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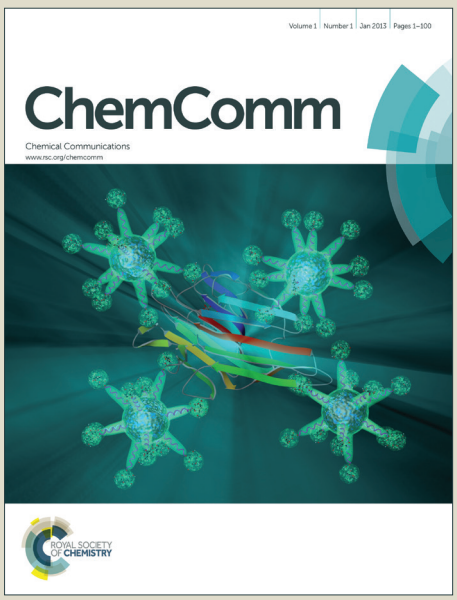

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Palladium-Catalysed Carbonylative α-Arylation of Nitromethane

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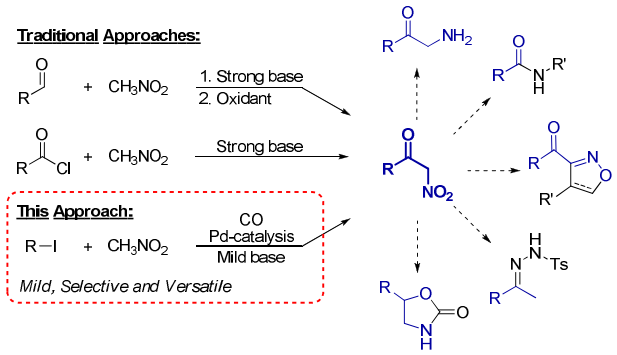
A simple and mild Pd-catalysed carbonylative α-arylation of nitromethane has been realised providing access to α-nitro aryl ketones from an array of aryl and heteroaryl iodides. The methodology requires only a mild base and uses the convenient solid CO releasing molecule, COgen in a two-chamber system. Changing to the isotopically labelled ^{13}COgen, [^{13}C]-acyl labelling can be effected through the generation of a near stoichiometric amount of ^{13}CO. Lastly, the significance of the generated products as synthetic intermediates is demonstrated.

α-Nitro ketones represent a useful class of carbonyl derivatives, which have been exploited as versatile synthons in organic synthesis.[1] Transformations applying this multipurpose motif for heterocycle synthesis are plentiful and include the preparation of oxazolidinones,[2] isoxazoles,[3] pyrroles[4] and furoxans[5], while acyclic amides,[6] ketones,[7] aminoketones[9] and tosyl hydrazones[10] have also been realized. Despite these wide applications, only a limited number of approaches toward the synthesis of α-nitro ketones have been reported in the literature (Scheme 1).[11] These routes rely on either the C-acylation of nitromethane[11a–d] or the oxidation of β-nitro alcohols generated from Henry-type reactions.[11e,12] However, the former class of procedures requires activated carboxylic acid derivatives such as acid chlorides or variations thereof, which are not only unattractive from the point of view of functional group tolerance, but also produce significant waste. On the other hand, the latter class of transformation necessitate the use of an oxidant, which also restricts their utility in organic synthesis. In addition, both these approaches require that the carbonyl group is already installed in the molecule; a feature, which may not always be appealing during a multistep synthesis as other nucleophiles may be needed.

Over the past couple of years, carbonylative α-arylations have emerged as an attractive method for the simultaneous generation of two new C–C bonds and the installation of a carbonyl group.[13] The employment of malonate-type substrates bearing two electron withdrawing functionalities has enabled the employment of mild base in combination with magnesium chloride.[13a–b] Alternatively, substrates bearing only one electron withdrawing group require stronger base and generally provide



Scheme 1. Approaches towards α-nitro ketones.

poorer yields.[13c–f] One recent example disclosed by the Beller group and us features the Pd-catalysed carbonylation of isobutyronitrile to access α-cyano ketones using a strong and hygroscopic base, hexamethyldisilazide.[13f] Appreciating that nitro groups lower the pK_a of α-protons significantly, we speculated if nitromethane could serve as an efficient coupling partner, in spite of its ambivalent and relatively poor nucleophilicity.[14] To this end, we report herein the carbonylative α-arylation using this simple and cheap building block applying only mild base.

Relying on the COware two-chamber system along with 9-methyl-9*H*-fluorene-9-carbonyl chloride (COgen) as the carbon monoxide releasing molecule, identification of the reaction conditions was carried out in a safe and convenient manner.[15,16] Staring from 4-iodoanisole (**1a**), α-nitro ketone **2a** was initially secured in a 67% NMR yield when employing a catalytic system based on $Pd(dba)_2$ and XantPhos in combination with triethylamine and $MgCl_2$ in nitromethane (Table 1, entry 1).[13a–b] Screening other palladium sources only improved the yield of **2a** marginally in the case of $Pd(OAc)_2$ (entries 2–4), while the reaction proved very sensitive to the choice of the supporting ligand (entries 5–9). Utilising the more flexible DPEPhos proved detrimental (entry 5), as did the use of the more bulky monodentate ligands tri-*tert*-butylphosphine and cataCXium A (entries 7 and 8), despite their previous success in carbonylation chemistry.[17] The Buchwald ligand XPhos did provide conversion to product, albeit in an inferior yield (entry 9). Changing the base to the more bulky Cy_2NMe ensured a compatible yield (entry 10), while the stronger base, DBU, shut down the reaction (entry 11). The use of $MgCl_2$ was found to be essential for this transformation as its omission resulted in only trace conversion to product (entry 12). Increasing the amount of COgen to 2.5 equivalents, while reducing the reaction temperature to 60 °C,

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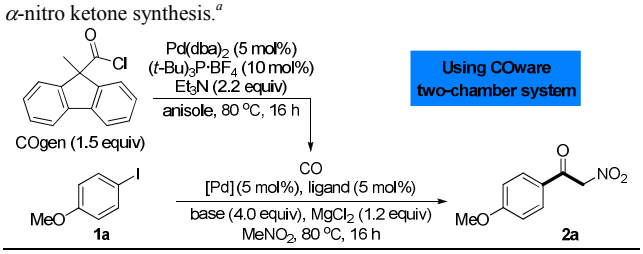
boosted the NMR yield of **2a** to 82% with 4-methoxybenzoic acid observed as the main side-product (entry 13).

Table 1. Selected result from the optimization of this carbonylative α-nitro ketone synthesis.[a]



Entry	[Pd]-catalyst	Ligand	Base	Yield[b] (%)
1	$Pd(dba)_2$	XantPhos	Et_3N	67
2	$[Pd(cinnamyl)Cl]_2$	XantPhos	Et_3N	56
3	$Pd(COD)Cl_2$	XantPhos	Et_3N	63
4	$Pd(OAc)_2$	XantPhos	Et_3N	68
5	$Pd(OAc)_2$	DPEPhos	Et_3N	0
6[c]	$Pd(OAc)_2$	PPh_3	Et_3N	0
7[c]	$Pd(OAc)_2$	$(tBu)_3P•HBF_4$	Et_3N	0
8[c]	$Pd(OAc)_2$	CataCXium A	Et_3N	0
9[c]	$Pd(OAc)_2$	XPhos	Et_3N	22
10	$Pd(OAc)_2$	XantPhos	Cy_2NMe	61
11	$Pd(OAc)_2$	XantPhos	DBU	0
12[d]	$Pd(OAc)_2$	XantPhos	Et_3N	trace
13[e]	**$Pd(OAc)_2$**	**XantPhos**	**Et_3N**	**82**

[a] Reaction condition: Chamber 1: **1a** (0.20 mmol), [Pd] (0.01 mmol), ligand (0.01 mmol), base (0.80 mmol), $MgCl_2$ (0.24 mmol) and nitromethane (2.0 mL) at 80 °C for 16 h. Chamber 2: COgen (0.30 mmol), $Pd(dba)_2$ (0.015 mmol), $(tBu)_3P•HBF_4$ (0.030 mmol), Et_3N (0.80 mmol) and anisole (2.0 mL) at 80 °C for 16 h. [b] ^1H NMR yields with 1,3,5-trimethoxybenzene as internal standard. [c] Ligand (0.02 mmol). [d] $MgCl_2$ was omitted. [e] COgen (0.50 mmol), $Pd(dba)_2$ (0.025 mmol), $(tBu)_3P•HBF_4$ (0.050 mmol), Et_3N (1.33 mmol), at 60 °C.

Having identified optimal reaction conditions for this Pd-catalysed carbonylative α-arylation of nitromethane with aryl iodides, we set out to probe the scope of (hetero)aryl iodides, which could be employed (Scheme 2). Compound **2a** produced from the electron rich 4-iodoanisole was isolated in an 80% yield after 16 h at 60 °C. Alternatively, placing the methoxy-group in the *meta*-position, thus affording a more electron poor aryl iodide, furnished **2b** in a 66% isolated yield. With the methoxy positioned *ortho* to the iodide, carbonylation is known to be more difficult and often requires higher temperatures.[18] Under the optimised reaction conditions, this transformation was successful in furnishing α-nitro ketone **2c**, albeit in moderate yield. With an iodoveratrole the reaction produces **2d** in a good 78% yield, thus allowing the formation of dopamine-like structures after reduction. Similarly, sulphur-containing **2e** and the pyrrole substituted **2f** were realised in good isolated yields, which was also the case for **2g**.

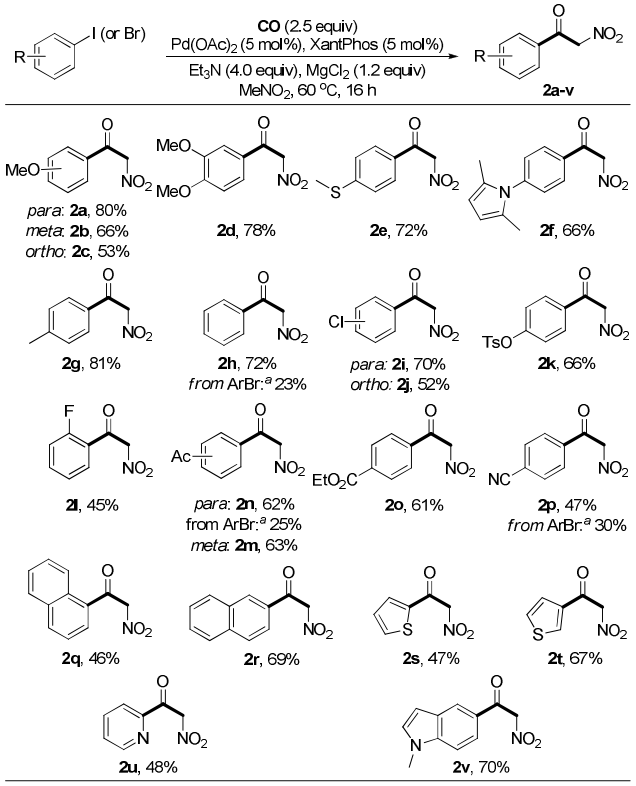
Starting from simple iodobenzene afforded **2h** in 72% isolated yield, while applying the more challenging bromobenzene at an increased temperature of 85 °C, only produced 23% of the desired product.

The ability of this transformation to selectively couple aryl iodides over chlorides and tosylates was demonstrated through the synthesis of **2i**, **2j** and **2k** in isolated yields ranging from 52–70%, with the moderate yield of **2j** being caused by the steric bulk associated with an *ortho*-chloride. Likewise, the presence of an *ortho*-fluoride caused the isolated yield of **2l** to be moderate. Despite the nucleophilic nature of the nitronate anion, aryl iodides bearing electrophilic substituents turn out to be competent substrates for this transformation. To this end, **2n** and **2m** were secured in yields of 62% and 63%, respectively, while a 61% of **2o** presenting an ester was furnished. Applying the corresponding aryl bromide to the synthesis of **2n** resulted in moderate conversion to product. Equivalently, when preparing **2p** from the aryl iodide, 47% of the product could be isolated, while the aryl bromide provided 30% of **2p**.

Extended aromatic systems like 1- and 2-iodonaphathalene also proved to be competent substrates, with the less sterically challenging coupling to afford **2r** outperforming the preparation of **2q**.

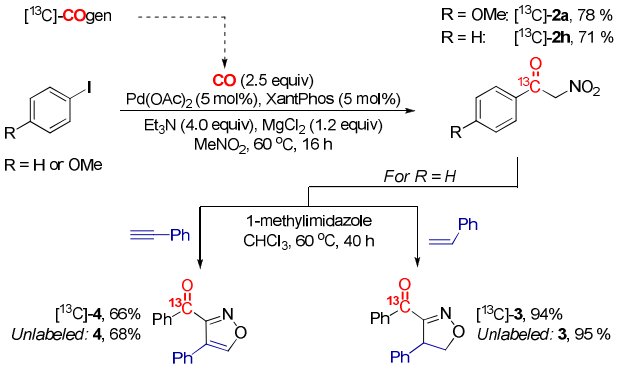
Heteroaromatic compounds occupy a central place in medicinal chemistry; yet these important motifs are often challenging substrates in any cross coupling reaction.[19] Subjecting 2- and 3-iodothiophene to the optimised coupling conditions allowed for the isolation of **2s** and **2t** in yields of 47% and 67%, respectively. Furthermore, heteroaryl iodides of the important nitrogen heterocycles such as pyridine and indole could be transformed into products **2u** and **2v** in a synthetically useful manner.

The impurity profile of this reaction mainly included the corresponding carboxylic acid, possibly formed through *O*-acylation, while full consumption of starting material was observed in all cases.[13d] Attempting to apply other nitroalkanes than nitromethane as substrates for this carbonylative transformation, was unfortunately unsuccessful in our hands.



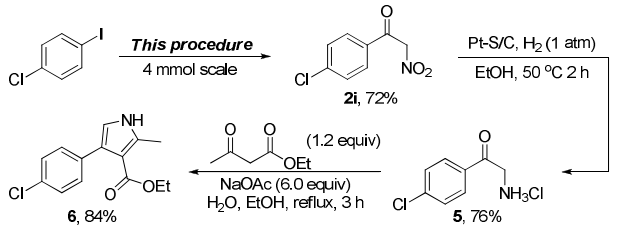
Scheme 2. Scope of Pd-catalysed α-arylation of nitromethane, see Supporting Information for details. [a] 85 °C.

With the carbonylative transformation presented herein only requiring 2.5 equivalents of carbon monoxide, carbonyl labelling should be feasible through the use of isotopically labelled COgen.[15a] Indeed, by applying [^{13}C]-COgen, α-nitro ketone [^{13}C]-**2a** and [^{13}C]-**2h** could be isolated in good yields with no other change in the reaction conditions (Scheme 3).



Scheme 3. [^{13}C]-Carbonyl labelling and formation of labelled heterocycles through [3+2] dipolar cycloaddition.

With a convenient, mild and selective synthesis of both isotopically labelled and unlabelled α-nitro ketones in hand, we set out to demonstrate the applicability of these products. Through [3+2] dipolar cycloaddition, [^{13}C]-**2a** was initially transformed into isoxazoline [^{13}C]-**3** and isoxazole [^{13}C]-**4** in 94% and 66% isolated yield, respectively,[20] the yields, which are compatible with the ones obtained in the non-isotopically labelled synthesis of **3** and **4**. Alternatively, the produced α-nitro ketones may be used in a Knorr pyrrole synthesis (Scheme 4).[21] After a 4 mmol scale preparation of **2i**, chemoselective hydrogenation of the nitro group using a sulfided platinum catalyst provides **5** in a 76% isolated yield. Treatment of this α-amino ketone hydrochloride salt with ethyl acetoacetate and sodium acetate cleanly furnishes pyrrole **6** in an 84% isolated yield.



Scheme 4. Pyrrole synthesis from α-nitro arylketone.

Mechanistically, we suggest that this carbonylative α-arylation follows a path equivalent to what has previously been proposed (Figure 1).[13b] Following oxidative addition into the (hetero)aryl halide, carbon monoxide coordination and insertion, the palladium acyl species is trapped by the nitronate carbanion. The oxophilic coordination of magnesium chloride to nitromethane does not only facilitate deprotonation by the mild base, but also increase product formation through favoured C- versus O-acylation. The initially formed product is more acidic than nitromethane itself and is consequently deprotonated, likely by the combined efforts of magnesium chloride and triethylamine. Upon acidic workup, the desired α-nitro ketone is reformed.

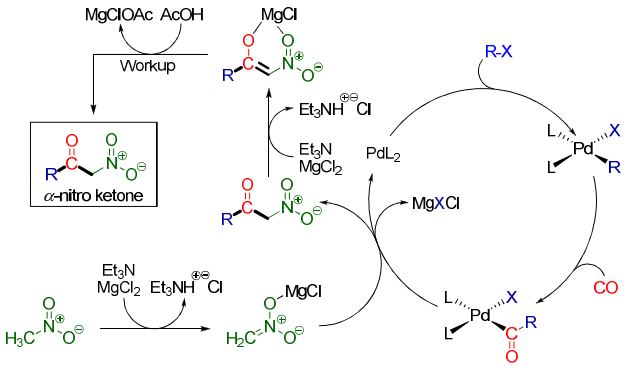


Figure 1. Proposed reaction mechanism for this carbonylative α-nitro ketone synthesis.

In summary, we have presented a mild, selective and versatile method for the preparation of α-nitro aryl ketones via the palladium-catalysed carbonylative α-arylation of nitromethane. The methodology efficiently transforms an array of aryl and heteroaryl iodides into this useful compound using only mild base. Additionally, because a near stoichiometric amount of carbon monoxide is applied, being generated from the safe and convenient solid precursor, COgen, the reaction was easily extended to isotopic labelling of the carbonyl carbon. Lastly, starting from α-nitro ketones, the convenient access to a number of important heterocycles was demonstrated.

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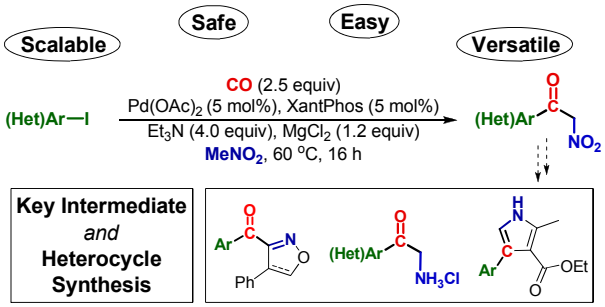

A palladium-catalysed approach to α-nitroketones via carbonylative α-arylation of nitromethane is presented, thus providing easy access to key intermediates and important heterocycles.