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Palladium-Catalyzed Carbonylative α-Arylation to β-Ketonitriles

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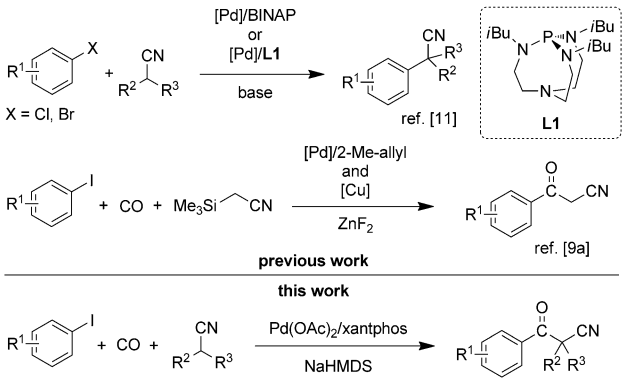
Abstract: A carbonylative α-arylation process employing unactivated nitriles for the first time is described. The reaction tolerates a range of (hetero)aryl iodides and several nitrile coupling partners. No prefunctionalization of the nitriles is necessary and the resulting β-ketonitriles are obtained in good to excellent yields. The methodology also allows for a convenient ^{13}C-labelling of the generated carbonyl moiety.

In the past few decades, the application of activated carbon nucleophiles has emerged as a key technology for the development of palladium-catalyzed (hetero)arylation reactions of esters, ketones, nitriles, and related α-CH-acidic substrates.[1] Stemming from the groundbreaking work of Miura, Buchwald, Hartwig, and others, catalytic α-arylation procedures have found multiple synthetic applications.[2] Careful mechanistic studies led to the development of efficient catalyst systems for α-arylations, which in turn have been utilized in the formation of allylic and benzylic carbonyl compounds through C(sp^2)–C(sp^3) bond formation starting from various α-CH-acidic compounds (i.e., ketones, esters, malonates, amides, aldehydes, nitriles).[3,4]

As an important extension of such methodologies, carbonylative α-arylations have been studied as well. Various efforts have been made in this area; however, initial protocols were mostly limited to the use of malonate derivatives as starting materials.[5] Recently, our groups developed catalyst systems that allow for the intermolecular carbonylative α-arylation of ketones, thereby preventing the alkoxycarbonylation of the enolate derivative to an acylated enol.[6] Unfortunately, these carbonylative α-arylation reactions were limited to the use of carbonyl-containing compounds as C-nucleophiles.

Thus, an extension of the carbonylative α-arylation towards nitriles as easily available coupling partners constitutes a worthwhile goal for further developments. The resulting β-ketonitriles are useful difunctional intermediates for the synthesis of many biologically active compounds.[7] Since the derived β-hydroxy nitriles are important optically active intermediates in the preparation of γ-amino alcohols, the diversity of the β-ketonitriles available has a significant impact on the range of structures that can be accessed.[8] In this context, conventional methods for the synthesis of β-ketonitriles through acylation of acetonitriles or carbonylative coupling of trimethylsilylacetonitrile are limited to the formation of β-ketones that are unsubstituted at the α-position (Scheme 1).[9]



Scheme 1. (Carbonylative) α-arylation of nitriles.

More recent approaches have provided access to α-substituted β-ketonitriles through the base-mediated, direct acylation of nitrile anions with unactivated esters or *N*-acylbenzotriazoles, although these protocols do not allow for the generation of a quaternary α-carbon center.[10] In addition, the direct α-arylation of nitriles has only been reported in a few protocols by Hartwig, Verkade, and co-workers (Scheme 1).[11] Therefore, the direct synthesis of β-ketonitriles from aryl halides, carbon monoxide, and nitriles as a simple and abundant feedstock would represent a desirable achievement. Herein, we report the first examples of such carbonylative α-arylation reactions. A commercially available catalyst system is employed ($Pd(OAc)_2$/4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos)) that allows for the selective formation of α-disubstituted β-ketonitriles under a low pressure of gaseous CO with the use of unactivated nitriles.

In our initial experiments, $Pd(OAc)_2$/2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) was tested as the catalyst system

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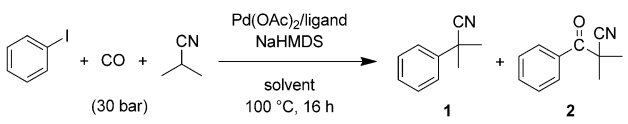
for the carbonylative coupling of bromobenzene and isobutyronitrile, because it had been successfully employed in the direct α-arylation of nitriles by Hartwig and co-workers.[11a] Unfortunately, attempts under different pressures of carbon monoxide (5 and 30 bar) did not lead to the formation of the desired β-ketonitrile, and only direct arylation of isobutyronitrile was observed. Instead, starting the reaction from iodobenzene at a CO-pressure of 30 bar enabled the formation of 2,2-dimethyl-3-oxo-3-phenylpropanenitrile (**2**) for the first time in 21% yield with a remarkable 21:1 selectivity towards the carbonylated product (Table 1, entry 1). Next, further optimizations were undertaken by using this model system. Changing the solvent did not lead to any positive effect and only nonpolar aromatic solvents such as toluene and benzene turned out to be suitable (Table 1, entries 1–6). Testing different bases showed that only strong ones provide sufficient deprotonation of the nitrile to enable the coupling process. Thus, organic and inorganic bases of moderate strength did not lead to any desired product formation, and lithiumdiisopropylamide (LDA) and sodium hexamethyl disilazide (NaHMDS) gave the desired product in 14 and 21% yield, respectively (Table 1, entries 1 and 7–12). Surprisingly, similarly basic KHMDS resulted in low conversion and no product formation.

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



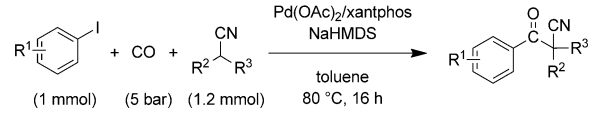
Entry	Ligand	Solvent	Base	Conv. [%][b]	Yield [%][b] 1	2
1	BINAP	toluene	NaHMDS	25	1	21
2	BINAP	dioxane	NaHMDS	30	1	0
3	BINAP	DMF	NaHMDS	59	0	4
4	BINAP	DMSO	NaHMDS	72	3	0
5	BINAP	benzene	NaHMDS	59	0	15
6	BINAP	THF	NaHMDS	73	1	0
7	BINAP	toluene	KHMDS	47	0	0
8	BINAP	toluene	LDA	93	2	14
9	BINAP	toluene	KO*t*Bu	60	0	0
10	BINAP	toluene	Cs_2CO_3	84	0	0
11	BINAP	toluene	NaOAc	5	0	0
12	BINAP	toluene	NEt_3	2	0	0
13[c]	PPh_3	toluene	NaHMDS	30	0	0
14[c]	*n*BuPAd$_2$	toluene	NaHMDS	58	0	0
15	DPPE	toluene	NaHMDS	55	0	0
16	DPPP	toluene	NaHMDS	68	0	10
17	DPPB	toluene	NaHMDS	42	0	0
18	DPPF	toluene	NaHMDS	62	0	0
19	xantphos	toluene	NaHMDS	90	35	27
20[d]	xantphos	toluene	NaHMDS	90	7	33
21[e]	xantphos	toluene	NaHMDS	>99	26	52
22[f]	xantphos	toluene	NaHMDS	>99	2	73

[a] General reaction conditions: iodobenzene (1 mmol), isobutyronitrile (1.2 mmol), $Pd(OAc)_2$ (2 mol%), ligand (2 mol%), base (1.3 mmol), solvent (2 mL), CO (30 bar), 100 °C, 16 h. [b] Conversions and yields were determined on the basis of calibrated GC data by using hexadecane as an internal standard. [c] 8 mol% of ligand. [d] $Pd(OAc)_2$ (4 mol%), xantphos (4 mol%). [e] $Pd(OAc)_2$ (4 mol%), xantphos (4 mol%), CO (5, bar), 80 °C. [f] $Pd(OAc)_2$ (4 mol%), xantphos (5 mol%), CO (5, bar), 80 °C.

Next, we turned our attention to determine the influence of different ligands on our model system. The use of standard monodentate phosphines, such as triphenylphosphine and di(1-adamantyl)-*n*-butylphosphine, as well as bidentate phosphine ligands, such as 1,2-bis(diphenylphosphino)ethane (DPPE), 1,2-bis(diphenylphosphino)butane (DPPB), and 1,1′-bis(di-phenylphosphino)ferrocene (DPPF), did not promote the model reaction (Table 1, entries 13–15 and 17–18). However, 2-bis(diphenylphosphino)propane gave **2** in 10% yield (Table 1, entry 16). Applying 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos) resulted in an enhanced conversion and yield, albeit a lack of selectivity induced the formation of both coupling products **1** and **2** in 35 and 27% yield, respectively (Table 1, entry 19). In further studies by using xantphos, a higher catalyst loading of 4 mol% was found to be advantageous for the selective formation of the β-ketonitrile in 33% yield (Table 1, entry 20). Multiple side reactions were accounting for the differences between conversion and desired product yield; thus, dehalogenation, formylation to benzaldehyde, as well as formation of benzonitrile and α-(trimethylsilyloxy)-phenylacetonitrile were observed as side-reactions. Applying milder reaction conditions (80 °C, 5 bar of CO) suppressed these side reactions in favor of the C–C-bond formation towards products **1** and **2**, which were formed in 26 and 52% yield, respectively (Table 1, entry 21). Finally, a high selectivity towards the formation of the β-ketonitrile (73% yield) could be achieved by using a slight excess of the ligand (5 mol%) with respect to the palladium precursor (4 mol%; Table 1, entry 21). This suggests that the loss of ligand owing to the reduction of Pd^{II} to the catalytically active Pd^0 species causes a minimal deficit of ligand, which eventually leads to the formation of less-selective catalyst species.

Once the optimized reaction conditions had been established, we turned our focus on the scope and limitations of the reaction. The model reaction with iodobenzene led to the isolation of 2,2-dimethyl-3-oxo-3-phenylpropanenitrile in 71% yield (Table 2, entry 1). Notably, 4-*tert*-butyliodobenzene was converted into the corresponding product in a gratifying yield of 83% (Table 2, entry 2). Similarly, *ortho*-, *meta*- and *para*-mono- as well as dimethyl-substitutions were well tolerated, resulting in good to excellent yields of 75–87% (Table 2, entries 3–6). The bicyclic 1-iodonaphthalene provided a slightly lower yield of 67% (Table 2, entry 7). Also the presence of alkoxy substituents on the aryl iodide substrate was tolerated in the coupling process and resulted in yields ranging from 69 to 78% (Table 2, entries 8 and 9). 4-Chloroiodobenzene proved to be an excellent substrate, generating the corresponding β-ketonitrile in 87% yield, and the products of 3- and 4-fluoroiodobenzene were obtained in good yields of 71 and 73%, respectively (Table 2, entries 10–12). Electron-deficient trifluoromethyl substitution was also tolerated in the *ortho*-, *meta*- and *para*-positions (63 to 79% yield; Table 2, entries 13–15). Additionally, we demonstrated that heterocyclic (thiophenyl)aryl iodides afforded the desired β-ketonitriles in good to excellent isolated yields (93 and 71%; Table 2, entries 16 and 17). Attempts to apply other aryl halides under similar reaction conditions resulted in consistently lower selectivities towards the

Table 2. Pd-catalyzed carbonylative α-arylation of nitriles with different aryliodides.[a]



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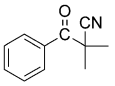
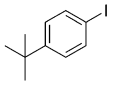
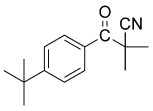
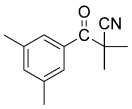
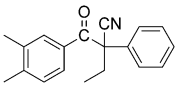
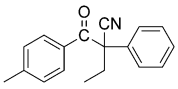
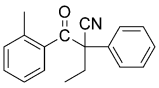
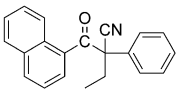
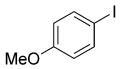
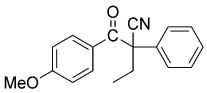
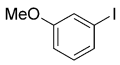
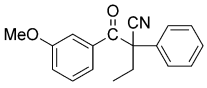
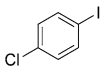
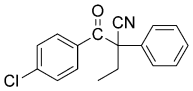
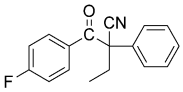
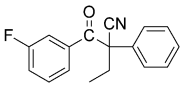
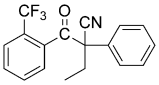
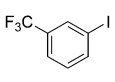
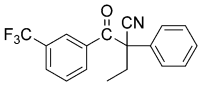
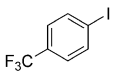
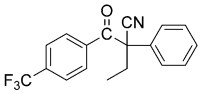
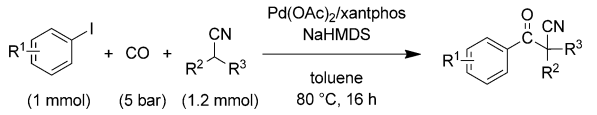
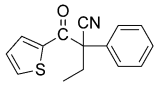
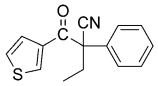
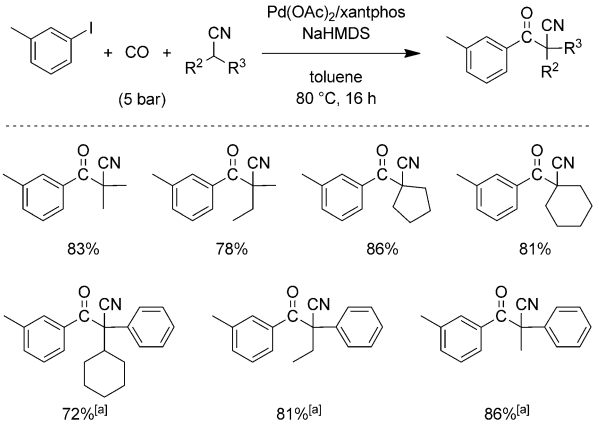
1			71
2			83
3			78
4[b]			85
5[b]			87
6[b]			75
7[b]			67
8[b]			69
9[b]			78
10[b]			87
11[b]			73
12[b]			71
13[b]			63
14[c]			79
15[d]			68

Table 2. (Continued)



Entry	Aryl iodide	Product	Yield [%]
16[c]			93
17[b]			71

[a] General reaction conditions: aryl iodide (1 mmol), nitrile (1.2 mmol), $Pd(OAc)_2$ (4 mol%), xantphos (5 mol%), NaHMDS (1.3 mmol), toluene (2 mL), CO (5 bar), 80 °C, 16 h; isolated yields. [b] Nitrile (1 mmol), CO (10 bar), 100 °C. [c] Nitrile (1 mmol), CO (10 bar), 80 °C. [d] Nitrile (1 mmol), CO (10 bar), 60 °C.



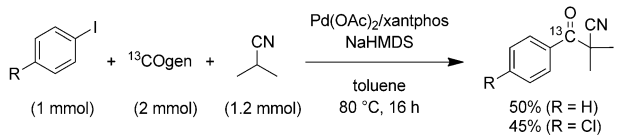
Scheme 2. Carbonylative α-arylation of different nitriles. General reaction conditions: 3-iodotoluene (1 mmol), nitrile (1.2 mmol), $Pd(OAc)_2$ (4 mol%), xantphos (5 mol%), NaHMDS (1.3 mmol), toluene (2 mL), CO (5 bar), 80 °C, 16 h; isolated yields. [a] Nitrile (1 mmol), CO (10 bar), 100 °C.

carbonylated coupling product (with ArBr) or low conversions (in the case of ArCl), thus requiring independently comprehensive investigations.

Next, we examined the scope of the nitrile coupling partners (Scheme 2). Starting from 3-iodotoluene and isobutyronitrile yielded the desired β-ketonitrile in 83% yield. By using 2-methylbutyronitrile, the corresponding product was isolated in 78% yield. Cyclic nitriles, such as cyclopentanecarbonitrile and cyclohexanecarbonitrile, were also well tolerated under these conditions, affording the β-ketonitriles in similarly high yields of 86 and 81%, respectively. In addition, aroylation of α-substituted benzyl cyanide substrates proceeded smoothly to generate the corresponding products in yields of 72–86%. However, attempts to convert benzyl nitrile and similar substrates having a CH_2-group in the α-position were not successful under these conditions, because subsequent aroylation of the products in their enol form occurred, leading to the corresponding enol-benzoates. This is in agreement with similar observations

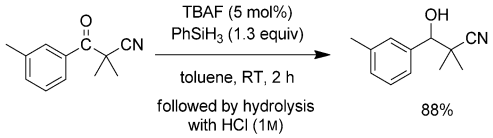
made by us for the carbonylative coupling of deoxybenzoins generating vinylbenzoates rather than 1,3-diketones.[12]

Making use of the two-chamber system (COware) with the ex situ generation of CO from 9-methyl-9*H*fluorene-9-carbonyl chloride (COgen), as described earlier,[13] allowed for the use of a low concentration of carbon monoxide. Thus, starting from iodobenzene and by using ^{13}COgen, the ^{13}C-labeled β-ketonitrile was obtained in 50% yield (Scheme 3).



Scheme 3. Labelling experiments by using COgen.

To prove the usefulness of the synthesized β-ketonitriles as building blocks, we demonstrated the straightforward synthesis of β-aryl-β-hydroxynitriles. More specifically, we applied a metal-free selective catalytic hydrosilylation procedure based on the use of tetrabutylammonium fluoride (TBAF) as catalyst, which has been reported by our group recently.[14] Thus, after the palladium-catalyzed coupling process was complete, the resulting β-ketonitrile was reacted with phenyl silane in the presence of a catalytic amount of TBAF at room temperature (Scheme 4). Notably, a selective reduction of the carbonyl group was observed, whereas the nitrile moiety remained untouched. After subsequent hydrolysis, the corresponding β-hydroxynitrile could be isolated in a very good yield of 88%.



Scheme 4. Selective reduction of β-ketonitriles to β-hydroxynitriles.

In conclusion, we have established the first carbonylative α-arylation of unactivated nitriles. The optimized reaction conditions were applicable to the synthesis of 24 different β-ketonitriles in 63–93% yield in a straightforward manner. Our protocol allows for the selective carbonylative α-arylation by using atom-economical molecular CO, as well as a CO surrogate, making the system suitable for ^{13}C-labeling of the generated carbonyl center. Furthermore, the transformation is performed with a simple and commercially available catalyst system at a relatively low catalyst loading.

Experimental Section

General procedure for the preparation of 2,2-dimethyl-3-oxo-3-phenylpropanenitrile (2)

In a glove box, six glass vials (4 mL) were charged with $Pd(OAc)_2$ (4 mol%, 8.9 mg), xantphos (5 mol%, 28.9 mg), NaHMDS (1.3 mmol, 238.5 mg), and a stir bar. All vials were placed into an alloy plate, sealed with a septum, and locked out of the glove box. The vials were then equipped with an inlet needle and flushed with argon. Toluene (2 mL) and isobutyronitrile (1.2 mmol, 108 μl) were injected into each vial. After stirring the reaction mixtures for 5 min, iodo benzene (1 mmol, 112 μL) was added to each vial. The alloy plate with the 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 pressurized to 5 bar. Afterwards, the autoclave was heated to 80 °C for 16 h, then cooled to room temperature, and the remaining CO was released slowly. After discharging, HCl (1.0 M; 0.5 mL) was added to each vial and the product was extracted with ethyl acetate. Then, 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 flash chromatography using heptane/ethyl acetate (1:0→20:1) to give 2,2-dimethyl-3-oxo-3-phenylpropanenitrile (**2**) as a pale yellow oil.

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Keywords: α-arylation · β-ketonitriles · carbonylation · palladium

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Synthetic Methods

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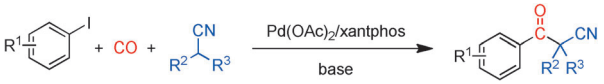
Palladium-Catalyzed Carbonylative α-Arylation to β-Ketonitriles



Three COmponent α-arylation: A carbonylative α-arylation process employing nitriles for the first time is described (see scheme). The reaction tolerates a range of (hetero)aryl iodides and several nitrile coupling partners. No prefunctionalization of the nitriles is necessary and the resulting β-ketonitriles are obtained in good to excellent yields. In addition, the methodology allows for a ^{13}C-labelling of the generated carbonyl moiety.