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Pd-Catalyzed Carbonylative Access to AroylPhosphonates from(Hetero)Aryl Bromides

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The first transition-metal catalysed carbonylation with a phosphorus nucleophile is presented. This transformation provides efficient and mild access to aroylphosphonates under mild conditions, thus ensuring a broad substrate scope. The 10 utility of aroylphosphonates as useful reagents, capable of participating in a number of transformations, is subsequently demonstrated. Furthermore, access to $\int^{13}C$ -carbonyl labelled aroylphosphonates is easily realised for the first time, as only a near stoichiometric amount of CO is required applying this 15 carbonylation.

Introduction

The formation of new carbon-phosphorus bonds has traditionally been undertaken via simple substitution reactions on carbon fragments possessing an appropriate leaving group.¹ Lately, a 20 number of transformations applying transition metal catalysis have been presented as viable alternatives.^{2m} These operate under milder conditions, include alternative substrates, and provide easy access to a wide range of phosphorus-containing products,² which are of increasing interest in both material science and biological 25 chemistry.^{1,3}

In contrast to the preparation of aryl phosphonates via transition metal catalysis, and despite the well-documented usefulness of aroylphosphonates, their preparation has only been undertaken through acyl substitution of acid chlorides with alkyl

- ³⁰ phosphite reagents (Michaelis-Arbuzov-type reaction).⁴ However, potential disadvantages associated with this approach includes poor functional group tolerance associated with acid chloride synthesis, their high reactivity, and the need for the carbonyl group to already be installed in the starting material. A Pd-
- 35 catalysed carbonylative strategy would have the potential to target these short comings. To this end, we set out to include phosphorus among the competent nucleophiles in carbonylation couplings, which are currently based on the following elements, H,⁵C,⁶N,⁷O,⁸F,⁹Si,¹⁰S,¹¹ and Cl¹² (Scheme 1).
- With the aim of developing a carbonylative route for the preparation of aroylphosphonates with the generation of two new bonds, one of these being a C-P bond, we settled on Hphosphonates as nucleophiles. These air stable, easy to handle, and inexpensive P(V)-reagents are in equilibrium with their



Scheme 1. Carbonylative couplings employing different nucleophiles

corresponding diorganophosphites and display both P- and O nucheophilicity.^{1,13} Initiating our search for suitable conditions which would ensure a satisfactory level of P- versus O-selectivity 55 in this carbonylative cross coupling, we subjected equimola amounts of aryl bromide 1a and diethyl phosphite (2a) to carbo. monoxide (1.5 equiv), triethylamine (1.5 equiv), Pd(dba)₂ (5 mol%) and XantPhos (5 mol%) in dioxane at 80 °C for 16 hours. (Table 1, entry 1).¹⁴ This ensured full conversion of the ary' 60 bromide and a 75% NMR yield of the desired product **3a** with the corresponding carboxylic acid as the main side-product. Although

- various palladium sources proved effective for this carbonylatio. (entries 2-6), Pd(dba)₂ remained the ideal palladium source. Applying a selection of mono- and bidentate phosphine ligar we observed a significant superiority of XantPhos-type ligands
- (entries 7-12).15 Employing more sterically encumbered bases (Cy₂NMe or DIPEA) only served to reduce reaction efficiency (entries 13 and 14), while using the stronger base DBU resulted in O-acylation, ultimately leading to the corresponding carboxylic 70 acid (entry 15). Finally, increasing the temperature to 90 °C and employing a 0.5 equivalent excess of 1a boosted the NMR yiel

to 87% (entry 17). Having developed suitable reaction conditions for thi. carbonylative preparation of aroylphosphonates, we next turned 75 our attention towards the substrate scope of this C-P bond forming transformation (Scheme 2). Product 3a resulting from the coupling of the electron rich 4-bromoanisole (1a) was isola ed in 79% yield. In comparison with the observed 86% NMR yield slight decomposition of 3a had occurred during purification ⁸⁰ possibly via hydrolysis to 4-methoxylbenzoic acid.¹⁶ The methoxy-group in the meta-position also provided the product in a good isolated yield of 3b. Other electron donating substituents such as methyl, tert-butyl and dimethylamino were also tolerate under the optimised reaction conditions, thus providing products

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Table 1. Optimisation of Pd-catalysed carbonylative aroylphosphonate synthesis with selected examples.

synthesis with selected examples.				
MeO 1 (1.0 c	Br O + H ^P OEt - a 2 equiv) (1.0 equiv)	1.5 equiv CO 'Pd' (5 mol%) <u>Phosphine (10 mol%)</u> Base (1.5 equiv) Dioxane (0.1 M), 80 °C, 1	→ 6 h MeO	P.OEt 0 OEt 3a
Entry	[Pd]-catalyst	Ligand	Base	Yield ^a (%)
1	Pd(dba) ₂	XantPhos	Et₃N	75
2	[Pd(cinnamyl)Cl] ₂	XantPhos	Et₃N	40
3	PdCl ₂	XantPhos	Et₃N	60
4	Pd(PPh ₃) ₂ Cl ₂	XantPhos	Et₃N	47
5	Pd(COD)Cl ₂	XantPhos	Et₃N	53
6	Pd(OAc) ₂	XantPhos	Et₃N	55
7	Pd(dba) ₂	PPh₃	Et₃N	0
8	Pd(dba) ₂	(<i>t</i> Bu)₃P•HBF₄	Et₃N	0
9	Pd(dba) ₂	CataCXium A	Et₃N	0
10	Pd(dba) ₂	XPhos	Et₃N	0
11	Pd(dba) ₂	DPEPhos	Et₃N	34
12	Pd(dba) ₂	NiXantPhos	Et₃N	58
13	Pd(dba) ₂	XantPhos	Cy ₂ NMe	44
14	Pd(dba) ₂	XantPhos	DIPEA	34
15	Pd(dba) ₂	XantPhos	DBU	0
16 ^b	Pd(dba) ₂	XantPhos	Et₃N	83
17 ^{b,c}	Pd(dba) ₂	XantPhos	Et₃N	87
all INMO solutions intermediate dand (1.2.5 to inset here 1.				

⁵ ^b90 °C. ^c 1.5 equiv of (Het)Ar-Br.

3c, **3d** and **3e** in isolated yields of 80%, 69% and 92%, respectively. Likewise, the disubstituted **3f** was obtained from 4-bromoveratrole in an 88% yield after flash column chromatography.

- The use of bromobenzene led to better *P* versus *O*-selectivity at a slightly lower reaction temperature of 80 °C, resulting in a 75% isolated yield of **3g**. Tolerance towards other halides on the aryl-ring was demonstrated by the synthesis and isolation of compounds **3h** and **3i** in yields of 61% and 62%, respectively.
- ¹⁵ The reduced stability of these more electron poor products, which are prepared at 70 °C, is highlighted by the corresponding 75% and 78% NMR yields of **3h** and **3i**, respectively. Coupling of 4-bromobiphenyl was most efficient at 70 °C and gave product **3j** in a satisfactory yield of 77%, while the corresponding aryl ²⁰ triflate produced the product in a slightly lower yield. Aroylphosphonate **3k** displaying a ketone was, despite the electrophilic nature of this functionality, isolated in a 50% yield with no detection of side-products involving this ketone. Bromonaphthalenes also proved to be competent substrates for
- 25 this transformation, providing **31** and **3m** in 76% and 67% yield, respectively.

Shifting focus towards heteroaryl bromides, *N*-methyl protected 5-bromoindole was transformed into aroylphosphonate **3n** in a 51% isolated yield, while a 60% yield of the ³⁰ benzofuranderivative **30** could be secured. Bromothiophene

displaying substrates also underwent successful coupling to afford **3p** and **3q** in 58% and 41% isolated yield, respectively.

Next, we turned our attention to the other H-phosphonate nucleophiles. Under the optimised reaction conditions, **1a** readily ³⁵ reacts with both di-*n*-butyl phosphite, as well as the more sterically encumbered diisopropylphosphite, thus furnishing aroylphosphonates **3r** and **3s** in yields of 80% and 88%, respectively. Unfortunately, diarylphosphites were not suitable substrates for this chemistry.



Scheme 2. Scope of the carbonylative aroylphosphonate synthesis. For reaction conditions, see supporting information and yields are calculated from the amount of H-phosphonate.^{*a*} 90 °C. ^{*b*} 80 °C. ^{*c*} 70 °C.

As this new carbonylative transformation only requires a ⁴⁵ slight excess of CO generated from 1.5 equivalents of COgen, the methodology is adaptable to isotope labelling.¹⁴ Simply applying ¹³COgen instead of COgen, allowed products [¹³C]-**3a** and [¹³C]-**3e** to be prepared in good yields after subjection to the optimised reaction conditions (Scheme 3).¹⁷

⁵⁰ Having established a mild and efficient Pd-catalyset. carbonylative strategy for the synthesis of aroylphosphonates, we set out to underline the utility of these products (Scheme 4). α -Fluorination was easily effected in a 55% yield by treating benzoylphosphonate **3g** with DAST.¹⁸ Tertiary alcohol **5** was ⁵⁵ easily assembled in an excellent yield by using acetone as the nucleophile under enamine-catalysis.¹⁹



Scheme 3. ¹³C-Labelling of aroylphosphonates using ¹³COgen.

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Scheme 4. Utilisation of the aroylphosphonate products. Reaction conditions: (a) DAST (4.0 equiv), 0 °C to r. t. (b) *L*-proline (0.5 equiv), acetone, rt, 24 h.(c) NH₂NMe₂ (1.4 equiv), AcOH, rt, 2 h. (d) PhCHO (1.1 5 equiv), KCN (0.3 equiv), DMF, rt, 6 h. (e) PMe₃ (1.0 equiv), THF, rt, 2 h.

Hydrazine also proved reactive towards **3g**, producing the hydrazone derivative **6** in good yield.²⁰ Aroylphosphonates can be converted into aroyl nucleophiles by treatment with cyanide, and after phosphonate-phosphate rearrangement, the formed ¹⁰ carbanion can be trapped to form for example cross-benzoin products like **7**.²¹ Furthermore, the carbonyl group of aroylphosphonates can be chemoselectively reduced under mild conditions by treatment with PMe₃, thus affording benzylic alcohols like **8**.²²

- Finally, a plausible mechanism for this Pd-catalyzed carbonylative approach towards aroylphosphonates is illustrated in Figure 1. Initially, oxidative addition of palladium(0) into the (hetero)aryl bromide (or triflate) bond, coordination of carbon monoxide and migratory insertion affords the palladium-acyl 20 complex A. Diorgano H-phosphonates B are in equilibrium with their corresponding diorganophosphites C, and coordination of this P(III) reagent to palladium, affords either O-bound complex D or P-bound complex E. These are like to be equilibrium as demonstrated for enolates.²³ Subsequent deprotonation of E with 25 the mild amine base used, would provide palladium(II) complex F, which upon reductive elimination forms the desired product while regenerating the ligated palladium(0). Observation of carboxylic acid as the major side-product may be rationalised by deprotonation of the O-bound complex **D**, followed by reductive 30 elimination to form G. Upon exposure to moisture, G is easily
- hydrolysed into the corresponding benzoic acid.



Figure1. Proposed mechanism of carbonylative aroylphosphonate synthesis.

In summary, we have presented the first transition metalcatalysed carbonylation employing a phosphorus-bac view Article Online high yielding access to a selection of aroylphosphonates unde mild reaction conditions, thus allowing for a broad substrate scope. The effectiveness of this transformation, even under a near stoichiometric amount of carbon monoxide, also allows fo isotopic acyl labelling, as demonstrated herein by the incorporation of ¹³CO. Consequently, we believe thi, methodology provides an attractive alternative to the classically 45 employed acyl substitution of acid chlorides.

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This first carbonylative coupling employing a phosphorusbased nucleophile provides easy and safe access to acyl ⁵ phosphonates under mild conditions.

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