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Palladium-Catalyzed Synthesis of 1,2-Diketones from Aryl Halides and Organoaluminum Reagents Using *tert*-Butyl Isocyanide as the CO Source

Bo Chen and Xiao-Feng Wu*

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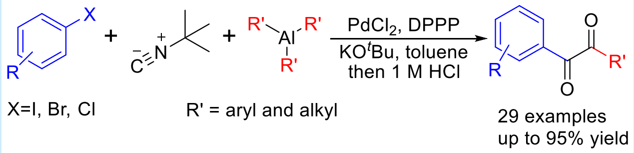
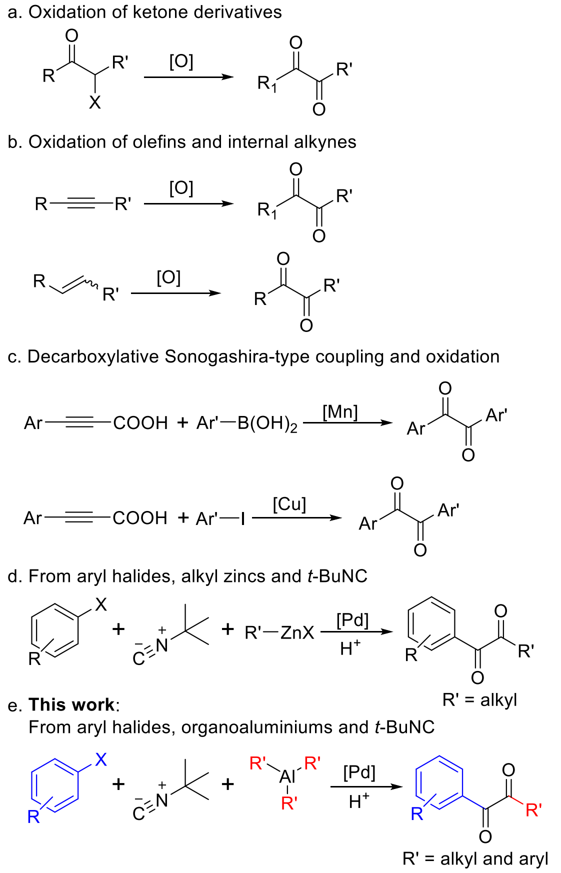
ABSTRACT: In this work, an interesting and practical procedure for the synthesis of 1,2-diketones from aryl halides and organoaluminum reagents has been developed. Employing *tert*-butyl isocyanide as the CO source and palladium as the catalyst, the desired 1,2-diketones were isolated in good to excellent yields with good functional group tolerance. Concerning the reaction partners, besides aryl halides, both alkyl- and arylaluminum reagents were all suitable substrates here.



Scheme 1. Methodologies for 1,2-Diketone Synthesis



1,2-Diketones compose a class of structural motif with important applications in the synthesis of biologically active heterocycles and natural products.[1,2] Additionally, 1,2-diketones have also been found to be present in molecules with antitumor activities.[3] Furthermore, they have also been used as photochemical materials[4] and ligands to stabilize various metal complexes.[5] Because of their recognized importance, many synthetic methods were developed for their preparation in recent years (Scheme 1). Traditionally, 1,2-diketones can be prepared by the oxidation of ketone derivatives[6] or olefins and internal alkynes (Scheme 1, eqs a and b).[7] Alternatively, 1,2-diketones can also be synthesized through metal-catalyzed/mediated cross-coupling of arylboronic acids[8] or aryl iodides[9] with alkynyl carboxylic acids (Scheme 1, eq c). The reaction proceeds through a decarboxylative coupling and then an oxidation sequence. More recently, Blackmond, Dechert-Schmitt and their co-workers developed an attractive procedure for the synthesis of unsymmetrical 1,2-diketones from aryl halides and alkyl zincs employing *tert*-butyl isocyanide as the CO source (Scheme 1, eq d).[10] Quinoxalines were prepared in moderate to good yields after reaction with *o*-phenylenediamine.

On the other hand, organoaluminum reagents are attractive coupling partners in synthetic chemistry due to their relatively low cost and low toxicity as well as the readily availability of aluminum metal.[11] The first report on using organoaluminum in a transition-metal-catalyzed cross-coupling reaction can be traced back to 1976 by Negishi and co-workers.[12] Since then,

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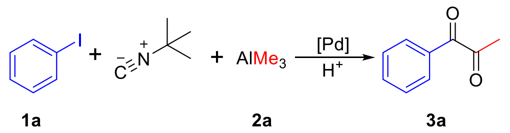
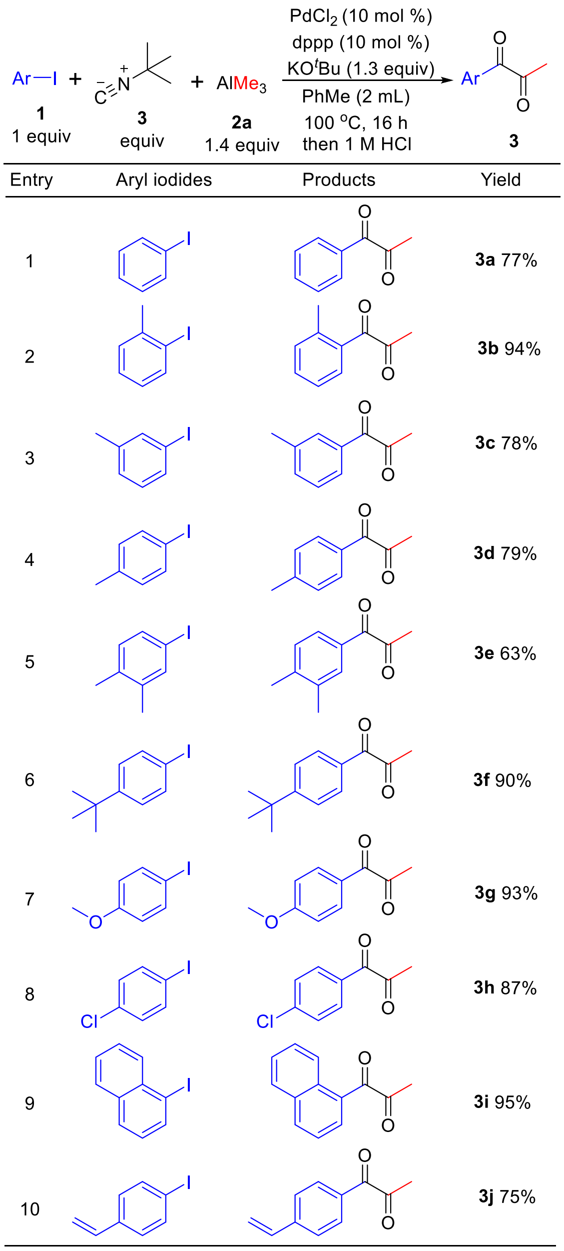
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	ligand	solvent	base	yield (%)
1	Pd_2dba_3	DPPF	PhMe	NaO^{t}Bu	53
2	Pd_2dba_3	DPPF	PhMe	NaO^{t}Bu	45[b]
3	$Pd(PPh_3)_4$	–	PhMe	NaO^{t}Bu	42
4	$Pd(OAc)_2$	PPh_3	PhMe	NaO^{t}Bu	50
5	$PdCl_2$	DPPF	PhMe	NaO^{t}Bu	67
6	$PdCl_2$	–	PhMe	NaO^{t}Bu	41
7	$PdCl_2$	DPEphos	PhMe	NaO^{t}Bu	56
8	$PdCl_2$	Xantphos	PhMe	NaO^{t}Bu	63
9	$PdCl_2$	DPPM	PhMe	NaO^{t}Bu	30
10	$PdCl_2$	DPPE	PhMe	NaO^{t}Bu	59
11	$PdCl_2$	DPPP	PhMe	NaO^{t}Bu	70
12[c]	$PdCl_2$	DPPP	PhMe	NaO^{t}Bu	58
13	$PdCl_2$	DPPP	PhMe	LiO^{t}Bu	trace
14	$PdCl_2$	DPPP	PhMe	K_2CO_3	trace
15	$PdCl_2$	DPPP	PhMe	Et_3N	trace
16	$PdCl_2$	DPPP	PhMe	DBU	trace
17	$PdCl_2$	DPPP	PhMe	KO^{t}Bu	80(77)[d]
18	$PdCl_2$	DPPP	THF	KO^{t}Bu	56
19	$PdCl_2$	DPPP	1,4-dioxane	KO^{t}Bu	63
20[e]	$PdCl_2$	DPPP	PhMe	KO^{t}Bu	69
21[f]	$PdCl_2$	DPPP	PhMe	KO^{t}Bu	9

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.7 mmol in pentane), *tert*-butyl isocyanide (3 equiv), [Pd] (10 mol %), ligand (10 or 20 mol %), solvent (2.0 mL), base (0.65 mmol) 100 °C, 16 h, then 1 M HCl, 1 h, NMR yield. [b] *tert*-Butyl isocyanide (2 equiv). [c] 5 mol % $PdCl_2$ and 5 mol % DPPP. [d] Isolated yield. [e] Bromobenzene instead of **1a**. [f] Chlorobenzene instead of **1a**.

Scheme 2. Synthesis of 1,2-Diketones: Variation of Aryl Iodides[a]



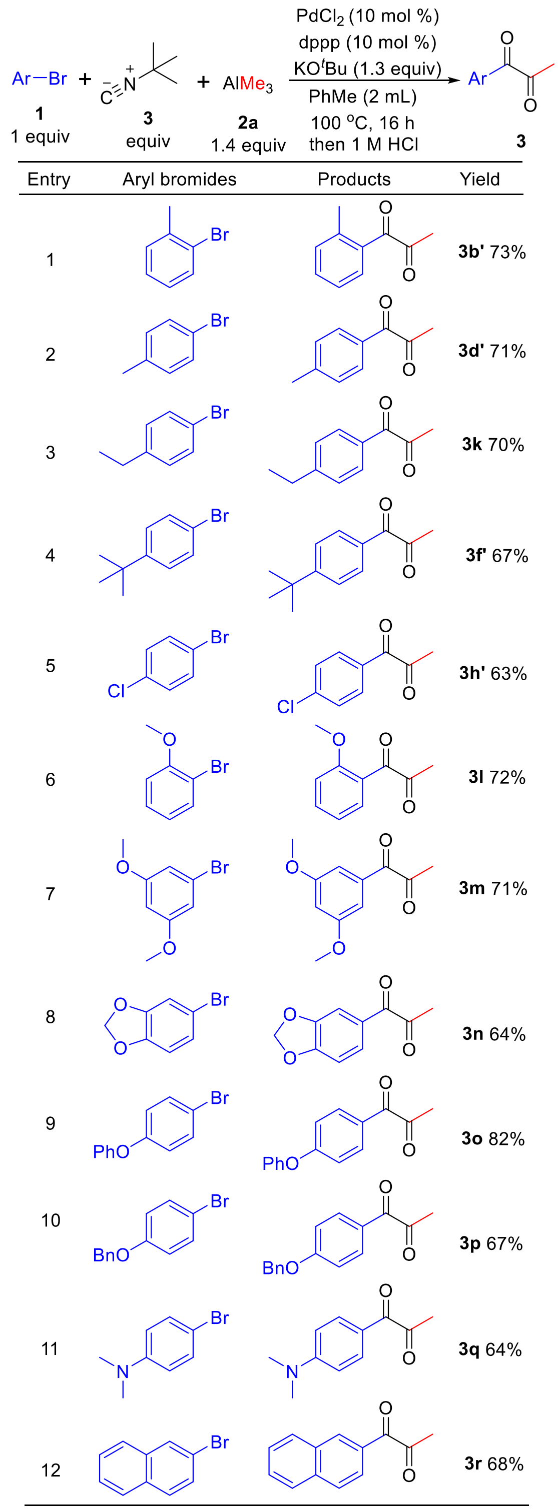
[a] Reaction scale: 0.50 mmol, isolated yields.

various examples of cross-coupling reactions with organoaluminum reagents were reported.[13]

For examples, Knochel and co-workers reported a novel method for preparing organoaluminum reagents in 2010.[13i] Promoted by catalytic amounts of selected metallic chlorides in the presence of LiCl, aluminum powder inserts into the C−X bond of many unsaturated iodides and bromides. The resulted organoaluminum reagents were applied in palladium-catalyzed cross-coupling and acylation reactions. More recently, Uchiyama, Wang and their co-workers performed a systematic study on nickel-catalyzed cross-coupling reactions of organoaluminum reagents with organic halides as well as phenolic/alcoholic C−O and ammonium C−N bonds.[14] Various C−C bonds were formed in an effective manner with commercially available $NiCl_2(PCy_3)_2$ as the catalyst. However, application of an organoaluminum reagent in 1,2-diketone synthesis has not been reported yet.

Under the aforementioned backgrounds, we herein report a new protocol for the synthesis of 1,2-diketones starting from organoaluminums and aryl halides. The initial investigations were carried out with iodobenzene and trimethylaluminum as the substrates employing *tert*-butyl isocyanide as the CO source. To our delight, the target 1-phenylpropane-1,2-dione **3a** can be successfully obtained in 53% yield with Pd_2dba_3 as the catalyst, DPPF as the ligand, and NaO*t*Bu as the base in toluene at 100 °C for 16 h, with subsequent use of 1 M HCl for hydrolysis (Table 1, entry 1). The yield of **3a** decreased to 45% if we decrease the loading of *tert*-butyl isocyanide to 2 equiv (Table 1, entry 2). Then, different palladium precursors and ligands were tested and we found $PdCl_2$ and DPPP were the best catalysis system to give a 70% yield of **3a** in this reaction (Table 1, entries 3−11). Interestingly, we found the desired product can still be obtained in 41% yield in the absence of ligand (Table 1, entry 6). The reaction efficiency decreased significantly if we decrease the loading of palladium catalyst (Table 1, entry 12). Bases screening disclosed that KO*t*Bu is the optimal base for this reaction system. The other tested inorganic and organic bases could not provide any desired product here (Table 1, entries 13−17). The testing of different reaction media could not further improve the reaction outcome (Table 1, entries 18−19). Finally, bromobenzene was checked as the substrate instead of iodobenzene and the target product was achieved in 69% yield (Table 1, entry 20).

Scheme 3. Synthesis of 1,2-Diketones: Variation of Aryl Bromides[a]

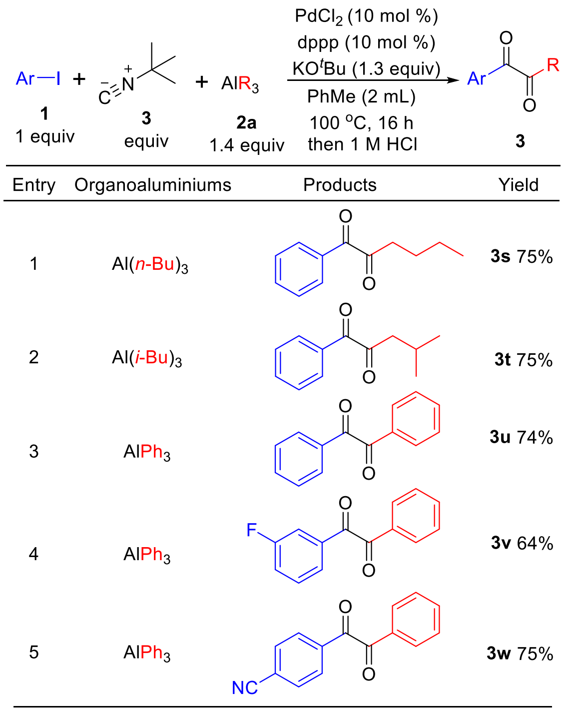


[a]Reaction scale: 0.50 mmol, isolated yields.

However, a very low yield of the target product was obtained when chlorobenzene was used (Table 1, entry 21). Additionally, a 51% yield of the desired diketone was obtained when decrease the loading of trimethylaluminum to 1.1 equiv.

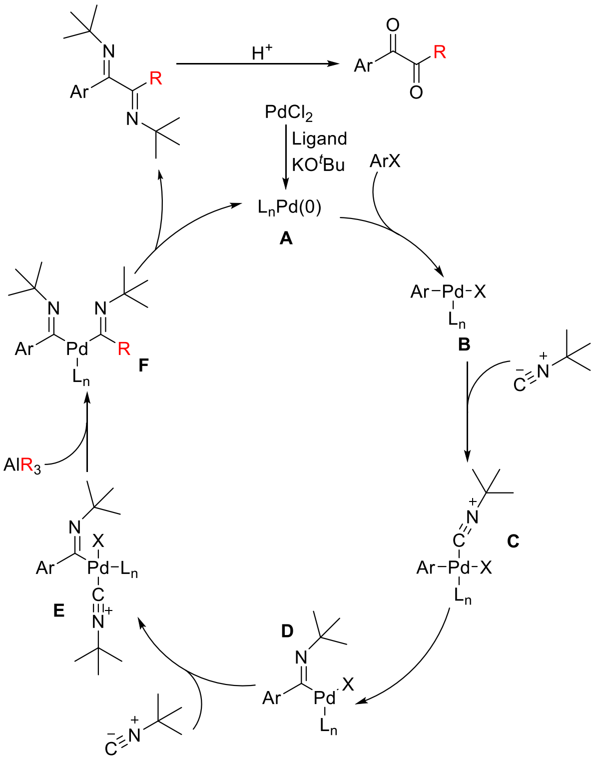
With the optimal reaction conditions in hand, we explored the scope of this new method with various aryl halides and organoaluminum employing *tert*-butyl isocyanide as the CO source. Initially, we tested the generality of substituted aryl iodides. As shown in Scheme 2, iodobenzenes with substituents at different positions can be well tolerated, delivering the desired products in good to excellent yields

Scheme 4. Synthesis of 1,2-Diketones: Variation of Organoaluminums[a]



[a]Reaction scale: 0.50 mmol, isolated yields.

Scheme 5. Proposed Reaction Mechanism



(**3a**−**3f**). Then we tried substrates with electron-donating and -withdrawing substituents; the desired products were obtained with 93% and 87% yields, respectively (**3g**, **3h**). Additionally, the reaction with 1-iodonaphthalene proceeds smoothly as well and gave the target product in 75% yield (**3i**). Gratifyingly, vinyl-substituted iodobenzene was also well tolerated in this transformation, delivering the corresponding 1,2-diketones in 75% yield (**3j**).

To our delight, aryl bromide can be applied as the substrate for this reaction as well. Under our standard conditions, a wide range of functional groups with varied electronic properties can be well tolerated (Scheme 3). The corresponding products **3b′**−**3r** were isolated in 63−82% yields successfully.

Organoaluminum reagents including aryl- and alkylaluminum reagents were tested with aryl iodides as well (Scheme 4). The applied organoaluminum reagents are either commercially available or can be easily prepared from aluminum trichloride and Grignard reagent or organolithium reagent. The reactions with triisobutylaluminum and tributylaluminum under our standard reaction conditions proceed well, and the desired products were obtained in 75% and 75% yields, respectively (**3s**, **3t**). Subsequently, triphenylaluminum as a representative arylaluminum reagent was checked. Likewise, the reaction gave the corresponding benzil derivatives in good yields (**3u**−**3w**). Furthermore, $PhB(OH)_2$ and $PhSi(OMe)_3$ were tested under our standard conditions as well, instead of an organoaluminum reagent, but only a trace amount of the target product was detected.

Concerning the reaction pathway, a plausible reaction pathway is proposed on the basis of our results and literature (Scheme 5).[10,15] First, the active catalyst **A** will be generated from $PdCl_2$ and DPPP. After oxidative addition of aryl halides to the catalyst **A**, organopalladium complex **B** can be obtained. After the coordination and insertion of isocyanide, complex **D** will be formed which will afford complex **F** after the coordination and insertion of the second molecule of isocyanide. Finally, the complex **F** undergoes a reductive elimination to yield the diimine product which can deliver the final 1,2-diketone products after hydrolysis and meanwhile regenerate the active catalyst **A** for the next catalytic cycle.

In conclusion, a novel and practical procedure for the synthesis of 1,2-diketones from aryl halides and an organoaluminum reagent has been developed. Employing *tert*-butyl isocyanide as the CO source and palladium as the catalyst, the desired 1,2-diketones were isolated in good to excellent yields with good functional group tolerance. Notably, both alkyl- and arylaluminum reagents were all suitable substrates here.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04414.

General comments, experimental procedures, and analytic data and NMR spectra for products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Xiao-Feng Wu − *Zhejiang Sci-Tech University, Hangzhou, People's Republic of China, and Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Rostock, Germany;* orcid.org/0000-0001-6622-3328; Email: Xiao-Feng.Wu@catalysis.de

Other Author

Bo Chen − *Zhejiang Sci-Tech University, Hangzhou, People's Republic of China, and Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Rostock, Germany*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.9b04414

Notes

The authors declare no competing financial interest.

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