C–C Coupling

DOI: 10.1002/anie.201101638

Palladium-Catalyzed C–C Bond Formation To Construct 1,4-Diketones under Mild Conditions**

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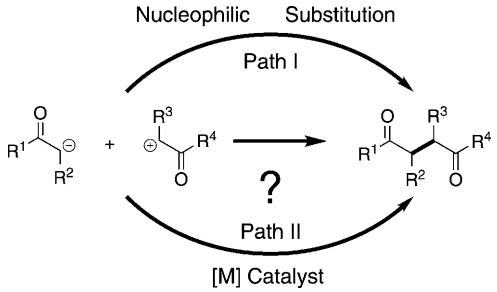
Carbon–carbon bond formation is the central transformation in synthetic organic chemistry. Although there are a number of strategies to construct C–C bonds, nucleophilic substitution is perhaps the oldest and most widely used of these methods. These transformations typically involve primary alkyl halides or tosylates as electrophiles to couple with a variety of different nucleophiles.[1] Direct substitution of a leaving group at a C(sp^2) center is not possible, while substitution is well known for secondary alkyl (C(sp^3)) positions even though this can still prove problematic.

Since the early 1970s, transition-metal-catalyzed cross-coupling reactions have been widely used to couple C(sp^2) electrophiles with various carbon nucleophiles to form C(sp^2)–C bonds.[2] Although a few examples exist, cross-couplings involving secondary α-carbonyl alkyl halides (C(sp^3)) to construct C–C bonds in the presence of transition-metal catalysts are still rare.[3]

Reactions between α-carbonyl alkyl halides and metal enolates are of high importance, as the products (1,4-dicarbonyl compounds) are often common substructures of natural products and precursors for five-membered heteroarenes.[4] In particular, the direct C–C bond formation between two carbonyl-substituted methyl groups to construct 1,4-diketones is an important example. Nucleophilic substitution reactions have been used to form bonds between two carbonyl-substituted methyl groups when the electrophile is a primary α-carbonyl alkyl halide (Scheme 1, Path I, $R^3 = H$).[5] In some cases, when tin enolates and α-haloketones are used as substrates, transition-metal salts are used as Lewis acids to increase the yields and control the selectivity for 1,4-diketone synthesis.[6] Formation of 2,3-disubstitued 1,4-diketones by nucleophilic substitution is less straightforward with only one known example, in which R^3 is an alkyl group such as Me or Et.[7] There are no known examples of nucleophilic substitution reactions forming 2,3-disubstituted 1,4-diketones where R^2 and R^3 are both aryl groups.[8] Therefore, we suggest that transition-metal catalysts can be used to accomplish this type of bond formation (Scheme 1, Path II).



Scheme 1. Approaches to 1,4-diketone synthesis between two carbonyl-substituted methyl units.

One approach is to use oxidative enolate homocoupling in the presence of stoichiometric amounts of transition-metal salts and other oxidants to gain access to symmetric 1,4-dicarbonyl derivatives.[9] Furthermore, oxidative enolate cross-coupling can be used to construct unsymmetric 1,4-dicarbonyl compounds,[10] although the selectivity for the unsymmetric cross-coupled products are moderate. Consequently, C–C bond formations between secondary α-carbonyl alkyl electrophiles and metal ketone enolates to produce 2,3-disubstituted 1,4-diketones under mild conditions and in a highly selective manner is a major challenge. Herein, we communicate our progress in this area by reporting the palladium-catalyzed C–C bond formation between substituted α-chloroketones and zinc ketone enolates to construct 2,3-diaryl 1,4-diketones in high yields under mild conditions.

Recently, our research group has reported that α-haloketones can be employed as an oxidant in both oxidative coupling reactions and oxidative carbonylation, thus indicating that the transmetalations of both Pd–X and palladium–enolate bonds (generated from the oxidative addition of α-haloketones to Pd^0) with nucleophiles like arylzinc reagents and arylboronic acids are very facile.[11] This finding indicates that α-haloketones are poor coupling partners with nucleophiles in the presence of transition-metal catalysts. However, the functionalization of α-haloketones is important. Both we and the research group of Fu have been able to demonstrate the direct functionalization of α-haloketones using Ni catalysts. This methodology only worked with α-haloketones substituted at the α position with an alkyl group or a hydrogen atom.[3] No α-aryl-substituted substrates were applied, per-

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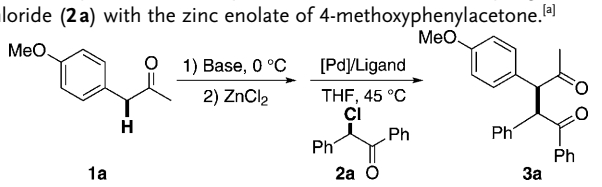
[**] This work was supported by the National Natural Science Foundation of China (21025206, 20832003, 20972118, and 20772093) and the "973" Project from the MOST of China (2011CB808600). We are also grateful for the support from "the Fundamental Research Funds for the Central Universities" and the Program for New Century Excellent Talents in University (NCET).
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201101638.

haps owing to the higher steric hindrance of the aryl group. To use α-aryl-substituted haloketones as an electrophilic cross-coupling partner instead of an oxidant, we sought a nucleophilic metal enolate which might favor transmetalation with the Pd–X bond instead of the palladium–enolate bond. Subsequent reductive elimination would then release the important 1,4-diketone compound. With this idea in mind, the reaction of the zinc enolate of 4-methoxyphenylacetone (prepared in situ) and desyl chloride **2a** was used as the model to test this new type of bond formation (Table 1). After considerable efforts, we established that 5 mol% of [$PdCl_2$(dppf)] in THF effects this C–C bond formation in an excellent yield at 45°C (98%; Table 1, entry 4). Table 1 illustrates the impact of a variety of reaction parameters on the cross-coupling process. Firstly, the influence of the base was investigated (Table 1, entries 1–4).[12] Sodium bis(trimethylsilyl)amide (NaHMDS) was found to be the most effective base and gave excellent results. Other bases such as sodium hydride and *n*-butyllithium proved ineffective, and afforded less than 5% of the desired product. It was interesting to find that lithium bis(trimethylsilyl)amide (LiHMDS) was also ineffective.

Upon decreasing the reaction temperature to room temperature, the yield was lower (86%; Table 1, entry 4). The concentration was found to be important, as only 34% of the desired product was formed with significant amounts of the homocoupling by-products of both **1a** and **2a** when the reaction was carried out at a higher concentration (Table 1, entry 4). In the absence of a Pd catalyst, no desired coupling product was observed and instead large amounts of unchanged desyl chloride **2a** and trace amounts of its dehalogenation by-product were detected (Table 1, entry 5). The ligand effect was examined too (Table 1, entries 6–13). Flexible bidentate phosphine ligands were less effective (Table 1, entries 6–9). The P-Olefin ligand and the *trans*,*trans*-dibenzylideneacetone (dba) ligand, which can both accelerate reductive elimination, only gave poor yields of the desired product (Table 1, entries 10 and 11).[13] In the case of monodentate phosphine ligands, PPh_3 in either [$PdCl_2(PPh_3)_2$] or [$Pd(PPh_3)_4$] precursors was more effective than the electron-rich phosphine ligand PBu_3 (Table 1, entries 12–14).

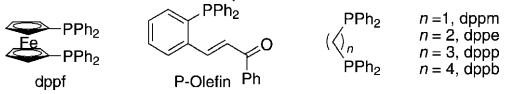
Table 1: Impact of reaction parameters on the cross-coupling of desyl chloride (**2a**) with the zinc enolate of 4-methoxyphenylacetone.[a]



1a **2a** **3a**

Entry	Base	[Pd]/ligand	Yield [%][b]
1	NaH	[$PdCl_2$(dppf)]/–	< 5
2	*n*BuLi	[$PdCl_2$(dppf)]/–	< 5
3	LiHMDS	[$PdCl_2$(dppf)]/–	< 5
4	**NaHMDS**	**[$PdCl_2$(dppf)]/–**	**98** (86,[c] 34[d])
5	NaHMDS	–	n.d.
6	NaHMDS	[$PdCl_2(CH_3CN)_2$]/dppm	< 5
7	NaHMDS	[$PdCl_2(CH_3CN)_2$]/dppe	< 5
8	NaHMDS	[$PdCl_2(CH_3CN)_2$]/dppp	19
9	NaHMDS	[$PdCl_2(CH_3CN)_2$]/dppb	12
10	NaHMDS	[$PdCl_2(CH_3CN)_2$]/P-Olefin	20
11	NaHMDS	[$Pd(dba)_2$]/–	11
12[e]	NaHMDS	[$PdCl_2(CH_3CN)_2$]/PBu_3	13
13	NaHMDS	[$PdCl_2(PPh_3)_2$]/–	75
14	NaHMDS	[$Pd(PPh_3)_4$]/–	73

[a] Unless otherwise noted, the reaction was carried out with **1a** (0.50 mmol), **2a** (0.25 mmol), base (0.50 mmol), $ZnCl_2$ (0.60 mmol), catalyst (0.0125 mmol), ligand (0.0125 mmol), THF (2 mL), 45°C, 12 h. [b] Yield determined by GC analysis with *m*-terphenyl as the internal standard. [c] At room temperature. [d] The reaction was carried out on a 0.25 mmol scale in 0.5 mL of THF. [e] 0.025 mmol of PBu_3. n.d. = not determined, THF = tetrahydrofuran.

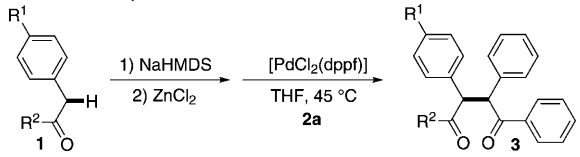


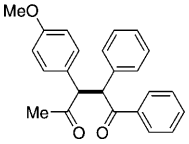
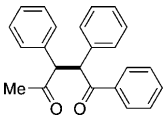
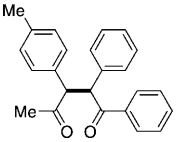
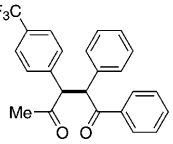
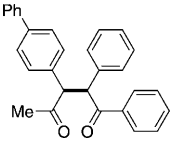
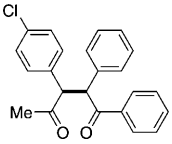
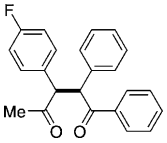
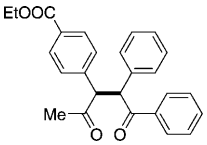
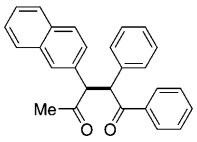
The procedure was later employed with other arylacetones using **2a** as the electrophile (Table 2). Phenylacetone offered the cross-coupling product in 89% yield (Table 2, entry 2). The addition of electron-donating (*p*-OMe; Table 2, entry 1) or electron-withdrawing groups (*p*-CF_3; Table 2, entry 4) to the 4-position on the phenylacetones gave excellent yields. Carbon–halogen bonds could be well-tolerated under the coupling conditions (Table 2, entries 6 and 7) and the desired cross-coupling product could be generated even when an ester group was introduced (Table 2, entry 8). A substrate bearing a more sterically bulky aromatic group also afforded the desired product with an excellent yield (Table 2, entry 9).

Next, we demonstrated this palladium-catalyzed C–C bond formations with other α-chloroketones (Table 3). Firstly, **2b** was employed to perform the cross-coupling with two typical arylacetones. Good to excellent yields of the desired cross-coupling products were obtained (Table 3, entries 1 and 2). When **2c** was employed as the substrate, we found that the $C(sp^2)$–Cl bonds in the electrophiles could be well-tolerated and that the $C(sp^3)$–Cl bond was much more reactive than $C(sp^2)$–Cl bonds in these substrates (Table 3, entries 3 and 4). Even the $C(sp^2)$–Br bonds were not as reactive as $C(sp^3)$–Cl bond when **2d** was used as the substrate and the desired cross-coupling products were obtained in good yields (Table 3, entries 5 and 6). This outcome provides the possibility for further functionalization of the coupling products. In contrast to the nucleophiles (see above), the electrophiles are more sensitive to the nature of the substituents on the aromatic rings. This effect can be seen when the reaction with an electron-donating group (OMe; **2e**) proceeded well and produced the desired products in high yields (Table 3, entries 7–9), while the strong electron-withdrawing group (CF_3) only afforded trace amounts of the desired products (Table 3, entries 10 and 11).

Next, we sought to use 1,2-diaryl ethanones as substrates in these cross-coupling reactions to form tetraaryl-substituted 1,4-diketones. These compounds are difficult to synthesize by traditional methods. By employing our palladium-catalyzed C–C bond-formation conditions between α-chloroketones and zinc ketone enolates, the tetraaryl-substituted 1,4-dike-

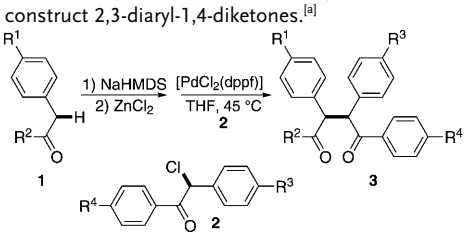
Table 2: Scope of palladium-catalyzed C–C bond formations to construct 2,3-diaryl-1,4-diketones.[a]



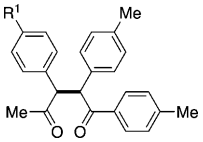
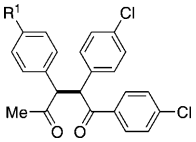
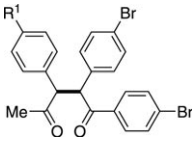
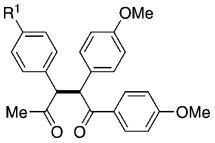
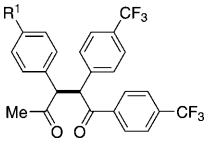
Entry		Product **3**	Yield [%][b] (d.r.)[c]
1	**3a**		92 (1.0:1)
2	**3b**		89 (0.8:1)
3	**3c**		88 (1.0:1)
4	**3d**		95 (0.6:1)
5	**3e**		99 (0.8:1)
6	**3f**		91 (0.3:1)
7	**3g**		97 (0.9:1)
8	**3h**		97 (0.7:1)
9	**3i**		95 (0.7:1)

[a] Reaction conditions: ketone **1** (0.50 mmol), NaHMDS in THF (2.0 M, 0.25 mL), $ZnCl_2$ (0.60 mmol), desyl chloride (0.25 mmol), [$PdCl_2$(dppf)] (0.0125 mmol, 5 mol%), THF (2 mL), 45 °C, 10–16 h. [b] Yield of isolated product. [c] Diastereomeric ratios determined by ^{1}H NMR spectroscopy.

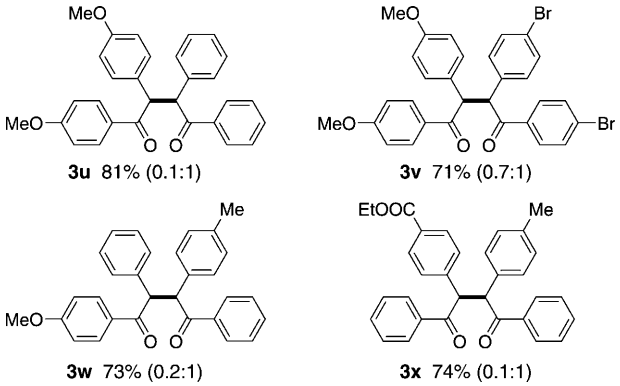
Table 3: Scope of palladium-catalyzed C–C bond formations to construct 2,3-diaryl-1,4-diketones.[a]



2b: R^3, R^4 = Me
2c: R^3, R^4 = Cl
2d: R^3, R^4 = Br
2e: R^3, R^4 = OMe
2f: R^3, R^4 = CF_3

Entry	**2**	Product **3**	Yield [%][b] (d.r.)[c]
1	**2b**		**3j**, R^1 = OMe, 98 (0.2:1)
2			**3k**, R^1 = CF_3, 68 (0:1)
3	**2c**		**3l**, R^1 = OMe, 59 (0.7:1)
4			**3m**, R^1 = CF_3, 85 (0.3:1)
5	**2d**		**3n**, R^1 = OMe, 72 (0.5:1)
6			**3o**, R^1 = CF_3, 66 (0.4:1)
7	**2e**		**3p**, R^1 = Me, 77 (0.6:1)
8			**3q**, R^1 = F, 98 (0.8:1)
9			**3r**, R^1 = CF_3, 86 (0.1:1)
10	**2f**		**3s**, R^1 = OMe, trace[d]
11			**3t**, R^1 = CF_3, trace[d]

[a] Reaction conditions: ketone **1** (0.50 mmol), NaHMDS in THF (2.0 M, 0.25 mL), $ZnCl_2$ (0.60 mmol), α-chloroketone **2** (0.25 mmol), [$PdCl_2$-(dppf)] (0.0125 mmol, 5 mol%), THF (2 mL), 45 °C, 10–16 h. [b] Yield of isolated product. [c] Diastereomeric ratios determined by ^{1}H NMR spectroscopy. [d] Detected by GC-MS methods.



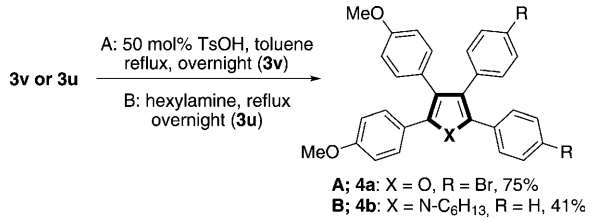
Scheme 2. Palladium-catalyzed C–C bond formation to form tetraaryl-substituted 1,4-diketone (Reaction conditions: see Table 2; the right-hand part of these products come from the corresponding electrophiles.)

tones were obtain in a straightforward manner. The products are illustrated in Scheme 2. Symmetric 1,2-diaryl ethanones such as the commercially available 4,4′-dimethoxy deoxyanisoin were coupled with **2a** and **2d** to afford the coupled products in high yields (**3u**, **3v**; Scheme 2). Unsymmetric 1,2-

diaryl ethanones were also employed and offered the corresponding 1,2,3,4-tetraayl-substituted 1,4-diketones in good yields (**3w**, **3x**; Scheme 2).

In the Paal–Knorr synthesis,[14] 1,4-diketones are used as precursors for the preparation of five-membered heteroarenes such as pyrroles, furans, and thiophenes. We decided to subject our products to the Paal–Knorr reaction and synthesize tetraaryl-substituted five-membered heteroarenes. Such compounds are important structural motifs with many interesting optoelectronic and biological properties, furthermore, they are found in a variety of natural products, pharmaceuticals, and serve as versatile building blocks in organic synthesis.[15] Other routes[16] involve the direct multiple arylation of furans and thiophenes to get tetraaryl-substituted heteroarenes as reported by the research groups of Miura and Itami. Alternative methods have also been reported.[17]

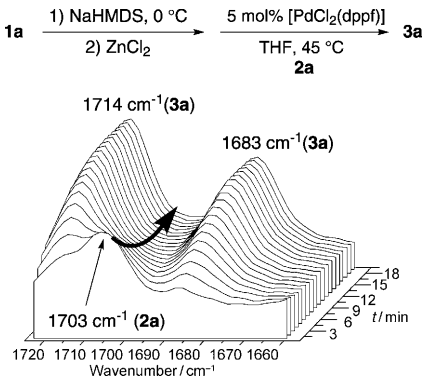
Our Paal–Knorr reaction involved heating **3v** in toluene at reflux with catalytic amounts of TsOH and the tetraaryl-substituted furan **4a** was obtained in 75% yield (Scheme 3).



Scheme 3. Synthesis of tetraaryl-substituted furan and pyrrole from 1,4-diketones. Ts = 4-toluenesulfonyl.

The methoxy and bromo substituents on the phenyl rings provided good potential for further functionalization to extend the carbon chain and thus make a teraaryl-substituted furan unit that could be used as a cell structure for polymers and functional materials. The tetraaryl-substituted pyrrole **4b** was also prepared in 41% yield by heating **3u** in hexylamine at reflux (Scheme 3).

To gain greater insight into our palladium-catalyzed C–C bond formations, the reaction of **1a** with **2a** was monitored by using ReactIR. The kinetic profile (Scheme 4) shows a peak at 1703 cm^{-1} representing the desyl chloride **2a** and two peaks



Scheme 4. Kinetic profiles of the reaction rate for **1a** with **2a.**

at 1714 cm^{-1} and 1683 cm^{-1} representing the C–C coupling product: the 1,4-diketone **3a**. To our surprise, the reaction was very fast and was finished within 10 minutes to afford the coupling product **3a** in a 92% yield (based on GC analysis). The mechanism of this palladium-catalyzed cross-coupling reaction is believed to involve oxidative addition, transmetalation, and reductive elimination. The overall fast reaction rate indicates an unusually fast reductive elimination of the two bulky α-carbon atoms on the ketones from the palladium center. Such a facile elimination is unexpected and inexplicable. Further investigation into the mechanism is currently underway.

In conclusion, we have developed a novel palladium-catalyzed C–C bond formation between α-chloroketones and zinc ketone enolates to construct 2,3-diaryl-substituted 1,4-diketones under mild conditions. The complex [$PdCl_2$(dppf)] was shown to be an ideal catalyst and various ketones could also be employed. Reaction monitoring showed that these C–C bond formations between two bulky carbon centers are surprisingly fast. In addition, two of the cross-coupling products were used as precursors for the Paal–Knorr synthesis to afford tetraaryl-substituted furan and pyrrole compounds.

Experimental Section

General procedure for the synthesis of **3a**: 4-Methoxyphenylacetone (82.0 mg, 0.50 mmol) was dissolved in THF (2.0 mL) and added to a Schlenk tube (25 mL) under nitrogen and the tube was then placed in an ice-water bath. Then a solution of NaHMDS (2.0 M) in THF (0.25 mL) was injected into the Schlenk tube via a syringe. With stirring, $ZnCl_2$ (81.8 mg, 0.60 mmol) was then added under nitrogen. After stirring for 10 min, [$PdCl_2$(dppf)] (9.1 mg, 0.0125 mmol) and desyl chloride (**2a**, 57.7 mg, 0.25 mmol) were added, respectively. The reaction was then heated up to 45 °C and stirred for 12 hours. After completion of the reaction, it was quenched with diluted HCl solution and extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and the pure product was obtained by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5:1). The yield of isolated product was 92% (d.r. = 1.0:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, J = 7.4 Hz, 2H), 7.85 (d, J = 7.4 Hz, 2H), 7.57–6.84 (m, 20H), 6.79 (d, J = 8.5 Hz, 2H), 6.71 (d, J = 8.5 Hz, 2H), 5.53 (d, J = 11.3 Hz, 1H), 5.14 (d, J = 11.0 Hz, 1H), 4.78 (d, J = 11.3 Hz, 1H), 4.54 (d, J = 11.0 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 2.18 (s, 3H), 1.92 ppm (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.21, 206.95, 199.73, 197.96, 158.84, 136.91, 136.66, 136.35, 132.97, 132.87, 129.90, 129.83, 129.02, 128.86, 128.82, 128.61, 128.45, 128.41, 127.46, 127.03, 114.21, 114.03, 62.45, 61.01, 57.28, 55.11, 30.70, 29.33 ppm. HRMS (MALDI): m/z calcd for $C_{24}H_{22}O_3$ $[M+Na]^+$: 381.1467; found: 381.1478.

Received: March 6, 2011
Revised: May 18, 2011
Published online: July 7, 2011

Keywords: α-chloroketones · 1,4-diketones · enolate coupling · Paal–Knorr reaction · palladium

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