			42
10			74
11			47
12			54
13			48
14			56
15			41

[a] General reaction conditions: aryl iodide (1 mmol), acetone (2 mL), [{Pd(cinnamyl)Cl}$_2$] (1 mol%), *n*BuPAd$_2$ (4 mol%), Cs_2CO_3 (2 mmol), CO (3 bar), 60°C, 36 h. [b] Yields of the isolated products.

Table 3. Pd-catalysed carbonylative α-arylation of ketones.[a]



Entry	Ketone	Product	Yield [%][b]
1			73
2			84
3			71
4			81
5			49
6			51
7			54
8			42

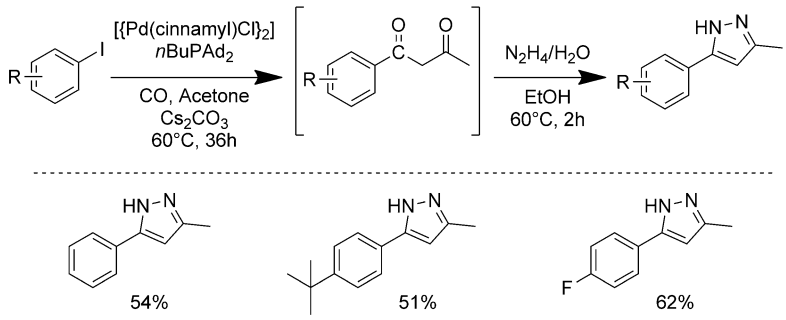
[a] General reaction conditions: aryl iodide (1 mmol), ketone (2 mL), [{Pd(cinnamyl)Cl}$_2$] (1 mol%), *n*BuPAd$_2$ (4 mol%), Cs_2CO_3 (2 mmol), CO (3 bar), 60°C, 36 h. [b] Yields of the isolated products.

Hence, after the palladium-catalysed coupling process was finished, the remaining acetone was removed in vacuo, an aqueous solution of hydrazine and ethanol were added and the reaction mixture was heated at 60°C for an additional 2 h. In general, the corresponding 5-aryl-3-methyl-1*H*-pyrazoles were synthesised in acceptable overall yields (51–62%; Scheme 2).

In conclusion, we have established the first carbonylative α-arylation of acetone, as well as acetophenones. The optimised reaction conditions were applicable to the synthesis of 23 different 1,3-diketones in 41–84% yields in a straightforward manner. Our protocol allows for selective carbonylative α-arylation by using atom-economical CO for the first time and is a valuable extension of the recently published carbonylative α-arylation requiring the prior synthesis of a CO surrogate.[7] Furthermore, the transformation is performed with a simple and commercially available catalyst system at relatively low catalyst loadings. The ketone coupling partner could be used in excess, which eliminates the need for additional solvent. Additionally, based on this coupling process, a one-pot synthesis of 5-aryl-3-methyl-1*H*-pyrazoles has been developed that exploits the usefulness of these 1,3-diketones as building blocks.

Experimental Section

General procedure for the preparation of 1-phenylbutane-1,3-dione: In a glovebox, six glass vials (4 mL) were charged with [{Pd(cinnamyl)Cl$_2$] (1 mol%, 5.2 mg), cataCXium A (4 mol%, 14.3 mg), Cs_2CO_3 (2 mmol, 651.6 mg) and a stirring bar. All vials were put into an alloy plate, sealed with a septum and locked out of the glovebox. The vials were then equipped with an inlet needle and flushed with argon. Acetone (2 mL) and iodobenzene (1 mmol, 112 μL) were injected into each vial. The alloy plate with six vials was then placed in an autoclave (300 mL; Parr Instruments 4560 series). At room temperature, the autoclave was flushed with CO three times and pressurised to 3 bar. Afterwards, the autoclave was heated to 60°C for 36 h, then cooled to room temperature and the remaining CO was released slowly. After discharging, water (0.5 mL) was added to each vial and the product was extracted with ethyl acetate. The aqueous phase was extracted three times. After drying the combined organic phases over magnesium sulphate and evaporating the solvent, the crude product was purified by column chromatography using heptane/ethylacetate (1:0→20:1) to give 1-phenylbutane-1,3-dione as a white solid.



Scheme 2. One-pot synthesis of pyrazoles by (carbonylative) α-arylation of ketones. 1) aryl iodide (1 mmol), acetone (2 mL), [{Pd(cinnamyl)Cl}$_2$] (1 mol%), *n*BuPAd$_2$ (4 mol%), Cs_2CO_3 (2 mmol), CO (3 bar), 60°C, 36 h; 2) N_2H_4 (6 mmol), EtOH (0.5 mL), 60°C, 2 h. Yields of the isolated products.

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Keywords: arylation · diketones · acetone · carbonylation · palladium

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