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Synthesis of α -Arylphosphonates Using Copper-Catalyzed α -Arylation and Deacylative α -Arylation of β -Ketophosphonates

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Abstract

Efficient methods for the direct arylation and deacylative arylation of β -ketophosphonates with iodoarenes in presence of a copper(I) or a copper(II) salt as the catalysts were developed. The corresponding α -arylphosphonates were obtained in high yields. A tentative mechanism for the deacylative arylation reaction was proposed on the basis of the experimental data.

Keywords

α -arylphosphonates; deacylation; iodoarenes; arylation; coupling

α -Aryl substituted methylphosphonate and β -ketophosphonate derivatives are frequently used as anti-inflammatory agents.^[1] For example, they have been shown to be potent dual inhibitors of neutrophil cathepsin G and mast cell chymase, which are associated with asthma and chronic obstructive pulmonary diseases.^[1a-c] They are also useful precursors for the synthesis of other biological active compounds.^[1b] In organic chemistry, these compounds are vital starting materials for the synthesis of alkene derivatives.^[2] Traditional methods for the synthesis of α -arylmethylphosphonates involves the reaction of arylmethylhalides^[3a] or arylmethylpyridinium iodides^[3b] with trialkyl phosphites and the Michaelis-Arbuzov rearrangement of arylmethylphosphites.^[3c,d] Other reported methods include the rhodium-catalyzed coupling reaction of (OEt)₂P(O)CH₂ZnI and PhI,^[3e] and the coupling reaction of chloromethylphosphonates with arylbromide mediated by CuI and *t*-BuLi.^[3f] As for the synthesis of α -aryl substituted β -ketophosphonates, only a handful of reports are available, namely, the addition of trialkyl phosphites in the presence of TiCl₄,^[3g] or dialkyl phosphites in the presence of DBU/TMSCl,^[3h] to nitroalkenes followed by *m*-CPBA oxidation; the reaction of diethylphosphonocarboxylic acid chlorides and organocuprates or Grignard reagents,^[3i] the rearrangement of substituted epoxyphosphonates,^[3j] and the reaction of arylsulfonylepoxides and sodium dialkylphosphate.^[3k] As summarized above, most of these reported methods for the synthesis of these two types of compounds require either drastic reaction conditions or some special reagents. Moreover, to our knowledge, there is no general method for the synthesis α -aryl substituted methylphosphonates and β -ketophosphonates from a common starting material using readily available catalysts.

As part of our ongoing efforts in developing novel synthetic methods for α -substituted phosphonates,^[4] we became interested in the synthesis of α -aryl substituted phosphonates through the direct α -arylation of the readily available β -ketophosphonates. Although there is

no such precedence in the literature, there are a few reports on the direct α -arylation of active methylene compounds.^[5] For example, Ma and coworkers have reported a copper-catalyzed coupling of β -ketoesters and aryl iodides.^[5a-d] Inspired by these reports, we envisioned that α -aryl substituted β -ketophosphonates could be synthesized from β -ketophosphonates and aryl halides with a suitable catalyst. Herein we report a copper-catalyzed direct synthesis of α -aryl substituted β -ketophosphonates and methylphosphonates from β -ketophosphonates and aryl iodides via a cross-coupling reaction and a cascade cross-coupling and deacylation reaction, respectively. We believe this is the first method where these two types of compounds are prepared from a common β -ketophosphonate derivative.

With diethyl (2-oxopropyl)phosphonate (**1a**) and iodobenzene (**2a**) as the model substrates, we first studied the α -arylation reaction using the reaction conditions similar to those reported by Ma and coworkers.^[5a] The results of this study are summarized in Table 1. As shown by the results, in presence of CuI (20 mol %), L-proline (40 mol %) and Cs₂CO₃ (3 equiv.) in DMSO, the desired α -arylated product **3a** was isolated with 64% yield after reacting for 24 h at 50 °C (entry 1). While copper(I) bromide (entry 2), copper(II) acetate monohydrate (entry 3), copper(II) sulfate pentahydrate (entry 4), and copper(II) tosylate monohydrate (entry 5) all catalyze this coupling reaction, their reactivity is much lower. Screening of the solvents revealed that good reactivity was also obtained in DMF (entry 6). However, no reaction was observed in dioxane and toluene (entries 7 and 8). Similarly, other bases tested in this reaction, such as K₂CO₃ (entry 9), KOH (entry 10), and K₃PO₄·3H₂O (entry 11), are not effective. It is also noteworthy that the reaction did not proceed in absence of L-proline (entry 12) or when L-proline was replaced with PPh₃ (entry 13). Gratifyingly, the yield of this arylation reaction may be improved to 84% by carrying out the reaction at 70 °C (entry 14). Under these optimized reaction conditions, less reactive bromobenzene also affords compound **3a** in 61% yield (entry 15).

Next, we studied the scope of reaction with different iodobenzenes bearing electron-withdrawing or electron-donating functional groups (Table 2). As shown by the results, this catalytic system tolerates iodobenzenes with both an electron-withdrawing group and an electron-donating group at the *para*-position of the benzene ring and different β -ketophosphonate starting materials to afford the desired α -arylated β -ketophosphonates **3a-3k** in good yields (74-84%, entries 1-11). Interestingly, for 1,4-diiodobenzene (entry 4), we only observed the monoarylated **3d**. No trace of the diarylated product was detected even when the reaction was carried out in the presence of 6 equiv. of Cs₂CO₃ and 3 equiv. of **1a** after 48 h (data not shown).

During the course of the above study, we noted that Cu(II) salts also can catalyze the arylation reaction (Table 1, entries 3-5), albeit in lower efficiency as compared to CuI. Because Cu(II) salts are cheaper than CuI, it was our intention to optimize the reaction conditions to improve the efficiency of the Cu(II)-catalyzed arylation. Since higher temperature works better for CuI (Table 1, entry 14), we attempted the copper(II) acetate monohydrate-catalyzed coupling reaction at higher temperature. Surprisingly, increasing the reaction temperature to 110 °C led to the formation of the deacylated coupling product **4a** in 72% yield; whereas the expected **3a** was only isolated in 12% yield (Table 3, entry 1). This result represents the first catalytic method for the direct preparation of arylmethylketophosphonates from readily available β -ketophosphonates. In this regard, it should be pointed out that palladium acetate-catalyzed deacylative coupling between β -ketoesters and aryl halides^[6] and copper(I) iodide-catalyzed deacylative coupling between β -ketoesters^[7] or 1,3-diketones^[8] and aryl halides have been reported recently. Nevertheless, deacylative coupling reaction of β -ketophosphonates is unprecedented and copper(II) salts have never been used for such a purpose.

When K_2CO_3 was used as the base, the reaction also proceeded without L-proline to yield **4a** in 61% yield (entry 2). When 2,2'-bipyridine was used as the ligand, the yield was improved to 89% (entry 3). However, using phenanthrene as the ligand showed no improvement in the yield of **4a** (entry 4). It should be pointed out that, although the deacylation is most favorable with 5 equiv. of K_2CO_3 , it does proceed with less amount of base. For example, with 0.5, 1.0, 2.0, 3.0, and 4.0 equiv. of K_2CO_3 , product **4a** was obtained in 12%, 23%, 38%, 51%, and 72% yield, respectively (data not shown). Other bases, such as Cs_2CO_3 , KOH, and $K_3PO_4 \cdot 3H_2O$ are less effective in promoting the reaction (entries 5-7). Similarly, this reaction does not work in solvents like ethylene glycol, toluene, and DMF (entries 8-10). Under the optimized conditions, copper(I) iodide, copper(II) tosylate monohydrate, and copper(II) nitrate monohydrate also lead to the deacylative α -arylation product **4a**, albeit in lower yields (entries 11-13). Replacing iodobenzene with bromobenzene afforded **4a** in only 13% yield even at 130 °C (entry 14).

Then we further investigated the scope of this deacylative arylation reaction (Table 4) under the optimized conditions. Besides iodobenzene (entry 1), iodobenzene derivatives bearing an electron-withdrawing group, such as, 4-fluoro (entry 2), 4-bromo (entry 3), 4-iodo (entry 4), 4-ethoxycarbonyl (entry 5), 4-cyano (entry 6), and 4-nitro (entry 7), all undergo the expected reaction smoothly to provide the corresponding deacylated cross-coupling products **4b-4g** in high yields (85-91%). Again 1,4-diiodobenzene (entry 4) gave only the monoarylated phosphonate **4d**. No formation of diarylated product was observed. Nonetheless, with iodobenzenes bearing an electron-donating group, such as 4-methyl and 4-methoxy groups, no deacylative arylation products, such as, **4h** and **4i**, could be isolated. Only low yields of the arylation products **3h** and **3i** were obtained, respectively (Table 4, entries 8 and 9). On the other hand, 1-iodonaphthalene underwent this reaction smoothly to provide corresponding deacylated cross-coupling product **4h** in 92% yield (entry 10). This deacylative arylation reaction may also be applied to other β -ketophosphonate substrates. When the terminal methyl group of **1a** was changed to ethyl (**1b**, entry 11) and phenyl (**1c**, entry 12) groups, reactions with iodobenzene under similar conditions produced the expected deacylated product **4a** in 85% and 93% yields, respectively.

Although the mechanism of the reported copper or palladium-catalyzed deacylative coupling reactions^[6-8] remains elusive, a C-C bond activation^[9] was proposed to be a possible mechanism in the deacylative arylation of 1,3-diketones.^[8] In order to find out the possible mechanism of the current reaction, some additional experiments were carried out. Firstly, four separate reactions were carried out with the authentic α -phenyl substituted β -ketophosphonate **3a**, which is a potential intermediate in the deacylative arylation reaction. As shown in Scheme 1, in the presence of 2 equiv. of K_2CO_3 , the reaction of **3a** at 110 °C in DMSO for 3 h led to the full conversion of **3a**, and **4a** was isolated in 79% yield. Similarly, in the presence of 2 equiv. of K_2CO_3 and 10 mol % of $Cu(OAc)_2 \cdot H_2O$, as well as 20 mol % of 2,2'-bipyridine **4a** was isolated in 89% yield (Scheme 1). However, under these conditions, no reaction was observed without the addition of any of these reagents. Similarly, $Cu(OAc)_2 \cdot H_2O$ alone cannot catalyze the conversion of **3a** under these conditions (data not shown). It is also noteworthy that we did not observe any dephosphorylation product, such as $PhCH_2COMe$, in all these cases. These results indicate that, if **3a** is formed, the deacylation is mainly due to the action of K_2CO_3 . However, $Cu(OAc)_2$ also promotes the deacylation reaction in the presence of the ligand (2,2'-bipyridine).

Next, the deacylation of compound **3i** was studied. As we have mentioned previously, the direct deacylative coupling of 1-iodo-4-methoxybenzene and **1a** fails to proceed (Table 4, entry 9). However, the deacylation of **3i** works well in the presence of $Cu(OAc)_2/K_2CO_3$ or K_2CO_3 alone (Scheme 2). The data again verify that, although the reaction takes place with K_2CO_3 alone, $Cu(OAc)_2$ / 2,2'-bipyridine is also a promoter of the deacylation reaction.

These data also hint that the direct deacylative arylation reaction is a cascade reaction beginning with the arylation reaction.

On the basis of these facts and the mechanism proposed for deacylative arylation of 1,3-diketones,^[8] a plausible mechanism (Scheme 3) is proposed to account for the above deacylation reaction. As shown in Scheme 3, Cu(I) formed in situ from Cu(II) acetate reacts with **1** in the presence of K₂CO₃ to give the Cu(I) intermediate **5**. Oxidative addition of iodoarene to **5** forms a Cu(III) intermediate **6**. Intermediate **6** may undergo a reductive elimination to yield the coupling reaction product **3** and simultaneously regenerate the Cu(I) species to complete the catalytic cycle. As our data show, compound **3** may be decarboxylated by K₂CO₃ directly to generate the carbanion intermediate **7** (Pathway a), which produces the deacylative product **4** after protonation. On the other hand, by acting as a Lewis acid, Cu salts may enhance the efficiency of the deacylation of **3** (Pathway b). Alternatively, intermediate **6** may react with K₂CO₃ directly to generate a copper(III) intermediate **8**,^[8] which undergoes rearrangement and elimination to yield product **4** and the copper(I) to complete the catalytic cycle (Pathway c). Both Pathways b and c can account for the observed acceleration of the deacylation reaction in the presence of the copper catalyst (Schemes 1 and 2).

To provide further support of this mechanism and to clarify the role of copper in the deacylation process, several additional experiments were carried out. Firstly, the deacylation of compound **3a** was studied with K₂CO₃ (2 equiv.) and different Lewis acids (10 mol %), such as La(NO₃)₃·6H₂O, Fe(NO₃)₃·6H₂O, Ni(NO₃)₂·6H₂O, and Cu(OAc)₂·H₂O under the optimized reaction conditions (DMSO, 110 °C), and the corresponding deacylative product **4a** was obtained in 59%, 51%, 51%, and 0%, respectively. Comparing these data with those reported in Scheme 1, it is clear that these Lewis acids do not promote the deacylation of compound **3a** since the obtained yields are worse than that obtained with K₂CO₃ alone (79%). Thus, it is unlikely that Cu(OAc)₂·H₂O is behaving as a Lewis acid in promoting the deacylation reaction and, therefore, Pathway b in Scheme 3 is unlikely. Secondly, the deacylation reaction of β-ketophosphonate **1a**, which is the substrate used this deacylative coupling reaction, was carried out. As shown in Scheme 4, upon the treatment with K₂CO₃ (5 equiv.) in DMSO at 110 °C for 10 h, no formation of the desired deacylated product **10** was observed; instead, the rearranged product **9** was obtained in low yield.^[10] Formation of **9** may be rationalized through a rearrangement of the enolate intermediate formed from **1a** under the action of a base. Similarly, the attempted deacylation using stoichiometric amount of Cu(OAc)₂·H₂O under the optimized reaction conditions also failed (Scheme 4). Moreover, compounds **11** and **12**^[11] (Figure 1) failed to deacylate under the optimized reaction conditions, too. These results again evince that the presence of a α-aryl group is essential for the deacylation of β-ketophosphonates. These results are in agreement with both Pathways a and c. Most likely both pathways are working under the reaction conditions. For Pathway a, the aryl group can stabilize the carbanion intermediate **7** to facilitate the direct deacylation of **3** by K₂CO₃. For Pathway c, the presence of an aryl group can facilitate the insertion of the copper(I) reagent into the carbon-aryl bond of **3** to form the intermediate **6**, which may deacylate through **8**. Copper(II) acetate itself cannot insert into **3** to generate **6** and, therefore, it alone cannot deacylate compound **3** (vide supra).

In conclusion, we have described an efficient synthesis of α-aryl substituted β-ketophosphonates and methylphosphonates from β-ketophosphonates and aryl iodides via an arylation reaction and a tandem arylation and deacylation reaction, respectively, using Cu(I) or Cu(II) salts as the catalysts. The corresponding α-aryl substituted β-ketophosphonates and α-arylmethylphosphonates were obtained in high yields. A plausible mechanism of this reaction is proposed and the role of the base and the Cu(II) salt in the deacylation reaction is discussed.

Experimental Section

General procedure for the α -arylation of β -ketophosphonates

A mixture of β -ketophosphonate **1** (1.2 mmol), iodobenzene **2** (1.0 mmol), CuI (0.2 mmol, 20 mol %), L-proline (0.4 mmol, 40 mol %) and Cs_2CO_3 (3.0 mmol) in DMSO (1.0 mL) was stirred under N_2 at 70 °C. Upon the completion of the reaction (monitored by TLC) and after being cooled to rt, the reaction mixture was quenched with saturated aqueous NH_4Cl (2.0 mL). The mixture was extracted with ethyl acetate (3×5 mL). The organic layers were combined and dried over sodium sulfate. The drying agent and the solvent were then removed and the residue was purified by flash column chromatography on silica gel to afford product **3**. All the known compounds (**3a**,^[3i] **3j**,^[3i] and **3k**^[12a]) gave satisfactory spectroscopic data that are in agreement with the reported data in the literature. All the new compounds were fully characterized.^[13]

General procedure for the α -arylation and deacylation reaction

A mixture of β -ketophosphonates **1** (1.2 mmol), iodobenzenes **2** (1.0 mmol), $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.10 mmol, 10 mol %), 2,2'-bipyridine (0.20 mmol, 20 mol %) and K_2CO_3 (5.0 mmol) in DMSO (1.0 mL) was stirred under N_2 at 110 °C. Upon the completion of the reaction (monitored by TLC) and after being cooled to rt, the reaction was quenched with saturated aqueous NH_4Cl (2.0 mL). The mixture was extracted with ethyl acetate (3×5 mL). The organic layers were combined and dried over sodium sulfate. The drying agent and the solvent were then removed and the residue was purified by flash column chromatography on silica gel to afford compounds **4**. All the known compounds (**4a**,^[3c] **4b**,^[12b] **4c**,^[12c] **4d**,^[12d] **4e**,^[12e] **4f**,^[12f] **4g**,^[12g] **4i**,^[3e,12b] and **4j**^[12h]) gave satisfactory spectroscopic data that are in agreement with the reported data in the literature.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

- For examples, see: de Garavilla L, Greco MN, Sukumar N, Chen Z-W, Pineda AO, Mathews FS, Di Cera E, Giardino EC, Wells GI, Haertlein BJ, Kauffman JA, Corcoran TW, Derian CK, Eckardt AJ, Damiano BP, Andrade-Gordon P, Maryanoff BE. *J. Bio. Chem.* 2005; 18:18001. [PubMed: 15741158]; Almond MN, Harold R, De Garavilla L, Hawkins MJ, Maryanoff BE, Qian Y, Walker DM, Sergio C-C, Nilsen CN, Patel MN, Humora MJ. *PCT Int. Appl.* 2003:2003035654. Greco MN, Hawkins MJ, Powell ET, Almond HR Jr. Corcoran TW, Garavilla LD, Kauffman JA, Recacha R, Chattopadhyay D, Andrade-Gorden P, Maryanoff BE. *J. Am. Chem. Soc.* 2002; 124:3810. [PubMed: 11942800]; Johnson RA. *PCT Int. Appl.* 1994:WO 9407501 A1 19940414.. For a review, see: Hartley FH. *The Chemistry of Organophosphorous Compounds.* 1996WileyNew York
- For reviews, see: Wardworth WS Jr. *Org. React.* 1977; 25:73.; Walker BJ. Cadogan JLG. *Organophosphorous Reagent in Organic Synthesis.* 1974Academic PressNew York; Boutagy J, Thomas R. *Chem. Rev.* 1974; 74:87.; Stec WJ. *Acc. Chem. Res.* 1983; 16:411.
- a Odinets IL, Matveeva EV, Sharova EV, Artyushin OI, Kozlov VA, Vorob'eva DV, Osipov SN, Roschenthaler GV. *Phosphorus Sulfur Silicon.* 2008; 183:383.b Fresneda PM, Molina P. *Synthesis.* 1981; 3:222.c Pierre-Yves V, Philippe L, Eric E, Valleix A, Mioskowski C. *Angew. Chem.* 2003; 115:2491. *Angew. Chem. Int. Ed.* 2003; 42:2389.d Barney RJ, Richardson RM; Wiemer DF. *J. Org. Chem.* 2011; 76:2875. [PubMed: 21405073] e Takahashi H, Inagaki S, Yoshii N, Gao F, Nishihara

- Y, Takagi K. *J. Org. Chem.* 2009; 74:2794. [PubMed: 19267488] f Poindexter MK, Katz TJ. *Tetrahedron Lett.* 1988; 29:1513. g Kim DY, Mang YJ, Lee JW, Oh DY. *Bull Korean Chem. Soc.* 1993; 14:526. h Kim DY, Lee K, Oh DY. *J. Chem. Soc. Perkin Trans.* 1992; 1:2451. i Coutrot P, Ghribi A. *Synthesis.* 1986:661. j Sprecher M, Kost D. *Tetrahedron Lett.* 1969; 9:703. k Koh YJ, Oh DY. *Tetrahedron Letter.* 1993; 34:2147.
4. a Samanta S, Zhao C-G. *J. Am. Chem. Soc.* 2006; 128:7442. [PubMed: 16756289] b Dodda R, Zhao C-G. *Org. Lett.* 2006; 8:4911. [PubMed: 17020334] c Dodda R, Zhao C-G. *Org. Lett.* 2007; 9:165. [PubMed: 17192111] d Dodda R, Zhao C-G. *Tetrahedron Lett.* 2007; 48:4339. [PubMed: 18560473] e Mandal T, Samanta S, Zhao C-G. *Org. Lett.* 2007; 9:943. [PubMed: 17284048] f Samanta S, Zhao C-G. *Arkivoc.* 2007:218. g Samanta S, Perera S, Zhao C-G. *J. Org. Chem.* 2010; 75:1101. [PubMed: 20085234] h Perera S, Naganaboina VK, Wang L, Zhang B, Guo Q, Rout L, Zhao C-G. *Adv. Synth. Catal.* 2011; 353:1729. [PubMed: 21918646] i Abbaraju S, Bhanushali M, Zhao C-G. *Tetrahedron.* 2011; 67:7479. [PubMed: 21921970]
 5. Xie X, Cai G, Ma D. *Org. Lett.* 2005; 7:4693. [PubMed: 16209512] ; Xie X, Chen Y, Ma D. *J. Am. Chem. Soc.* 2006; 128:16050. [PubMed: 17165754] ; Yip SF, Cheung HY, Zhou Z, Kwong FY. *Org. Lett.* 2007; 9:3469. [PubMed: 17637034] ; Chen Y, Wang Y, Sun Z, Ma D. *Org. Lett.* 2008; 10:625. [PubMed: 18193883] ; Hennessy EJ, Buchwald SL. *Org. Lett.* 2002; 4:269. [PubMed: 11796067] ; Okuro K, Furuune M, Miura M, Nomura M. *J. Org. Chem.* 1993; 58:7606.; Pivsa-Art S, Fukui Y, Miura M, Nomura M. *Bull. Chem. Soc. Jpn.* 1996; 69:2039.; Konopelski JP, Hottenroth JM, Oltra HM, Véliz EA, Yang Z-C. *Synlett.* 1996:609.; Pinhey JT, Rowe BA. *Tetrahedron Lett.* 1980; 21:965.; Bruggink A, McKillop A. *Tetrahedron.* 1975; 31:2607.; Hurlley WRH. *J. Chem. Soc.* 1929:1870.; Fang Y, Li C. *J. Org. Chem.* 2006; 71:6427. [PubMed: 16901126] . For a review, see: Ma D, Cai Q. *Acc. Chem. Res.* 2008; 41:1450. [PubMed: 18698852]
 6. Zeevaart JG, Parkinson CJ, de Koning CB. *Tetrahedron Lett.* 2004; 45:4261.
 7. Zeevaart JG, Parkinson CJ, de Koning CB. *Tetrahedron Lett.* 2007; 48:3289.
 8. He C, Guo S, Huang L, Lei A. *J. Am. Chem. Soc.* 2010; 132:8273. [PubMed: 20518466]
 9. For selected examples, see: Murakami M, Takahashi K, Amii H, Ito Y. *J. Am. Chem. Soc.* 1997; 119:9307.; Seiser T, Cramer N. *J. Am. Chem. Soc.* 2010; 132:5340. [PubMed: 20345153] ; Kim S, Takeuchi D, Osakada K. *J. Am. Chem. Soc.* 2002; 124:762. [PubMed: 11817946] ; Bart SC, Chirik PJ. *J. Am. Chem. Soc.* 2003; 125:886. [PubMed: 12537484] ; Kondo T, Kaneko Y, Taguchi Y, Nakamura A, Okada T, Shiotsuki M, Ura Y, Wada K, Mitsudo T.-a. *J. Am. Chem. Soc.* 2002; 124:6824. [PubMed: 12059193] ; Winter C, Krause N. *Angew. Chem.* 2009; 121:2497.; *Angew. Chem., Int. Ed.* 2009; 48:2460.. For reviews, see: Jun C-H. *Chem. Soc. Rev.* 2004; 33:610. [PubMed: 15592626] ; Jun C-H, Park J-W. *Top. Organomet. Chem.* 2007; 24:117.
 10. Formation of this rearrangement product has been reported before, see: Pudovik AN. *Zh. Obshh. Khim.* 1955; 25:2173.; Machleidt H, Strehlke GU. *Angew. Chem.* 1964; 76:494.
 11. Compound **12** was synthesized according to: Calogeropoulou T, Hammond GB, Wiemer DF. *J. Org. Chem.* 1987; 52:4185.
 12. a Russel GA, Yao C-F. *J. Org. Chem.* 1992; 57:6508. b Laven G, Stawinski J. *Synlett.* 2009:225. c Iwase Y, Kamada K, Ohta K, Kondo K. *J. Mat. Chem.* 2003; 13:1575. d Rohlik Z, Holzhauser P, Kotek J, Rudovsky J, Nemec I, Hermann P, Lukes I. *J. Organo. Chem.* 2006; 691:2409. e Chaplais G, Le JB, Leclercq D, Vioux A. *Chem. Mat.* 2003; 15:1950. f Hulvat JF, Sofos M, Tajima K, Stupp SI. *J. Am. Chem. Soc.* 2005; 127:366. [PubMed: 15631487] g Anthony NG, Breen D, Clarke J, Donoghue G, Drummond AJ, Ellis EM, Gemmell CG, Helesbeux JJ, Hunter IS, Khalaf AI, Mackay SP, Parkinson JA, Suckling CJ, Waigh RD. *J. Med. Chem.* 2007; 50:6116. [PubMed: 17960927] h McGearry RP, Vella P, Mak JYW, Guddat LW, Schenk G. *Bioorg. Med. Chem. Lett.* 2009; 19:163. [PubMed: 19010677]
 13. For details, please see the Supporting Information.

Scheme 1.
Deacylation of **3a** under various conditions

Scheme 2.
Deacylation of **3i**

Scheme 3.

Proposed mechanism for the deacylative arylation reaction (Ln = ligand)

Scheme 4.
Attempted deacylation of **1a**

Figure 1.
Compounds attempted for the deacylation reaction

Table 1Optimization of the reaction conditions for arylation of **1a**^[a]

$\text{1a} + \text{2a} \xrightarrow[\text{Base, solvent}]{\text{Cu catalyst, L-Proline}} \text{3a}$

Entry	Catalyst	Solvent	Base	Yield [%] ^[b]
1	CuI	DMSO	Cs ₂ CO ₃	64
2	CuBr	DMSO	Cs ₂ CO ₃	24
3	Cu(OAc) ₂ ·H ₂ O	DMSO	Cs ₂ CO ₃	31
4	CuSO ₄ ·5H ₂ O	DMSO	Cs ₂ CO ₃	38
5	Cu(OTf) ₂ ·H ₂ O	DMSO	Cs ₂ CO ₃	35
6	CuI	DMF	Cs ₂ CO ₃	61
7	CuI	Dioxane	Cs ₂ CO ₃	0
8	CuI	Toluene	Cs ₂ CO ₃	0
9	CuI	DMSO	K ₂ CO ₃	0
10	CuI	DMSO	KOH	19
11	CuI	DMSO	K ₃ PO ₄ ·3H ₂ O	24
12 ^[c]	CuI	DMSO	Cs ₂ CO ₃	0
13 ^[d]	CuI	DMSO	Cs ₂ CO ₃	0
14 ^[e]	CuI	DMSO	Cs ₂ CO ₃	84
15 ^[f]	CuI	DMSO	Cs ₂ CO ₃	61

^[a]Unless otherwise indicated, all reactions were conducted with **1a** (1.2 mmol), **2a** (1.0 mmol), the copper salt (20 mol %), L-proline (40 mol %), and the specified base (3.0 mmol) in the indicated solvent (1.0 mL) under a N₂ atmosphere at 50 °C for 24 h.

^[b]Yield of the isolated product.

^[c]No L-proline was added.

^[d]PPh₃ was used instead of L-proline.

^[e]The reaction was carried out 70 °C.

^[f]The reaction was carried out bromobenzene at 90 °C.

Table 2

Copper(I) iodide-catalyzed arylation of β -ketophosphonates^[a]

1	2	3	
Entry	R ¹	R ²	Time [h]	Product	Yield [%] ^[b]
1	Me	H	24	3a	84
2	Me	F	26	3b	81
3	Me	Br	26	3c	74
4	Me	I	24	3d	81
5	Me	CO ₂ Et	24	3e	81
6	Me	CN	22	3f	81
7	Me	NO ₂	20	3g	80
8	Me	Me	26	3h	82
9	Me	MeO	26	3i	83
10	Et	H	24	3j	81
11	Ph	H	24	3k	75

^[a] All reactions were conducted with **1a** (1.2 mmol), **2** (1.0 mmol), CuI (20 mol %), L-proline (40 mol %), and Cs₂CO₃ (3.0 mmol) in DMSO (1.0 mL) under a N₂ atmosphere at 70 °C for the indicated reaction times.

^[b] Yield of the isolated product.

Table 3Optimization of the reaction conditions for the deacylative α -arylation of **1a**^[a]

$ \begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_3\text{C}-\text{P}(\text{O})(\text{OEt})_2 + \text{PhI} \xrightarrow[\text{Base, solvent}]{\text{Cu catalyst, Ligand}} \text{Ph}-\text{CH}_2-\text{P}(\text{O})(\text{OEt})_2 \\ \text{1a} \qquad \text{2a} \qquad \qquad \qquad \text{4a} \end{array} $				
Entry	Catalyst	Solvent	Base	Yield [%] ^[b]
1 ^[c]	Cu(OAc) ₂ ·H ₂ O	DMSO	CS ₂ CO ₃	72 ^[d]
2 ^[e]	Cu(OAc) ₂ ·H ₂ O	DMSO	K ₂ CO ₃	61
3	Cu(OAc) ₂ ·H ₂ O	DMSO	K ₂ CO ₃	89
4 ^[f]	Cu(OAc) ₂ ·H ₂ O	DMSO	K ₂ CO ₃	53
5	Cu(OAc) ₂ ·H ₂ O	DMSO	CS ₂ CO ₃	51
6	Cu(OAc) ₂ ·H ₂ O	DMSO	KOH	41
7	Cu(OAc) ₂ ·H ₂ O	DMSO	K ₃ PO ₄ ·3H ₂ O	62
8	Cu(OAc) ₂ ·H ₂ O	EG ^[g]	K ₂ CO ₃	0
9	Cu(OAc) ₂ ·H ₂ O	Toluene	K ₂ CO ₃	0
10	Cu(OAc) ₂ ·H ₂ O	DMF	K ₂ CO ₃	Trace
11	CuI	DMSO	K ₂ CO ₃	49
12	Cu(OTf) ₂ ·H ₂ O	DMSO	K ₂ CO ₃	57
13	Cu(NO ₂) ₂ ·H ₂ O	DMSO	K ₂ CO ₃	52
14 ^[h]	Cu(OAc) ₂ ·H ₂ O	DMSO	K ₂ CO ₃	13

^[a]Unless otherwise indicated, all reactions were conducted with **1a** (1.2 mmol), **2a** (1.0 mmol), the copper salt (10 mol %), 2,2'-bipyridine (20 mol %), and the specified base (5.0 mmol) in the indicated solvent (1.0 mL) at 110 °C for 24 h.

^[b]Yield of the isolated product.

^[c]The reaction was carried out with L-proline (40 mmol %) as the ligand.

^[d]Compound **3a** was also isolated in 12% yield in this case.

^[e]No ligand was added.

^[f]Phenanthrene was used as the ligand.

^[g]EG = ethylene glycol.

^[h]Bromobenzene was used at 130 °C.

Table 4

Synthesis of **4** from reaction of **1** and **2** with Cu(OAc)₂·H₂O^[a]

$$\begin{array}{c}
 \text{O} \\
 \parallel \\
 \text{R}^1-\text{CH}_2-\text{P}(\text{O})(\text{OEt})_2 \\
 \mathbf{1}
 \end{array}
 +
 \begin{array}{c}
 \text{Ar}-\text{I} \\
 \mathbf{2}
 \end{array}
 \xrightarrow[\text{K}_2\text{CO}_3, \text{DMSO}]{\text{Cu}(\text{OAc})_2 / \text{bipyridine}}
 \begin{array}{c}
 \text{Ar}-\text{CH}_2-\text{P}(\text{O})(\text{OEt})_2 \\
 \mathbf{4}
 \end{array}$$

Entry	R ¹	Ar	Time [h]	Product	Yield [%] ^[b]
1	Me	C ₆ H ₅	24	4a	89
2	Me	4-FC ₆ H ₄	40	4b	85
3	Me	4-BrC ₆ H ₄	34	4c	86
4	Me	4-IC ₆ H ₄	26	4d	88
5	Me	4-EtO ₂ CC ₆ H ₄	28	4e	87
6	Me	4-CNC ₆ H ₄	27	4f	90
7	Me	4-NO ₂ C ₆ H ₄	32	4g	91
8	Me	4-MeC ₆ H ₄	48	4h	0 ^[c]
9	Me	4-MeOC ₆ H ₄	48	4i	0 ^[d]
10	Me	1-Naphthyl	35	4j	92
11	Et	C ₆ H ₅	24	4a	85
12	Ph	C ₆ H ₅	24	4a	93

[a] All reactions were conducted with **1** (1.2 mmol), **2** (1.0 mmol), K₂CO₃ (5.0 mmol), Cu(OAc)₂·H₂O (0.10 mmol, 10 mol%), and 2,2'-bipyridine (0.20 mmol, 20 mol % in DMSO (1.0 mL) at 70 °C for the indicated reaction times.

[b] Yield of the isolated product.

[c] Only the coupling product **3h** was obtained in 28% yield.

[d] The coupling compound **3i** was obtained in 30% yield with a trace amount of **4i**.