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Pd-Catalyzed Carbonylative α-Arylation of Aryl Bromides: Scope and Mechanistic Studies

Dennis U. Nielsen,[a] Camille Lescot,[a] Thomas M. Gøgsig,*[a] Anders T. Lindhardt,*[b] and Troels Skrydstrup*[a]

Abstract: Reaction conditions for the three-component synthesis of aryl 1,3-diketones are reported applying the palladium-catalyzed carbonylative α-arylation of ketones with aryl bromides. The optimal conditions were found by using a catalytic system derived from $[Pd(dba)_2]$ (dba = dibenzylideneacetone) as the palladium source and 1,3-bis(diphenylphosphino)propane (DPPP) as the bidentate ligand. These transformations were run in the two-chamber reactor, COware, applying only 1.5 equivalents of carbon monoxide generated from the CO-releasing compound, 9-methylfluorene-9-carbonyl chloride (COgen). The methodology proved adaptable to a wide variety of aryl and heteroaryl bromides leading to a diverse range of aryl 1,3-diketones. A mechanistic investigation of this transformation relying on ^{31}P and ^{13}C NMR spectroscopy was undertaken to determine the possible catalytic pathway. Our results revealed that the combination of $[Pd(dba)_2]$ and DPPP was only reactive towards 4-bromoanisole in the presence of the sodium enolate of propiophenone suggesting that a [Pd(dppp)(enolate)] anion was initially generated before the oxidative-addition step. Subsequent CO insertion into an [Pd(Ar)(dppp)(enolate)] species provided the 1,3-diketone. These results indicate that a catalytic cycle, different from the classical carbonylation mechanism proposed by Heck, is operating. To investigate the effect of the dba ligand, the Pd^0 precursor, $[Pd(\eta^3\text{-}1\text{-}PhC_3H_4)(\eta^5\text{-}C_5H_5)]$, was examined. In the presence of DPPP, and in contrast to $[Pd(dba)_2]$, its oxidative addition with 4-bromoanisole occurred smoothly providing the [PdBr(Ar)(dppp)] complex. After treatment with CO, the acyl complex [Pd(CO)Br(Ar)(dppp)] was generated, however, its treatment with the sodium enolate led exclusively to the acylated enol in high yield. Nevertheless, the carbonylative α-arylation of 4-bromoanisole with either catalytic or stoichiometric $[Pd(\eta^3\text{-}1\text{-}PhC_3H_4)(\eta^5\text{-}C_5H_5)]$ over a short reaction time, led to the 1,3-diketone product. Because none of the acylated enol was detected, this implied that a similar mechanistic pathway is operating as that observed for the same transformation with $[Pd(dba)_2]$ as the Pd source.

Keywords: 1,3-diketones · carbonylation · palladium · reaction mechanisms · synthetic methods

Introduction

The palladium-catalyzed carbonylative coupling between an aryl halide (or a derivatized phenol), with a carbon- or heteroatom-based nucleophile represents a powerful method for the generation of a diverse array of benzoic acid and aryl ketone derivatives. The method has shown high interest because of its high compatibility to a wide variety of functional groups.[1] Nevertheless, there is still a constant strive dedicated to the development of new carbonylative transformations, as well as to the improvement of existing Pd-catalyzed carbonylations, including the identification of milder reaction conditions, alternative substrates, and the use of lower carbon monoxide pressures.[2] A number of research groups have been highly active in this field and have demonstrated great success including those of Beller,[3] Buchwald,[4] and Larhed.[5] Nevertheless, a particular but important drawback when working with this gaseous reagent is its inherent toxicity resulting in asphyxiation upon its inhalation due to the high competitive binding between CO and oxygen to hemoglobin. Hence, there have been some efforts undertaken toward the development of safer alternatives for the handling of this "synthetically" useful diatomic gas, and in this respect a variety of CO-releasing molecules (CORMs) have proven useful.[6]

In 2011, we reported a methodology for the controlled liberation of carbon monoxide by the activation of two crystalline and readily available CORMs, namely 9-methylfluorene-9-carbonyl chloride (COgen) and diphenylmethylsilacarboxylic acid.[7] This controlled CO generation could be

[a] D. U. Nielsen, Dr. C. Lescot, Dr. T. M. Gøgsig, Dr. T. Skrydstrup
Center for Insoluble Protein Structures (inSPIN)
Interdisciplinary Nanoscience Center (iNANO)
Department of Chemistry Aarhus University
Gustav Wieds Vej 14, 8000 Aarhus C (Denmark)
E-mail: ts@chem.au.dk

[b] Dr. A. T. Lindhardt
Interdisciplinary Nanoscience Center (iNANO)
Biological and Chemical Engineering
Department of Engineering, Aarhus University
Finlandsgade 22, 8200 Aarhus N (Denmark)
E-mail: lindhardt@chem.au.dk

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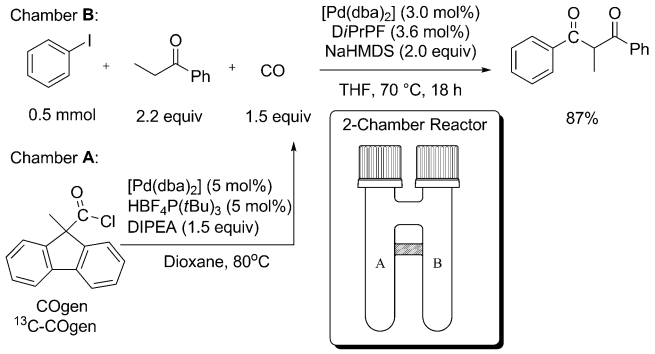
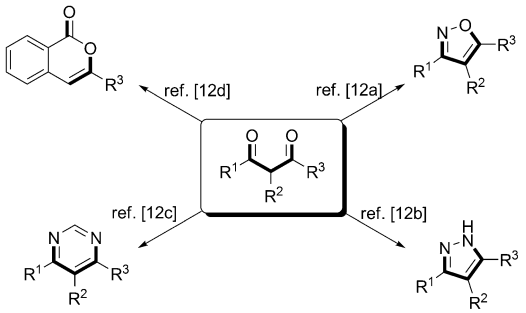
adapted to carbonylation reactions by using a two-chamber reactor (COware), in which CO is generated in the first chamber from one of the two CORMs, and then consumed in the second chamber in an ensuing Pd-catalyzed carbonylation. In particular, we found that the ex situ generation of only stoichiometric amounts of CO was sufficient to provide high coupling yields in a variety of these metal-catalyzed carbonylation reactions, including alkoxy-, amino- and thiocarbonylations, carbonylative Heck, Sonogashira and Suzuki, reductive formylations, and others.[7–9] Furthermore, the method was well-adapted to isotope-labeling studies for the incorporation of ^{13}C- and ^{14}C-carbon isotopes.[9]

By utilizing this strategy, we recently reported on the Pd-catalyzed carbonylative coupling between an aryl ketone and an aryl iodide for the preparation of a number of functionalized aryl 1,3-diketones (Scheme 1).[8f]



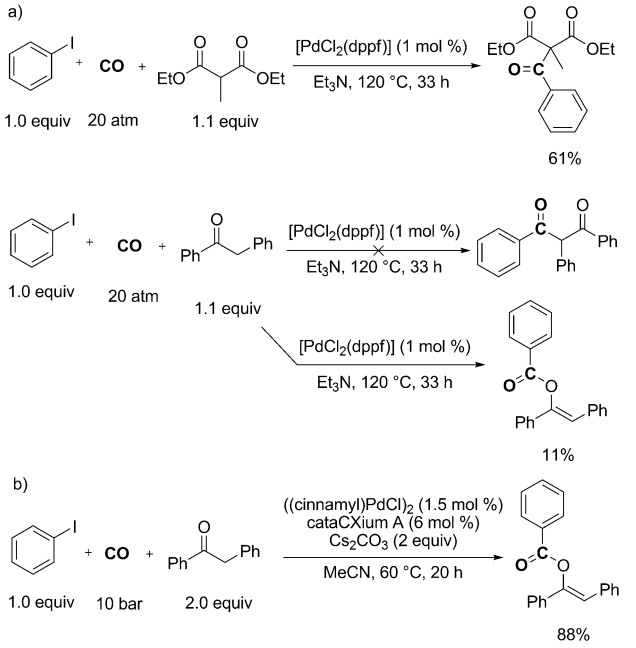
Scheme 1. The Pd-catalyzed carbonylative α-arylation of ketones with aryl iodides.

This transformation represents a carbonylative analogue to the well-established catalytic α-arylation of ketones, esters, amides and other enolizable reagents, pioneered by the groups of Hartwig and Buchwald.[10,11] The general interest in these compounds is underlined by their various transformations alone in 2012 utilizing a 1,3-keto carbonyl derivative for the preparation of heterocyclic systems, such as isoxazoles, pyrazoles, pyrimidines, and isocoumarins, representative examples of which are illustrated in Scheme 2.[12–14]



Scheme 2. Recent synthetic applications of 1,3-diketones.

Furthermore, a number of 1,3-diketones display a variety of biological activities, including antitumor, antioxidant, antimicrobial, antiviral, and antifungal activity.[13a] Of particular interest is the fact that our method is highly adaptable for the ^{13}C-labeling of these biologically important structures. Prior to our work, Tanaka and Kobayashi had successfully identified conditions for the intermolecular carbonylative α-arylation of malonates with aryl iodides (Scheme 3a).[15] However, besides the use of high carbon



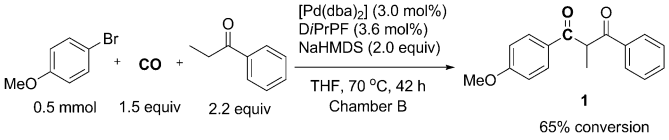
Scheme 3. a) Summary of Tanaka and Kobayashi's previous carbonylative α-arylation studies; b) Beller's synthesis of vinyl benzoates.

monoxide pressures (20 atm), when simple ketones were employed, only the acylated enol was obtained. Beller and co-workers have recently published a general method for the synthesis of such structures from the corresponding aryl iodides and bromides (Scheme 3b).[3t]

In this paper, we report on the successful identification of reaction conditions, which include aryl bromides as viable electrophiles for the Pd-catalyzed synthesis of aryl 1,3-diketones. This work significantly extends the value of this reaction due to the high number of commercially available aryl bromides. Moreover, we have carried out a mechanistic investigation of this Pd-catalyzed transformation by using ^{31}P and ^{13}C NMR spectroscopy to identify the plausible intermediates of the catalytic cycle and hence the pathway that is followed for the generation of these dicarbonyl compounds. Our results suggest that an alternative catalytic cycle to that of the traditional Heck-type mechanism is operating when employing sodium enolates in this palladium-catalyzed carbonylative reaction. Our data imply that a pre-coordination of an enolate to the Pd^0 species takes place prior to the oxidative addition generating an [Pd(Ar)(ligand)(enolate)] complex prior to CO insertion and reductive elimination.

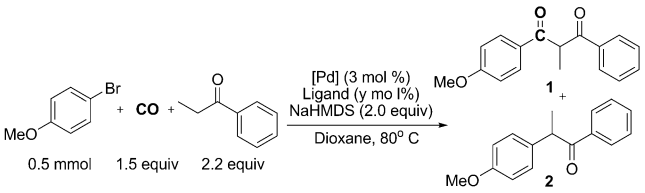
Results and Discussion

Carbonylative coupling with aryl bromides: In our initial report on the Pd-catalyzed carbonylative α-arylation of aryl iodides applying [Pd(dba)$_2$] as the palladium(0) source, 1,1′-bis(diisopropylphosphino)ferrocene (D*i*PrPF) as a bidentate diphosphine ligand, CO (1.5 equiv) and a sodium amide base (2 equiv) in THF, we found that 4-bromoanisole could also be coupled to ethylphenylketone under the same conditions providing the 1-(4-methoxyphenyl)-2-methyl-3-phenylpropane-1,3-dione (**1**). The reaction proved nonetheless to be sluggish and led only to a 65% conversion after a reaction time of 42 h (Scheme 4). Optimization of the reaction parameters was therefore carried out (Table 1). It should be noted that all reactions were run in a two-chamber reactor (COware) as previously described,[7a] and the stoichiometric carbon monoxide used was generated ex situ applying the Pd^0-catalyzed decarbonylation of 9-methylfluorene-9-carbonyl chloride (COgen).[16]



Scheme 4. Preliminary result on the carbonylative α-arylation of an aryl bromide.

Table 1. Optimization of the carbonylative α-arylation with 4-bromoanisole.[a]



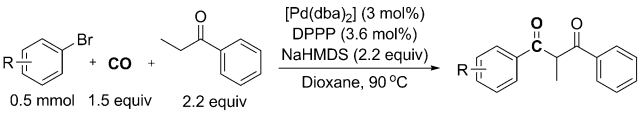
Entry	Pd source	Ligand [(mol%)]	Conv. [%][b]	Ratio [1:2]	Yield [%][c]
1	[Pd(dba)$_2$]	D*i*PrPF (3.6)	100	93:7	73
2	[PdCl$_2$(cod)][d]	D*i*PrPF (3.6)	100	87:13	–
3	[PdCl(cinnamyl)]$_2$	D*i*PrPF (3.6)	100	91:9	67
4	[Pd(OAc)$_2$]	D*i*PrPF (3.6)	100	90:10	50
5	[Pd(dba)$_2$]	DPPF (3.6)	100	86:14	–
6	[Pd(dba)$_2$]	*t*BuPPF (3.6)	100	91:9	–
7	[Pd(dba)$_2$]	D*t*BuPF (3.6)	100	5:95	–
8	[Pd(dba)$_2$]	BINAP (3.6)	100	81:19	–
9	[Pd(dba)$_2$]	Xantphos (3.6)	100	89:11	–
10	[Pd(dba)$_2$]	DPPE (3.6)	50	>95:5	–
11	[Pd(dba)$_2$]	DPPP (3.6)	90	91:9	68
12	[Pd(dba)$_2$]	HBF$_4$P(*t*Bu)$_3$ (7.2)	100	<5:95	–
13	[Pd(dba)$_2$]	CataCXium A (7.2)	100	36:64	–
14[e,f]	[Pd(dba)$_2$]	DPPP (3.6)	100	>95:5	79

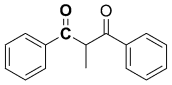
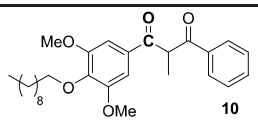
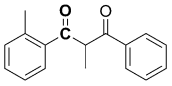
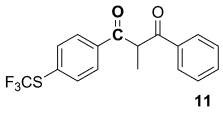
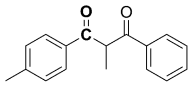
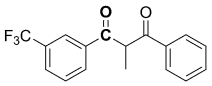
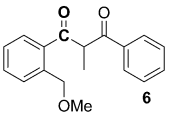
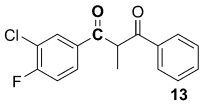
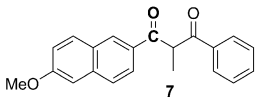
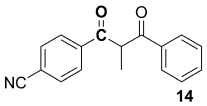
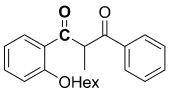
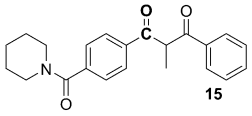
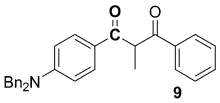
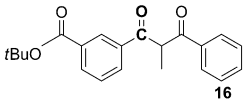
[a] General conditions: Chamber A: COgen[16] (182 mg, 0.75 mmol), [Pd(dba)$_2$] (4.3 mg, 1 mol%), HBF$_4$P(*t*Bu)$_3$ (2.2 mg, 1 mol%), DIPEA (195 μL, 1.5 equiv), and dioxane (3 mL). Chamber B: 4-bromoanisole (93.5 mg, 0.5 mmol), Pd^0 or Pd^{II}, ligand, NaHMDS (183 mg, 2.0 equiv), propiophenone (148 mg, 2.2 equiv), and dioxane (3 mL). Reaction time: 17 h. [b] Determined by ^{1}H NMR spectroscopic analysis. [c] Yield of the isolated product. [d] cod = 1,5-cyclooctadiene. [e] NaHMDS (202 mg, 2.2 equiv). [f] Reaction temperature increased to 90 °C.

Two products were observed during the optimization; the desired 1,3-diketone **1** and the direct coupling product **2**. Applying the same reaction conditions as for the aryl iodides, albeit increasing the reaction temperature to 80 °C and exchanging the solvent from THF (b.p. = 66 °C) to a higher boiling solvent such as dioxane (b.p. = 101 °C), resulted in full conversion and a good 93:7 selectivity for carbonylation over direct coupling. This led to the isolation of diketone **1** in a 73% yield (Table 1, entry 1). Variation of the palladium source did not improve the selectivity (Table 1, entries 2–4). Applying different phosphinoferrocene-based ligands gave similar product selectivities (Table 1, entries 5 and 6), whereas with D*t*BuPF instead of D*i*PrPF, this resulted in almost complete inversion of the product selectivity with a preference for compound **2** (entry 7). Hartwig and co-workers have previously reported the use of this more sterically encumbered ligand in α-arylations.[10f] Other diphosphine ligands such as BINAP and Xantphos proved inferior to D*i*PrPF also with respect to the product preference (Table 1, entries 8 and 9). On the other hand, with 1,2-bis(diphenylphosphino)ethane (DPPE) as the ligand, the reaction proved to be much cleaner than for the corresponding reaction with D*i*PrPF (Table 1, entry 10). Only the desired product **1** was formed, although the conversion was low. Exchanging DPPE for 1,3-bis(diphenylphosphino)propane (DPPP), which has a slightly larger bite-angle,[17] led to a modest drop in the selectivity for carbonylative α-arylation, but greatly improved the conversion, and a 68% yield of the diketone **1** could be isolated after column chromatography (Table 1, entry 11). This selectivity and the conversion could be improved by slightly increasing the number of equivalents of sodium bis(trimethylsilyl)amide (NaHMDS) to match that of propiophenone and elevating the reaction temperature to 90 °C. In this way, compound **1** could be isolated in 79% yield (Table 1, entry 14). Exploring the possibility of using bulky monodentate phosphine ligands such as cataCXium A and P(*t*Bu)$_3$ favored the undesired product **2** (Table 1, entries 12 and 13).[10f]

With the appropriate conditions in hand for the carbonylative α-arylations of 4-bromoanisole, we next turned to examine the feasibility of these reaction conditions in the carbonylative coupling of propiophenone with other aryl bromides (Table 2). Bromobenzene worked well providing the symmetrical diketone **3** in a 78% yield (Table 2, entry 1). The *ortho*-substituents were well tolerated and good coupling yields were obtained as illustrated with compounds **4**, **6**, and **8**. Aryl bromides carrying electron-donating groups coupled smoothly, and the corresponding 1,3-diketones could in general be isolated in high yields (**4**–**10**), but with a (*S*)-trifluoromethylsulfide group in the *para* position, as with **11**, only a modest yield could be secured. Applying aryl bromides bearing electron-withdrawing groups proved successful (**12**–**16**), and the presence of a chloride was even

Table 2. The carbonylative α-arylation of aryl bromides with propiophenone.[a]



Entry	Product	Yield[b] [%]	Entry	Product	Yield[b] [%]
1	 **3**	78	8	 **10**	72
2	 **4**	77	9	 **11**	46
3	 **5**	86	10	 **12**	77
4	 **6**	64	11	 **13**	76
5	 **7**	75	12	 **14**	35
6	 **8**	89	13	 **15**	68
7	 **9**	75	14	 **16**	60

[a] General conditions: Chamber A: COgen[16] (182 mg, 0.75 mmol), $[Pd(dba)_2]$ (4.3 mg, 1 mol%), $HBF_4P(tBu)_3$ (2.2 mg, 1 mol%), DIPEA (195 μL, 1.5 equiv), and dioxane (3 mL). Chamber B: Aryl bromide (0.5 mmol), $[Pd(dba)_2]$ (8.6 mg, 3 mol%), DPPP (7.4 mg, 3 mol%), NaHMDS (202 mg, 2.2 equiv), propiophenone (145 mg, 2.2 equiv), and dioxane (3 mL). Reaction time: 17 h. [b] Yield of the isolated product.

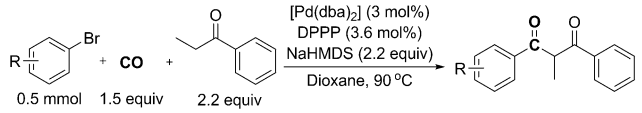
inert to these carbonylative coupling conditions as shown for product **13**. However, considerable byproducts were observed in the coupling of 4-cyanophenyl bromide (Table 2, entry 12), which explains the low carbonylative coupling yield obtained for the diketone **14**.

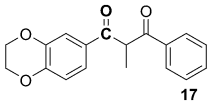
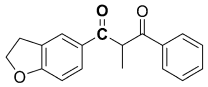
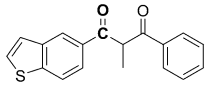
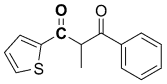
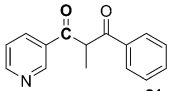
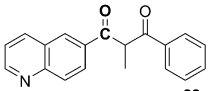
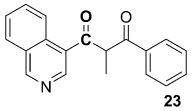
As shown in Table 3, different heterocyclic aryl bromides could also be applied to give the corresponding 1-heteroaryl-2-phenyl-1,3-diketones. Oxygen-based heterocycles, such as 6-bromo-2,3-dihydrobenzo[*b*][1,4]dioxine and 5-bromo-2,3-dihydrobenzofuran, coupled well providing **17** and **18**, respectively, in good yields. Sulfur-containing ring systems, represented by a 5-bromobenzo[*b*]thiophene and 2-bromothiophene, were also adaptable to the coupling conditions, leading to **19** and **20**, respectively, although **20** was isolated in a low yield due to competition with the direct coupling pathway. Finally, applying the pyridine, quinolone, and isoquinoline skeleton, the corresponding 1,3-diketones (**21**–**23**, respectively) could be isolated in reasonable yields.

A few ketones were then tested to investigate the structural influence of this coupling partner on the efficiency of the carbonylative coupling with an aryl bromide (Scheme 5). As with propiophenone, its homologues, butyrophenone and butyrothiophenone, also provided good coupling yields of the corresponding 1,3-diketones **24** and **25**, respectively. Even aliphatic ketones such as 2-methyl-3-heptanone, 3-pentanone, and methyl adamantyl ketone proved feasible for the carbonylative α-arylations (**26**–**28**). On the other hand, increasing the sterical bulk on the β-carbon of the ketone such as with 3-methyl-1-phenylbutan-1-one and 1,2-diphenylethanone proved detrimental for 1,3-diketone formation (results not shown). Employing acetophenone led to **29** being isolated in a low yield of only 15%.[3y] This could be explained by the simultaneous formation of different byproducts related to the higher reactivity of the corresponding less sterically encumbered sodium enolate.

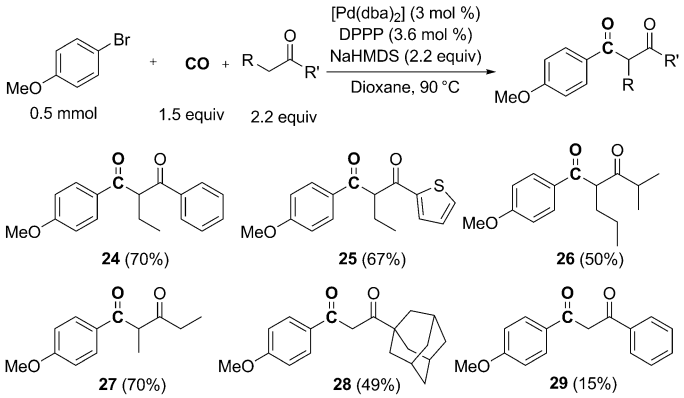
Mechanistic investigations: Having identified reaction conditions that include aryl bromides in the repertoire for the Pd-catalyzed carbonylative α-arylation of ketones, a mechanistic study was undertaken in an attempt to understand the

Table 3. The carbonylative α-arylation of heterocyclic bromides with propiophenone.[a]



Entry	Product	Yield[b] [%]
1	 **17**	72
2	 **18**	80
3	 **19**	70
4	 **20**	36
5	 **21**	44
6	 **22**	63
7	 **23**	70

[a] For general conditions, see Table 2. [b] Isolated Yields.

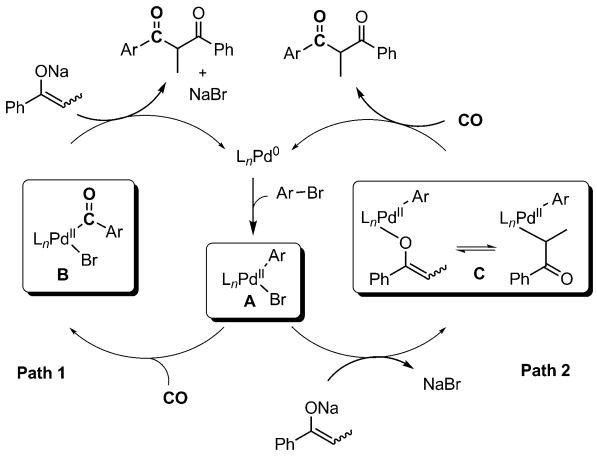


Scheme 5. The carbonylative α-arylation of 4-bromoanisole with ketones.

nature of the intermediates in the catalytic cycle of this transformation. The generally accepted mechanism for Pd-catalyzed carbonylation reactions involving an aryl halide and a nucleophile consists of three principle steps.[18] First, oxidative addition of the aryl halide followed by CO coordination and insertion generates an acylpalladium(II) complex. Depending on the reactivity of the nucleophile, this reagent can either participate directly by nucleophilic acyl substitution with the acyl-Pd^{II} complex to generate the product and Pd^0, or by exchange with the leaving group on the metal center and a subsequent reductive elimination step.

Recently, Lei and co-workers reported kinetic evidence for an alternative mechanism when studying the palladium-catalyzed alkoxycarbonylation of aryl iodides with sodium alkoxides instead of the corresponding alcohols in the presence of a secondary or tertiary amine base.[19] The catalytic cycle for these carbonylations proceeds through an initial oxidative addition with the aryl iodide and then halide–alkoxide exchange on the resulting arylpalladium(II) complex to generate an [Pd(Ar)(OR)] species. This is followed by CO insertion into the Pd–O bond, and finally reductive elimination of the intermediate [Pd(Ar)(COOR)] to generate ArCOOR. Considering the use of preformed sodium enolates in our Pd-catalyzed carbonylative α-arylation protocol, we speculated whether the Lei mechanism could be operating as well for this catalytic transformation.

The two hypothetical pathways for the carbonylative α-arylation of ketones are illustrated in Scheme 6. Path 1 represents the classical Heck mechanism involving initial oxidative addition of the aryl bromide followed by CO insertion



Scheme 6. Two different pathways considered for the carbonylative α-arylation of ketones.

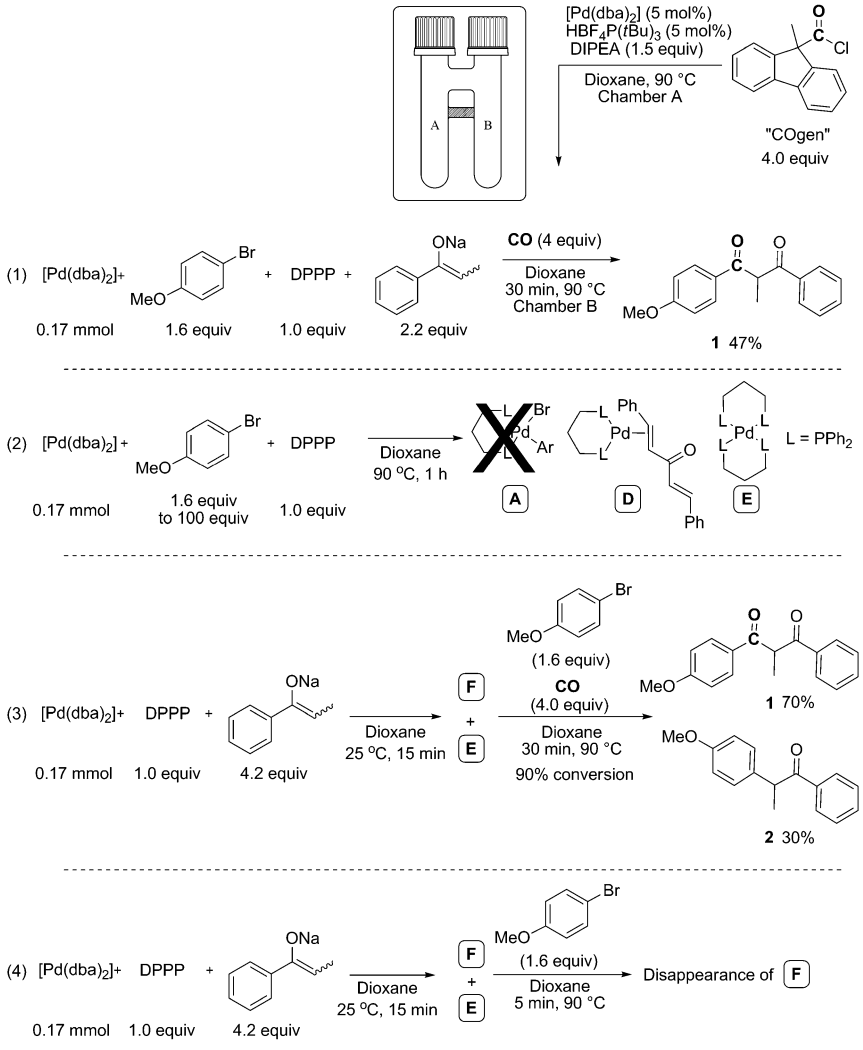
to form the benzoylpalladium(II) complex **B**. Ligation of the enolate to the Pd^{II}-center followed by reductive elimination or direct nucleophilic acyl substitution would then lead to 1,3-diketone formation. The other possibility (Path 2), inspired by the work of Lei and co-workers, involves the ligation of the enolate first to complex **A**, leading to intermediate **C** as either the C- or O-bound-Pd^{II} complex. Subsequent CO insertion and reductive elimination provides the desired product.

The earlier screening studies revealed that among the different metal sources examined, [Pd(dba)$_2$] (dba = dibenzylideneacetone) was found to be the most effective for the catalytic reaction; hence, stoichiometric experiments with [Pd(dba)$_2$] were conducted for the carbonylative coupling of propiophenone with 4-bromoanisole, with the objective of identifying the intermediate complexes involved. Initially, [Pd(dba)$_2$] was subjected to 1 equivalent of DPPP, 1.6 equivalents of 4-bromoanisole and 2.2 equivalents of the sodium enolate of propiophenone in the two-chamber system with 4.0 equivalents of CO ([Eq. (1)], Scheme 7). This reaction was performed to ascertain if the diketone could be generated from the stoichiometric reaction. Indeed, after 30 min at 90 °C followed by a work up, the diketone **1** could be isolated in a 47 % yield.[20,21]

Efforts were then concentrated on isolating the oxidative-addition complex **A**, which is the common denominator for the two different pathways. Earlier, Amatore and Jutand studied the rates and mechanism of the palladium species generated in situ from mixtures of [Pd(dba)$_2$] and bidentate phosphine ligands in the oxidative-addition process. They described that the palladium(0) complexes [Pd(dba)(dppp)] (**D**) and [Pd(dppp)$_2$] (**E**) were obtained from the addition of 1 equivalent of the diphosphine ligand to [Pd(dba)$_2$],[22] and furthermore determined that **D** is the active complex for oxidative addition to phenyl iodide, whereas complex **E** is inactive. When [Pd(dba)$_2$], DPPP, and 4-bromoanisole were stirred at 90 °C for 1 h in dioxane ([Eq. (2)], Scheme 7), and the reaction mixture was analyzed by ^{31}P NMR spectroscopy, the product of oxidative addition, complex **A**, could not be observed by NMR spectroscopy, even after increasing the aryl bromide addition to 100 equivalents.[23] Instead, two broad signals at $\delta = 13.4$ and 8.6 ppm of equal integration were observed along with a singlet at $\delta = 4.1$ ppm (Figure 1, top spectrum). These signals correspond well to those of the ^{31}P NMR spectrum of the nonsymmetrical Pd^0 species **D** and the symmetrical complex **E**, respectively, reported earlier by Amatore and Jutand in THF.[22,24]

Although no oxidative addition was observed for 4-bromoanisole, this process nevertheless occurs under catalytic, as well as the stoichiometric conditions, in the presence of all reagents. Hence, the influence of the presence of the sodium enolate for the oxidative addition was investigated. As shown in Equation (3) in Scheme 7, the sodium enolate of propiophenone was introduced together with [Pd(dba)$_2$] and DPPP in dioxane, and the solution was analyzed by ^{31}P NMR spectroscopy after 15 min at 25 °C (Figure 1, bottom spectrum). Whereas the [Pd(dba)(dppp)] signals had disappeared, two new signals were observed at $\delta = 11.5$ and 8.9 ppm corresponding to a new nonsymmetrical palladium complex **F**. On the other hand, the singlet for [Pd(dppp)$_2$] remained at $\delta = 4.1$ ppm. The aryl bromide and subsequently CO were introduced to this new species **F**, and the reaction mixture was heated to 90 °C for 30 min. Diketone **1** and ketone **2** were produced in a 7:3 ratio with a 90 % conversion according to the ^{1}H NMR spectral analysis of the crude product mixture.

This experiment suggests that the enolate is required to generate an active Pd^0 species capable of undergoing fast oxidative



Scheme 7. Stoichiometric studies applying [Pd(dba)$_2$] for the carbonylative α-arylation of propiophenone.

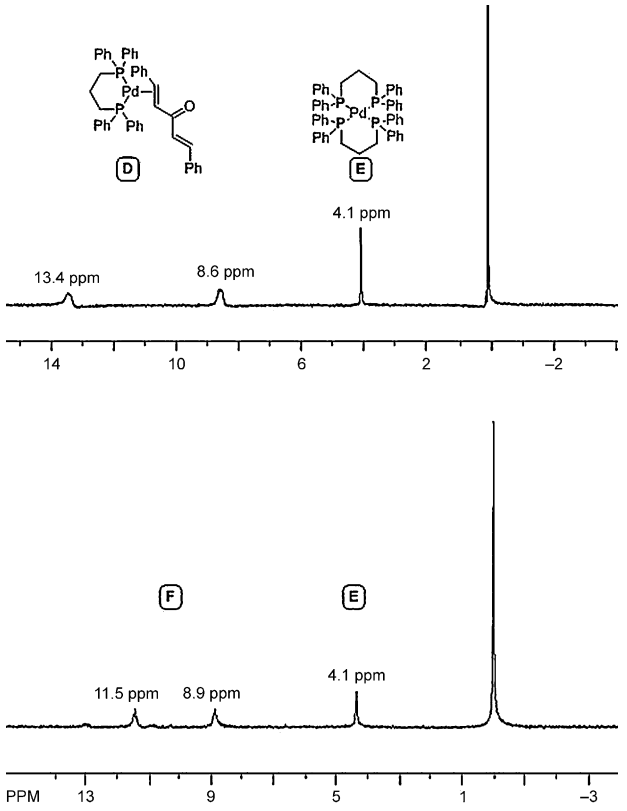


Figure 1. ^{31}P NMR spectra of the palladium(0) species **D**, **E**, and **F**.

addition with 4-bromoanisole. We propose that **F** is an anionic Pd^0 complex of the corresponding enolate in equilibrium between the O bond- and the C bond-forms of the complex (Figure 2).

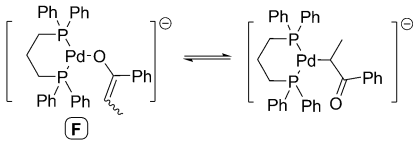


Figure 2. Proposed structure for intermediate **F**.

That complex **F** is more active towards oxidative addition with 4-bromoanisole than the corresponding neutral complex **D**is coherent with earlier results reported by Amatore and Jutand in their work on deciphering the role and positive effects of halide ion or acetate addition on the rates of oxidative addition of low ligated Pd^0 complexes with phenyl iodide.[25] In this work, anionic Pd^0 complexes, formed from halide or acetate coordination to Pd^0, were identified and found to be more reactive towards oxidative addition with aryl halides than their equivalent neutral species.

The same experiment was repeated without the addition of carbon monoxide, to characterize the oxidative-addition product generated from the reaction of 4-bromoanisole with the intermediate **F** ([Eq. (4)], Scheme 7). After addition of 4-bromoanisole to **F**, the reaction mixture was heated to 90 °C for 5 min. Although we observed the disappearance of **F** in the ^{31}P NMR spectrum, we were not able to characterize other species in the spectrum implying that the product of oxidative addition is not stable. Temperature variation experiments were also conducted to follow the transformation of **F** into the oxidative-addition complex by using NMR spectroscopy. The ^{31}P NMR spectra were recorded with 5 °C intervals in range of 25 to 90 °C. Again, no clear signals were observed at the intervals between 25–60 °C and the peaks corresponding to complex **F** were still detectable. Increasing the temperature beyond this point resulted in a poorly defined spectrum with only the $[Pd(dppp)_2]$ complex remaining at 80 °C according to the ^{31}P NMR spectrum. Nevertheless, the oxidative addition had occurred because the crude ^{1}H NMR spectrum of the sample showed the formation of the direct coupling product **2** (results not shown).

We then attempted to employ the sodium enolate derived from acetophenone because of its potentially higher reactivity compared with propiophenone and therefore its ability to form the oxidative-addition complex at lower reaction temperatures. A similar temperature variation experiment was conducted from 25 to 60 °C (Figure 3). Gratifyingly, a smooth transition was observed for the complex [Pd(dppp)(enolate)] (**F′**) present at 25 °C into a new species **G′**, which was completed at 60 °C. Complex **G′** appeared to be stable and after recooling to 25 °C another ^{31}P NMR spec-

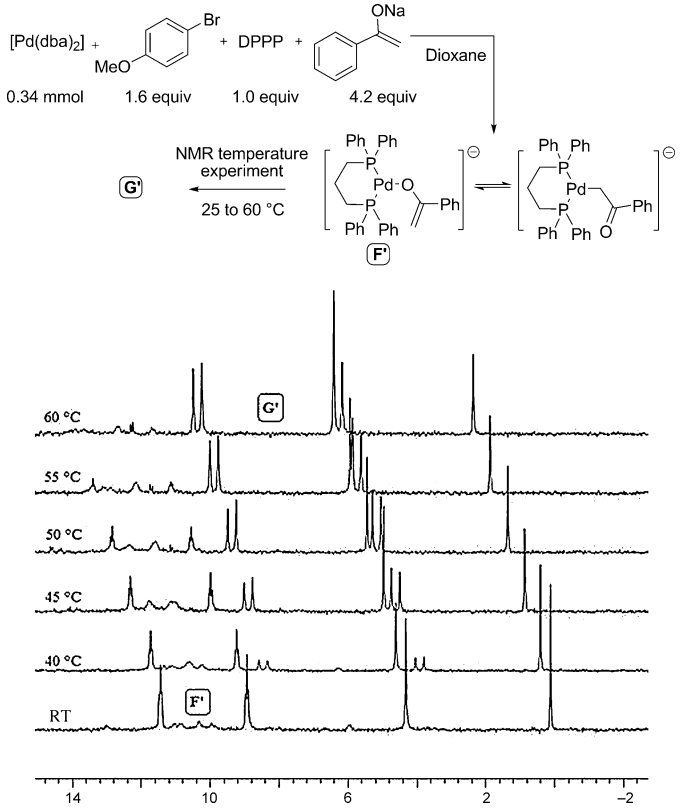


Figure 3. ^{31}P NMR temperature experiment using an acetophenone-derived enolate.

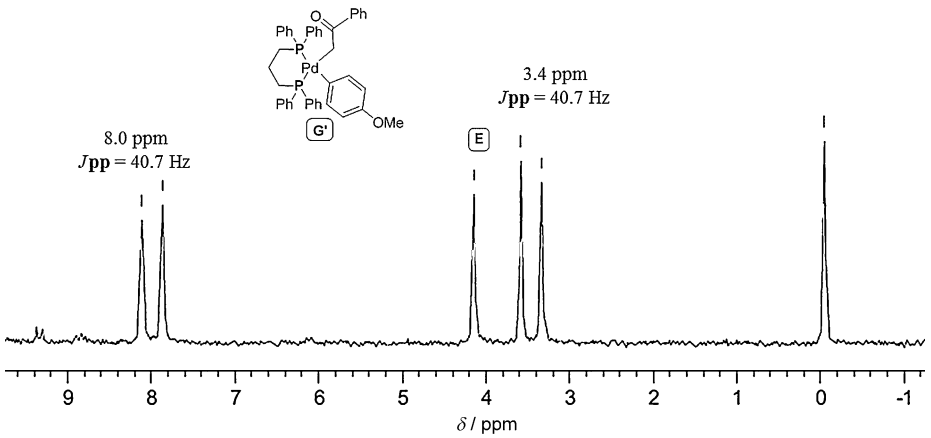
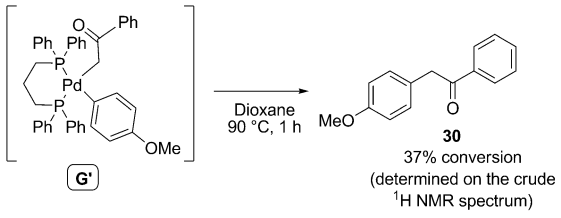


Figure 4. ^{31}P NMR of complex **G′** at 25 °C.

trum was recorded (Figure 4). As well as the singlet corresponding to the non-reactive complex **E**, two doublets were observed at $\delta = 8.0$ and 3.4 ppm with an identical P,P coupling constant of 40.7 Hz. The structure of this complex was attributed to the arylpalladium enolate species **G′** ligated with DPPP (Figure 4). This structure with a C-bound enolate is in accord to that previously published by the group of Hartwig in their study on the reductive elimination of similar arylpalladium enolate complexes with the bidentate phosphine ligand 1,2-bis(diphenylphosphino)benzene.[10n] In this work, the C-bound complex is preferred over the O-bound complex for the enolate derived from acetophenone.

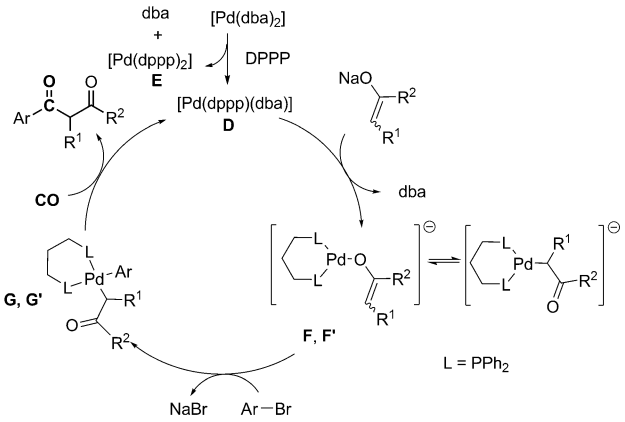
Heating complex **G′** for 1 h at 90 °C resulted in the formation of the direct coupling product **30**, although the conversion yield was not exceptional (Scheme 8). Adding ^{13}CO to



Scheme 8. Reductive elimination studies with complex **G′**.

complex **G′** led to a variety of different ^{13}CO-containing products observed in the ^{13}C NMR spectrum of the crude reaction. Nevertheless, it was pleasing to see that a signal at $\delta = 186.3$ ppm resulting from the ^{13}C-isotopically labeled 1,3-diketone **29** could be detected. Whether the acylpalladium complex is too reactive and results in decomposition or undergoes attack with the excess of enolate, is not clear. Nevertheless, it is interesting to note that for the catalytic carbonylative α-arylation of 4-bromoanisole with acetophenone, our best yield of the diketone **29** for this reaction was only 15% (Scheme 5).

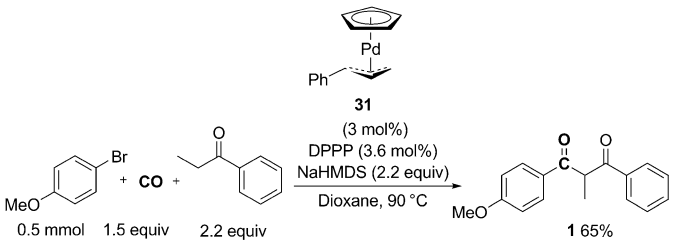
Although our studies on carbonylative α-arylation with [Pd(dba)$_2$] did not reveal the nature of the Pd-acyl complex in the catalytic cycle, these stoichiometric experiments did point to the importance of a possible Pd^0 anion with a bound enolate, necessary for promoting the oxidative addition to 4-bromoanisole. A catalytic cycle taking this observation into consideration is illustrated in Scheme 9.



Scheme 9. Catalytic cycle proposed with [Pd(dba)$_2$].

To examine whether this mechanistic pathway was confined only to carbonylative α-arylations using [Pd(dba)$_2$] as the palladium source, we repeated the aforementioned experiments with a DBA-free palladium(0) precursor. In this respect, we chose [Pd(η^3-1-PhC$_3$H$_4$)(η^5-C$_5$H$_5$)] (**31**) recently introduced by Baird.[26] This air-stable complex was shown, upon addition of a wide variety of mono- and bidentate tertiary phosphines, to rapidly and conveniently generate near quantitative yields of the corresponding bis(phosphine) Pd^0 complexes. First, the ability of this complex as an appropriate Pd source for the catalytic transformation was examined. Hence, treatment of the aryl bromide with 2.2 equivalents of the preformed sodium enolate of propiophenone in the presence of 1.5 equivalents of carbon monoxide, complex **31** and DPPP provided an acceptable yield (65%) of the diketone **1** (Scheme 10).

As in the studies with [Pd(dba)$_2$], a stoichiometric experiment was performed with propiophenone and 4-bromoanisole as shown in [Eq. (1)], Scheme 11. This furnished diketone **1**, isolated in 25% yield, as well as 15% of the direct coupling product **2**. In an attempt to identify the oxidative-addition complex **A**, complex **31** was mixed with one equivalent of DPPP and 1.6 equivalents of 4-bromoanisole in dioxane at 90 °C for 5 min ([Eq. (2)], Scheme 11). In contrast

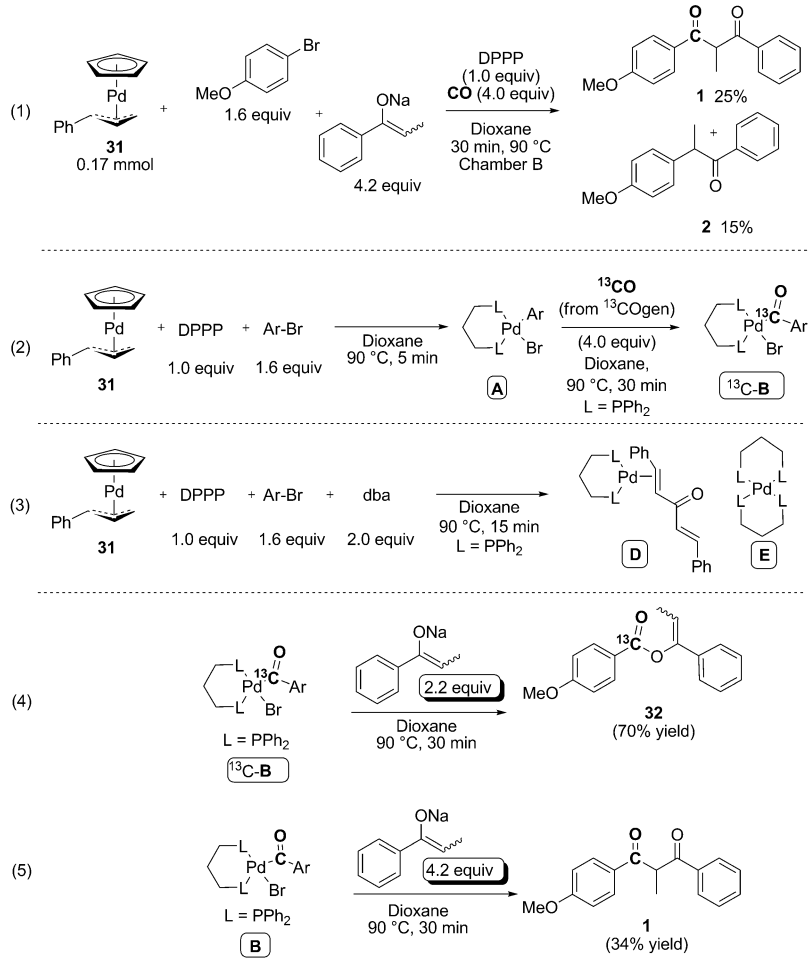


Scheme 10. Application of complex **31** as a Pd^0 precursor in the catalytic carbonylative α-arylation of propiophenone.

to the non-reactivity of the $[Pd(dba)_2]$/DPPP combination with 4-bromoanisole, in this case a fast transformation to a new species was observed after 5 min at 90 °C. The ^{31}P NMR spectrum displayed two doublets at $\delta = 11.6$ and -13.1 ppm with a coupling constant of 51 Hz (Figure 5). This data matches those reported by Jutand and co-workers for similar complexes,[22] and hence the structure of this new Pd species was assigned to complex **A**. The chemical shifts of the two doublets in the ^{31}P NMR spectrum of complex **A** are quite different from the oxidative-addition product bearing the enolate as observed for complex **G′** (Figure 4). This observation confirms that the structure of complex **G′** is not the [PdBr(Ar)(dppp)] complex (**A**) arising from the displacement of the Pd-bound enolate with bromide after oxidative addition. Pleasingly, when the same complex **A** was subjected to ^{13}CO and allowed to react for 30 min at 90 °C, the resulting benzoylpalladium(II) complex **B** was formed. This complex was assigned by ^{31}P and ^{13}C NMR spectroscopy (Figure 6). The ^{31}P NMR spectrum revealed two sets of double doublets at $\delta = 9.6$ and -10.3 ppm, with a P,P coupling constant of 72 Hz, a *cis*-P,C coupling constant of 17 Hz, and a *trans*-P,C coupling constant of 129 Hz. For the ^{13}C NMR spectrum, only a double doublet at $\delta = 232.0$ ppm was observed corresponding to the carbonyl shift, with a *cis*- and *trans*-C,P coupling constant of 17 and 129 Hz, respectively.

To study the possible negative influence of the presence of the DBA ligand on the oxidative-addition step, an experiment was performed in which complex **31**, DPPP (1 equiv), and 4-bromoanisole (1.6 equiv) were mixed together with two equivalents of DBA at 90 °C in dioxane for 10 min ([Eq. (3)], Scheme 11). According to the ^{31}P NMR spectrum of the reaction mixture, this resulted in the formation of the Pd^0 complexes **D** and **E** as earlier observed with $[Pd(dba)_2]$. Again, no oxidative-addition product **A** was observed, implying that the complexes **D** and **E** are rapidly formed preventing the oxidative-addition step.

With the ability to generate the acyl-Pd^{II} complex **B**, we subjected this organometallic species to 2.2 equivalents of the sodium enolate of propiophenone ([Eq. (4)], Scheme 11). Strikingly, after heating at 90 °C for 30 min and after work up, the 1,3-diketone **1** was not observed, but rather the vinyl benzoate **32** in a good (70 %) yield. No trace of compound **1** could be detected in the crude product mixture upon ^1H NMR analysis. The vinyl benzoate was undoubtedly formed by an alkoxycarbonylation mechanism with the sodium enolate, either by direct attack of the oxygen nucleophile to the acyl carbonyl of complex **B** or through reductive elimination of an intermediate acyl-Pd complex with an O-bound enolate. This result is interesting in light of the outcome from the Pd-catalyzed carbonylative α-arylation of propiophenone and 4-bromoanisole promoted by the metal



Scheme 11. Stoichiometric studies applying complex **31** for the carbonylative α-arylation of propiophenone.

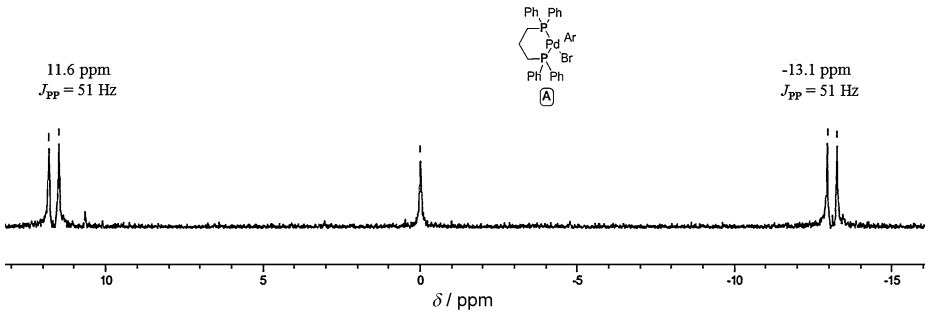


Figure 5. ^{31}P NMR spectrum of complex **A**[a].

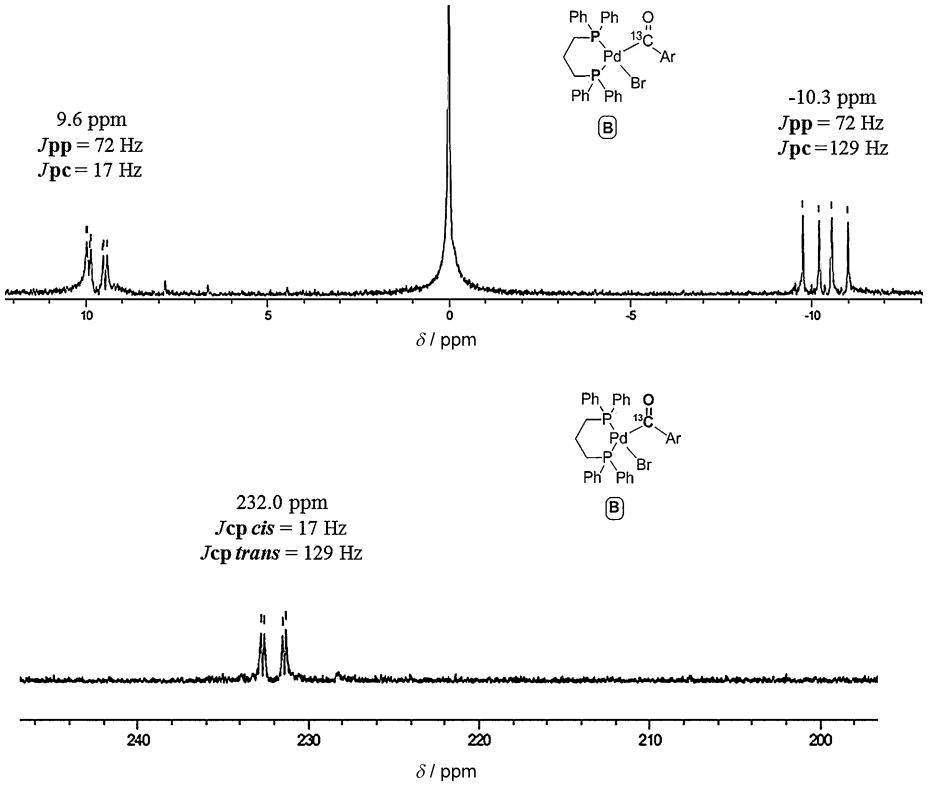


Figure 6. a) ^{31}P NMR spectrum of **B** with H_3PO_4 in $CDCl_3$ using H_3PO_4 as external standard. b) ^{13}C NMR spectrum of complex **B** in $CDCl_3$, ^{13}CO signal.

complex **31**, generating exclusively the diketone **1** in a 65% yield. We hypothesized therefore that the formation of **1** could result from the reaction of vinyl benzoate **32** with excess enolate as would be the situation in the catalytic reaction. Repeating the same experiment with 4.2 equivalents of enolate, as shown in Scheme 11 [Eq. (5)], led to full conversion after 30 min at 90 °C and only provided diketone **1** in a 34% yield. Furthermore, subjecting the vinyl benzoate to 1.0 equivalent of the sodium enolate of propiophenone overnight at 90 °C in dioxane led to full conversion to the 1,3-diketone according to the ^{1}H NMR spectrum of the crude product mixture (result not shown).

Although we prepare the vinyl benzoate in the stoichiometric reactions of the preformed acyl complex **31**, and this product can be converted to the desired diketone with excess enolate, it is not apparent that this is the mechanism operating under our catalytic conditions in which the enolate is present from the start. Furthermore, when 4-bromoanisole, DPPP and 2.2 equivalents of enolate are added at the same time together with the complex **31**, and the mixture is submitted to CO for only 10 min at 90 °C, a trace amount of the diketone **1** was observed in the crude ^{1}H NMR spectrum as indicated by the signals at $\delta = 5.20$ ppm (quartet) from the single α-carbon proton, and at $\delta = 1.59$ ppm (doublet) from the methyl group. No trace of vinyl benzoate **32** displaying among other signals at $\delta = 6.01$ or 1.76 ppm could be detected. With this in consideration including the results from the above experiment, which led to the vinyl benzoate **32** in good yield from the treatment of 2.2 equivalents of enolate with the acyl-Pd^{II} complex (^{13}C–**B** in [Eq. (4)], Scheme 11), these observations tend to lean towards the absence of a mechanism involving the formation of complex **B**, and instead a mechanism in which the 1,3-diketone is formed directly from a catalytic cycle as proposed in the case of [Pd(dba)$_2$]. Further studies must be performed to provide convincing evidence of this proposal, but the above results do reveal the potential pitfalls of the premature assignment of an intermediate in the catalytic cycle and thereby a possible description of an incorrect catalytic cycle.

Conclusion

We have identified reaction conditions for the three-component synthesis of aryl 1,3-diketones from the palladium-catalyzed carbonylative α-arylation of ketones with aryl bromides applying a catalytic system generated from [Pd(dba)$_2$] and the bidentate ligand DPPP. Notably, with this approach is the ability to run these reactions in the presence of only stoichiometric amounts of carbon monoxide generated from

COgen in the two-chamber reactor, COware. The methodology proved adaptable to a wide variety of aryl bromides exposing either electron-donating or -withdrawing substituents, including a number of heteroaryl bromides for accessing a diverse range of aryl 1,3-diketones. To provide mechanistic information of the catalytic cycle, ^{31}P and ^{13}C NMR spectroscopic analysis of a series of reactions with stoichiometric palladium complexes was undertaken. Our results indicated that a catalytic cycle is operating that is different from the classical carbonylation mechanism proposed by Heck, and which involves the initial formation of a Pd^0 anion with a C- or O-bound enolate. Subsequent oxidative addition into the aryl-halide bond to generate an aryl- and enolate-bound Pd^{II} complex, followed by CO insertion and reductive elimination generates the desired product. Further work is underway to understand the mechanistic pathway of alternative carbonylative enolate reactions that are being developed in this group.

Experimental Section

General procedure for the formation of 1,3-diketones

1-(4-Methoxyphenyl)-2-methyl-3-phenylpropane-1,3-dione (**1**): Chamber A: NaHMDS (202 mg, 1.10 mmol, 2.2 equiv) was weighed out in a glass vial (4 mL) and dissolved in dioxane (1 mL). Propiophenone (148 mg, 1.10 mmol, 2.2 equiv) dissolved in dioxane (1.0 mL) was added drop-wise to the NaHMDS solution and the reaction was stirred for 1 hour at room temperature. The solution was added to chamber A of the two-chamber system containing 1-bromo-4-methoxybenzene (93.5 mg, 0.50 mmol), DPPP (7.4 mg, 0.018 mmol, 3.6 mol%) and [Pd(dba)$_2$] (8.6 mg, 0.015 mmol, 3 mol%) in dioxane (1.0 mL). The chamber was fitted with a Teflon-sealed screwcap.

Chamber B: 9-Methylfluorene-9-carbonyl chloride (COgen; 182 mg, 0.750 mmol, 1.0 equiv), [Pd(dba)$_2$] (4.3 mg, 0.00750 mmol, 1.0 mol%), and $HBF_4P(tBu)_3$ (2.2 mg, 0.00750 mmol, 1.0 mol%) were added to chamber B of the two-chamber system and then dissolved in dioxane (3 mL). Diisopropylethylamine (DIPEA, 195 μL, 1.13 mmol, 1.5 equiv) was added as the final reagent and the chamber was fitted with a Teflon-sealed screw-cap.

The two-chamber system was heated at 90 °C for 17 h. The crude mixture was quenched with 1 M HCl (1.3 mL), extracted with CH_2Cl_2 (3×20 mL), dried over Na_2SO_4, concentrated in vacuo and purified by flash column chromatography eluting with pentane/CH_2Cl_2/Et_2O (2:1:3%) affording 106.6 mg (79% yield) of **1** as an yellow oil. ^1H NMR (400 MHz, [D$_1$]$CHCl_3$): $\delta = 7.95$ (d, $J = 8.40$ Hz, 4H), 7.54 (t, $J = 7.60$ Hz, 1H), 7.44 (t, $J = 8.00$ Hz, 2H), 6.93 (d, $J = 8.80$ Hz, 2H), 5.21 (q, $J = 7.20$ Hz, 1H), 3.85 (s, 3H), 1.59 ppm (d, $J = 7.20$ Hz, 3H); ^{13}C NMR (100 MHz, [D$_1$]$CHCl_3$): $\delta = 197.2$, 195.8, 163.8, 135.8, 133.3, 130.9, 128.8 (2 C), 128.6 (2 C), 128.5 (2 C), 114.1 (2 C), 55.5, 51.0, 14.5 ppm; HRMS: *m/z* calcd for $C_{17}H_{16}O_3$: 291.0997 [$M+Na^+$]; found: 291.0993.

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(dppp)$_2$]. The yield of diketone **1** could therefore be corrected to 47%.

[21] Considerable degradation was observed in this stoichiometric reaction. One concern would be the reaction of the sodium enolate with the stoichiometric amount of DBA. However, an experiment, in which the two were dissolved together in dioxane and heated to 80°C for 30 min, only revealed the presence of unreacted ethyl phenyl ketone and DBA according to the ^{1}H NMR spectrum of the crude product mixture after workup.

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