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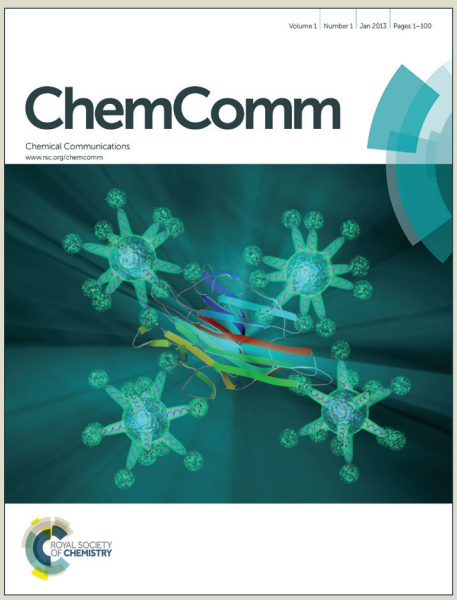

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ARTICLE TYPE

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

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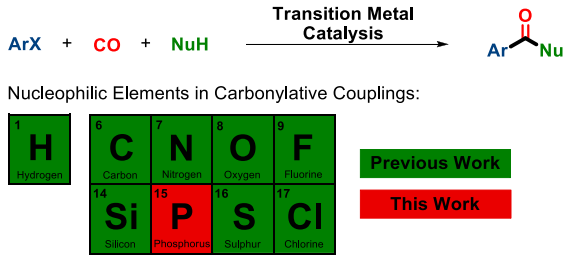
The first transition-metal catalysed carbonylation with a phosphorus nucleophile is presented. This transformation provides efficient and mild access to aroylphosphonates under mild conditions, thus ensuring a broad substrate scope. The utility of aroylphosphonates as useful reagents, capable of participating in a number of transformations, is subsequently demonstrated. Furthermore, access to [^{13}C]-carbonyl labelled aroylphosphonates is easily realised for the first time, as only a near stoichiometric amount of CO is required applying this 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 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 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 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-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,[5] C,[6] N,[7] O,[8] F,[9] Si,[10] S,[11] and Cl[12] (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 H-phosphonates 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 in this carbonylative cross coupling, we subjected equimola amounts of aryl bromide **1a** and diethyl phosphite (**2a**) to carbon 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 aryl 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 carbonylation (entries 2–6), Pd(dba)$_2$ remained the ideal palladium source. Applying a selection of mono- and bidentate phosphine ligands, we observed a significant superiority of XantPhos-type ligands (entries 7–12).[15] Employing more sterically encumbered bases (Cy_2NMe 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 acid (entry 15). Finally, increasing the temperature to 90 °C and employing a 0.5 equivalent excess of **1a** boosted the NMR yield to 87% (entry 17).

Having developed suitable reaction conditions for this carbonylative preparation of aroylphosphonates, we next turned 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 isolated in 79% yield. In comparison with the observed 86% NMR yield, slight decomposition of **3a** had occurred during purification 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 tolerated under the optimised reaction conditions, thus providing products

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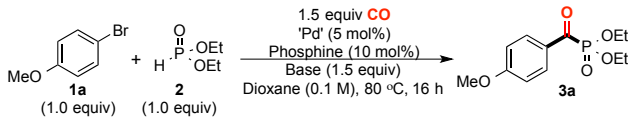
Table 1. Optimisation of Pd-catalysed carbonylative aroylphosphonate synthesis with selected examples.



Entry	[Pd]-catalyst	Ligand	Base	Yield[a](%)
1	$Pd(dba)_2$	XantPhos	Et_3N	75
2	$[Pd(cinnamyl)Cl]_2$	XantPhos	Et_3N	40
3	$PdCl_2$	XantPhos	Et_3N	60
4	$Pd(PPh_3)_2Cl_2$	XantPhos	Et_3N	47
5	$Pd(COD)Cl_2$	XantPhos	Et_3N	53
6	$Pd(OAc)_2$	XantPhos	Et_3N	55
7	$Pd(dba)_2$	PPh_3	Et_3N	0
8	$Pd(dba)_2$	$(tBu)_3P•HBF_4$	Et_3N	0
9	$Pd(dba)_2$	CataCXium A	Et_3N	0
10	$Pd(dba)_2$	XPhos	Et_3N	0
11	$Pd(dba)_2$	DPEPhos	Et_3N	34
12	$Pd(dba)_2$	NiXantPhos	Et_3N	58
13	$Pd(dba)_2$	XantPhos	Cy_2NMe	44
14	$Pd(dba)_2$	XantPhos	DIPEA	34
15	$Pd(dba)_2$	XantPhos	DBU	0
16[b]	$Pd(dba)_2$	XantPhos	Et_3N	83
17[b,c]	$Pd(dba)_2$	XantPhos	Et_3N	87

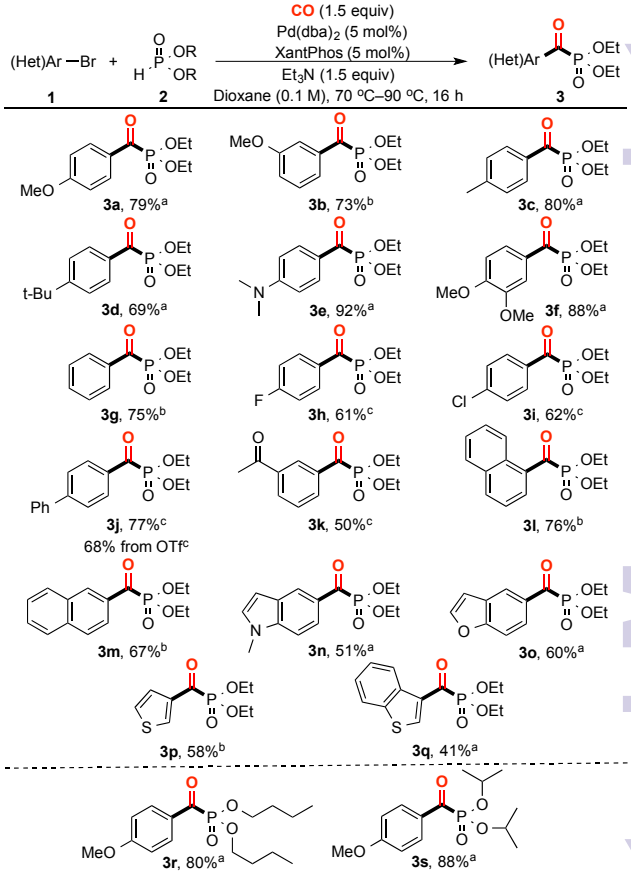
[a] ^{1}H-NMR yield using internal standard (1,3,5-trimethoxybenzene). [b] 90 °C. [c] 1.5 equiv of (Het)Ar-Br.

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. 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 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 this transformation, providing **3l** 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 benzofuranderivative **3o** could be secured. Bromothiophene displaying substrates also underwent successful coupling to afford **3p** and **3q** in 58% and 41% isolated yield, respectively.

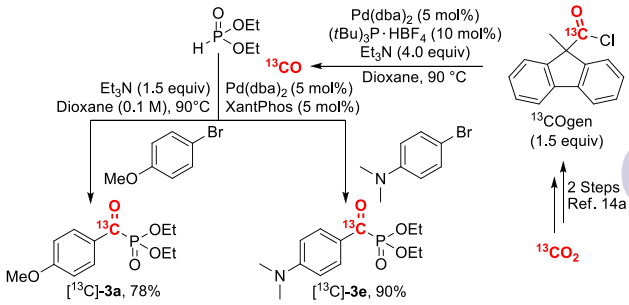
Next, we turned our attention to the other H-phosphonate nucleophiles. Under the optimised reaction conditions, **1a** readily reacts with both di-*n*-butyl phosphite, as well as the more sterically encumbered diisopropylphosphite, thus furnishing aroylphosphonates **3r** and **3s** in yields of 80%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



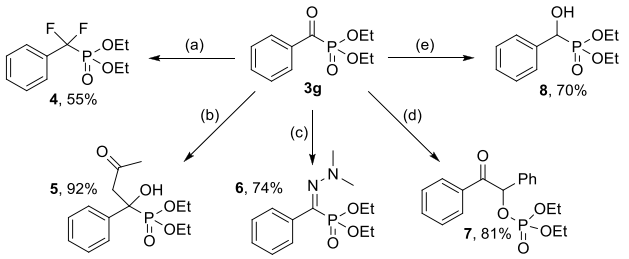
Scheme 2. Scope of the carbonylative aroylphosphonate synthesis. For reaction conditions, see supporting information and yields are calculated from the amount of H-phosphonate.[a] 90 °C. [b] 80 °C. [c] 70 °C.

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

Having established a mild and efficient Pd-catalysed 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 easily assembled in an excellent yield by using acetone as the nucleophile under enamine-catalysis.[19]



Scheme 3. ^{13}C-Labelling of aroylphosphonates using ^{13}COgen.



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) NH_2NMe_2 (1.4 equiv), AcOH, rt, 2 h. (d) PhCHO (1.1 equiv), KCN (0.3 equiv), DMF, rt, 6 h. (e) PMe_3 (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 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 PMe_3, 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 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 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 elimination to form **G**. Upon exposure to moisture, **G** is easily hydrolysed into the corresponding benzoic acid.

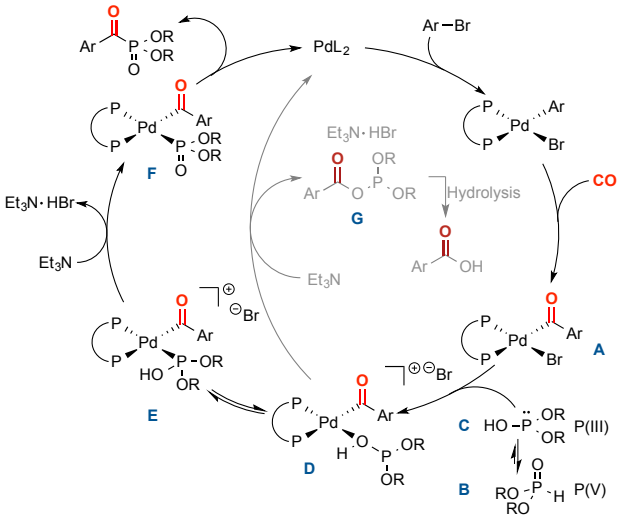


Figure1. Proposed mechanism of carbonylative aroylphosphonate synthesis.

In summary, we have presented the first transition metal-catalysed carbonylation employing a phosphorus-based nucleophile. This novel methodology provides easy, safe and high yielding access to a selection of aroylphosphonates under 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 for isotopic acyl labelling, as demonstrated herein by the incorporation of ^{13}CO. Consequently, we believe this methodology provides an attractive alternative to the classically employed acyl substitution of acid chlorides.

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Notes and references

1 (a) Engel, R. Handbook of Organophosphorus Chemistry; Marcel Dekker: New York, 1992. (b) The Chemistry of Organophosphorus Compou Hartley, F. R., Ed.; Wiley: New York, 1996; Vol. 4. (c) Quin, L. D. A Guide to Organophosphorus Chemistry; Wiley: New York, 2000.

2 (a) O. Berger, C. Petit, E. L. Deal and J. L. Montchamp, *Adv. Sy Catal.*, 2013, **355**, 1361-1373. (b) B. Q. Xiong, M. Li, Y. X. Liu, Y. F Zhou, C. Q. Zhao, M. Goto, S. F. Yin and L. B. Han, *Adv. Synth. Catal.*, 2014, **356**, 781-794. (c) K. Xu, F. Yang, G. D. Zhang and Y. J. Wu *Green Chem.*, 2013, **15**, 1055-1060. (d) A. J. Bloomfield and S. B. Herzo *Org.Lett.*, 2012, **14**, 4370-4373. (e) C. Huang, X. Tang, H. A. Fu, Y. Y. Jiang and Y. F. Zhao, *J. Org. Chem.*, 2006, **71**, 5020-5022. (f) H. H. R Y. Jin, H. Fu, Y. Y. Jiang and Y. F. Zhao, *Chem-Eur. J.*, 2006, **12**, 3636-3646. (g) Y. Matano, K. Matsumoto, Y. Terasaka, H. Hotta, Y. Araki, C Ito, M. Shiro, T. Sasamori, N. Tokitoh and H. Imahori, *Chem.-Eur. J.* 2007, **13**, 891-901. (h) N. T. McDougal, J. Streuff, H. Mukherjee, S. C. Virgil and B. M. Stoltz, *Tetrahedron Lett.*, 2010, **51**, 5550-5554. (i) M Toffano, C. Dobrota and J. C. Fiaud, *Eur. J. Org. Chem.*, 2006, 650-65 (j) E. L. Deal, C. Petit and J. L. Montchamp, *Org.Lett.*, 2011, **13**, 3270-3273. (k) M. Kalek, M. Jezowska and J. Stawinski, *Adv. Synth.Catal* 2009, **351**, 3207-3216. For a review, see: (l) F. M. J. Tappe, V. T. Trepoh and M. Oestreich, *Synthesis,* 2010, 3037-3062. (m) E. Jablonkai and G Keglevich, *Curr. Org. Synth.*, 2014, **11**, 429-453.

3 (a) Corbridge, D. E. C. Phosphorus: An Outline of Its Chemistry, Biochemistry and Uses, 5th ed.; Elsevier: Amsterdam, 1995. (b) Aminophosphonic and Aminophosphinic Acids: Chemistry Biological Activity; Kukhar, V. P., Hudson, H. R., Eds.; Wi Chichester, 2000. (c) E. Soulier, J. C. Clement, J. J. Yaouanc and H. des Abbayes, *Tetrahedron Lett.*, 1998, **39**, 4291-4294. (d) L. Devel, V. Rogakos, A. David, A. Makaritis, F. Beau, P. Cuniasse, A. Yiotakis and V Dive, *J. Biol. Chem.*, 2006, **281**, 11152-11160. (e) F. R. Alexandre, A Amador, S. Bot, C. Caillet, T. Convard, J. Jakubik, C. Musiu, B. Poddesu L. Vargiu, M. Liuzzi, A. Roland, M. Seifer, D. Standring, R. Storer and C B. Dousson, *J. Med. Chem.*, 2011, **54**, 392-395.

4 (a) M. Sekine, M. Satoh, H. Yamagata and T. Hata, *J. Org. Chem.*, 198 **45**, 4162-4167. (b) Y. Huang, F. Berthiol, B. Stegink, M. M. Pollard an A. J. Minnaard, *Adv. Synth.Catal.*, 2009, **351**, 1423-1430. (c) M. Sprech and D. Kost, *J. Am. Chem. Soc.*, 1994, **116**, 1016-1026.

5 For selected examples of carbonylative C–H cross coupling: (a) H. Neumann, R. Kadyrov, X. F. Wu and M. Beller, *Chem.-Asian J.*, 2012, 2213-2216. (b) W. Y. Hao, G. D. Ding and M. Z. Cai, *Catal. Commun.* 2014, **51**, 53-57. (c) S. Korsager, R. H. Taaning, A. T. Lindhardt and T. Skrydstrup, *J. Org. Chem.*, 2013, **78**, 6112-6120. (d) J. W. Jiang, P Wang and M. Z. Cai, *J. Chem. Res.*, 2014, 218-222.

6 For selected examples of carbonylative C–C cross coupling: (a) Z. Zhang, Y. Y. Liu, M. X. Gong, X. K. Zhao, Y. Zhang and J. B. Wang *Angew. Chem. Int. Edit.*, 2010, **49**, 1139-1142. (b) A. Park and S. Le *Org. Lett.*, 2012, **14**, 1118-1121. (c) Z. Lian, S. D. Friis and T Skrydstrup, *Angew. Chem. Int. Ed.*, 2014, **53**, 9582-9586. (d) K. T Neumann, S. R. Laursen, A. T. Lindhardt, B. Bang-Andersen and T. Skrydstrup, *Org. Lett.*, 2014, **16**, 2216-2219. (e) K. M. Bjerglund, T Skrydstrup and G. A. Molander, *Org. Lett.*, 2014, **16**, 1888-1891. (f) S Korsager, D. U. Nielsen, R. H. Taaning and T. Skrydstrup, *Angew. Chem.*

Int. Edit., 2013, **52**, 9763-9766. (g) Z. Lian, S. D. Friis and T. Skrydstrup, *Chem. Commun.*, 2015, **51**, 1870-1873. (h) Z. Lian, S. D. Friis and T. Skrydstrup, *Chem. Commun.*, 2015, **51**, 3600-3603.

7 For selected examples of carbonylative C–N cross coupling reaction: (a) X. F. Wu, H. Neumann and M. Beller, *Chem-Asian J.*, 2010, **5**, 2168-2172. (b) T. T. Dang, Y. H. Zhu, J. S. Y. Ngiam, S. C. Ghosh, A. Q. Chen and A. M. Seayad, *ACS Catal.*, 2013, **3**, 1406-1410. (c) S. R. Borhade, A. Sandstrom and P. I. Arvidsson, *Org. Lett.*, 2013, **15**, 1056-1059. (d) F. Tinnis, O. Verho, K. P. J. Gustafson, C. W. Tai, J. E. Backvall and H. Adolfsson, *Chem.-Eur. J.*, 2014, **20**, 5885-5889. (e) T. Fang, X. H. Gao, R. Y. Tang, X. G. Zhang and C. L. Deng, *Chem. Commun.*, 2014, **50**, 14775-14777. (f) S. D. Friis, T. Skrydstrup and S. L. Buchwald, *Org. Lett.*, 2014, **16**, 4296-4299. (g) Z. Lian, S. D. Friis, A. T. Lindhardt and T. Skrydstrup, *Synlett*, 2014, **25**, 1241-1245.

8 For selected examples of carbonylative C–O cross coupling reaction: (a) W. Magerlein, A. F. Indolese and M. Beller, *Angew. Chem. Int. Edit.*, 2001, **40**, 2856-2859. (b) C. M. Kormos and N. E. Leadbeater, *Org.Biomol. Chem.*, 2007, **5**, 65-68. (c) Z. Xin, T. M. Gogsig, A. T. Lindhardt and T. Skrydstrup, *Org. Lett.*, 2012, **14**, 284-287. (d) J. Schranck, A. Tlili, H. Neumann, P. G. Alsabeh, M. Stradiotto and M. Beller, *Chem.-Eur. J.*, 2012, **18**, 15592-15597. (e) H. Zhang, R. Y. Shi, A. X. Ding, L. J. Lu, B. R. Chen and A. W. Lei, *Angew. Chem. Int. Edit.*, 2012, **51**, 12542-12545.

9 (a) T. Sakakura, M. Chaisupakitsin, T. Hayashi and M. Tanaka, *J. Organomet. Chem.*, 1987, **334**, 205-211. (b) T. Okano, N. Harada and J. Kiji, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 1741-1743.

10 X. F. Wu, H. Neumann and M. Beller, *Tetrahedron Lett.*, 2012, **53**, 582-584.

11 (a) H. Cao, L. McNamee and H. Alper, *J. Org. Chem.*, 2008, **73**, 3530-3534. (b) Y. H. Hu, J. Liu, Z. X. Lu, X. C. Luo, H. Zhang, Y. Lan and A. W. Lei, *J. Am. Chem. Soc.*, 2010, **132**, 3153-3158. (c) M. N. Burhardt, Ahlburg, A. and T. Skrydstrup, *J. Org. Chem.*, 2014, **79**, 11830–11840. (d) S. M. Islam, R. A. Molla, A. S. Roy and K. Ghosh, *Rsc. Adv.*, 2014, **4**, 26181-26192.

12 J. S. Quesnel and B. A. Arndtsen, *J. Am. Chem. Soc.*, 2013, **135**, 16841-16844.

13 A. De Blieck, K. G. R. Masschelein, F. Dhaene, E. Rozycka-Sokolowska, B. Marciniak, J. Drabowicz and C. V. Stevens, *Chem. Commun.*, 2010, **46**, 258-260.

14 Carbon monoxide was delivered to the reaction by decarbonylative Pd-catalysis of COgen (9-methyl-9*H*-fluorene-9-carbonyl) in the two-chamber system COware, see: (a) P. Hermange, A. T. Lindhardt, R. H. Taaning, K. Bjerglund, D. Lupp and T. Skrydstrup, *J. Am. Chem. Soc.*, 2011, **133**, 6061-6071. For other CO releasing molecules in COware, see (b) S. D. Friis, R. H. Taaning, A. T. Lindhardt and T. Skrydstrup, *J. Am. Chem. Soc.*, 2011, **133**, 18114-18117. (c) P. Nordeman, L. R. Odell and M. Larhed, *J. Org. Chem.*, 2012, **77**, 11393-11398. (d) L. R. Odell, F. Russo and M. Larhed, *Synlett*, 2012, **23**, 685-698.

15 (a) P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek and P. Dierkes, *Chem. Rev.*, 2000, **100**, 2741-2770. (b) J. R. Martinelli, D. A. Watson, D. M. M. Freckmann, T. E. Barder and S. L. Buchwald, *J. Org. Chem.*, 2008, **73**, 7102-7107.

16 S. M. A. Kedrowski and D. A. Dougherty, *Org. Lett.*, 2010, **12**, 3990-3993.

17 In a similar matter, radioactive ^{14}C-labeled aroylphosphonates would also be easily accessible ascarbon-14 labelling using ^{14}COgen has been established using a setup equivalent to carbon-13 labelling. See: A. T. Lindhardt, R. Simonssen, R. H. Taaning, T. M. Gøgsig, G. N. Nilsson, G. Stenhagen, C. S. Elmore and T. Skrydstrup, *J. Labelled Compd. Radiopharm.*, 2012, **55**, 411-418.

18 T. R. Burke, M. S. Smyth, A. Otaka and P. P. Roller, *Tetrahedron Lett.*, 1993, **34**, 4125-4128.

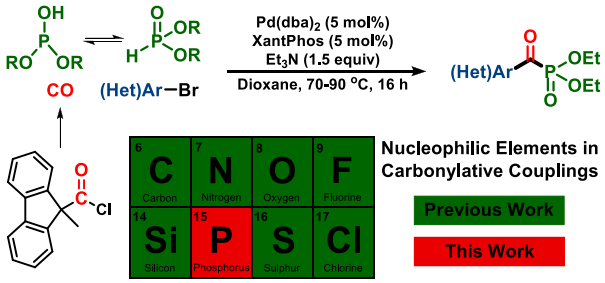
19 S. Samanta and C. G. Zhao, *J. Am. Chem. Soc.*, 2006, **128**, 7442-7443.

20 Z. H. Kudzin and A. Kotynski, *Synthesis*, 1980, 1028-1032.

21 A. S. Demir, O. Reis, A. C. Igdir, I. Esiringu and S. Eymur, *J. Org. Chem.*, 2005, **70**, 10584-10587.

22 W. Zhang and M. Shi, *Chem. Commun.*, 2006, 1218-1220.

23 D. A. Culkin and J. F. Hartwig, *Organometallics*, 2004, **23**, 3398-3416



This first carbonylative coupling employing a phosphorus-based nucleophile provides easy and safe access to acyl phosphonates under mild conditions.