P(O)R2 Directed Pd(II)-Catalyzed C(sp2)-H Acylation

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P(O)R_2 Directed Pd(II)-Catalyzed C(sp^2)-H Acylation

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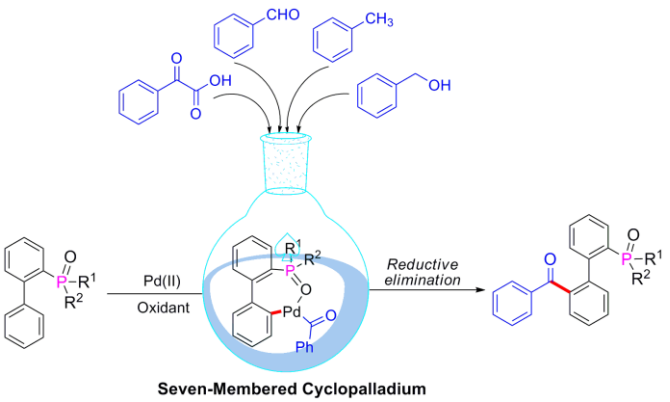
A novel method of Pd(II)-catalyzed C-H acylation of 2-phosphorylbiphenyl with *α*-oxocarboxylic acids, aldehyde, alcohol and toluene is described. This reaction provides efficient access to various substituted 2'-phosphorylbiphenyl-2-acyl compounds.

Within the field of organic chemistry, the carbonyl moiety is central to many broadly used synthetic modifications and fragment coupling steps.[1] Moreover, many aryl ketones are also key functionalities found in natural products, medicinally relevant molecules, and functional materials.[2] Therefore, the synthesis of various aryl ketones have led to continuous interest of the chemists. Generally, the preparation of aryl ketones mainly relys on the Friedel-Crafts acylation of aromatic compounds, however the limited functional group tolerance and large amounts of waste restrict its applications greatly.[3] In many cases, aryl ketones also have been oxidatived from the corresponding secondary alcohols by chromium reagents[4] or alkenes and alkynes by Wacker oxidation.[5] Recently, transition-metal-catalyzed decarboxylative cross-coupling reactions using aryl carboxylic acids as coupling parterners have emerged as a novel strategy and successfully applied to the construction of aryl ketones.[6] In particular, combine these discoveries with the transition-metal catalyzed *orth*-directed C-H functionalization,[7] a new pathway of palladium-catalyzed directed acylation of unactivated arenes with α-oxocarboxylic acids, aldehydes, alcohols and aryl methanes via *orth*-directed C-H bond activation and functionalization has been reported very recently.[8] Obviously, These methods provide a more simple and efficient approach for the preparation of aryl ketones. Furthermore, the procedures involved are environmentally friendly. In the last year, different R^2(O)P-directed C-H activation has attracted significant attentions.[9] Our group has also disclosed a series of R^2(O)P-directed Pd-catalyzed C-H functionalization involving olefination, hydroxylation and arylation through a seven-membered cyclopalladium pretransition state.[10] Based on these positive results, we have proposed an efficient approach for the synthesis of 2-phosphorylbiphenyl ketones by palladium-catalyzed C-H acylation with α-oxocarboxylic acids, aldehydes, alcohols and aryl methanes (scheme 1). In contrast to previous examples of various directing groups that guide selective C-H activation, the R^2(O)P group not only acts as the directing group, but also serves to the construction of the *P,O*-ligands. Furthmore, these compounds also could be converted into diversified other phosphorus ligand by appropriate carbonyl group transformation.

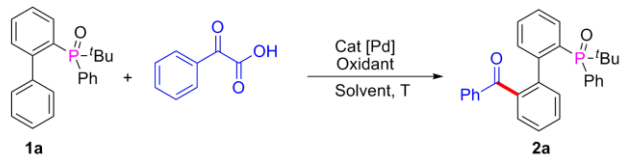


Scheme 1. Pd(II)-Catalyzed R^2(O)P-directed C-H Acylation.

In our initial investigation, we chose 2-(*tert*-butyl(phenyl) phosphoryl)biphenyl and phenylglyoxylic acid as the model substrates in the presence of $Pd(OAc)_2$ (10 mol %) and $K_2S_2O_8$ (2.5 eqiuv) in CH_3CN at 100 ℃. To our delighted, the desired product (**2a**) was obtained in 65% yield (Table 1, entry 1). Further solvents screening indicated that CH_3CN was still the best solvent (Table 1, entries 1-5). Interestingly, when we use other solvents such as CH_3NO_2, diglyme and DME carried out the reaction at 100 ℃, no product of **2a** was observed. If the temperature was decreased to 60 ℃, the product could be obtained in lower yields (Table 1, entries 3-5). Subsequently, we investigated the effect of other oxidants, including $(NH_4)_2S_2O_8$, oxone, Ag_2CO_3, Ag_2O, the results showed that $K_2S_2O_8$ was the best choice, but Ag_2CO_3 and Ag_2O were unactived at all (Table 1, entries 1, 6-9). Further studies showed that $Pd(TFA)_2$, $Pd(NO_3)_2$ and $Pd(acac)_2$ could also catalyze the reaction while $PdCl_2$ gave only a trace amount of the desired product **2a** (Table 1, entries 10-13). When the temperature was increased to 120 ℃ and 130 ℃, the yield of 2a was improved to 71% and 72% respectively (Table 1, entries 14-15). Increasing or reducing the

amount of $K_2S_2O_8$, the yield of 2a had not distinct change (Table 1, entries 16-17). If decrease the loading of $Pd(OAc)_2$ to 5 mol %, the yield of **2a** also descend synchronously (Table 1, entry 18). Moreover, the control experiment showed that $Pd(OAc)_2$ was necessary for the reaction (Table 1, entry 19). Thus, we decided to set 2.5 equiv $K_2S_2O_8$ in the presence of 10 mol % $Pd(OAc)_2$ at 130 ℃ as our standard conditions (Table 1, entry 15).

Table 1. Reaction Conditions Screening.[a]

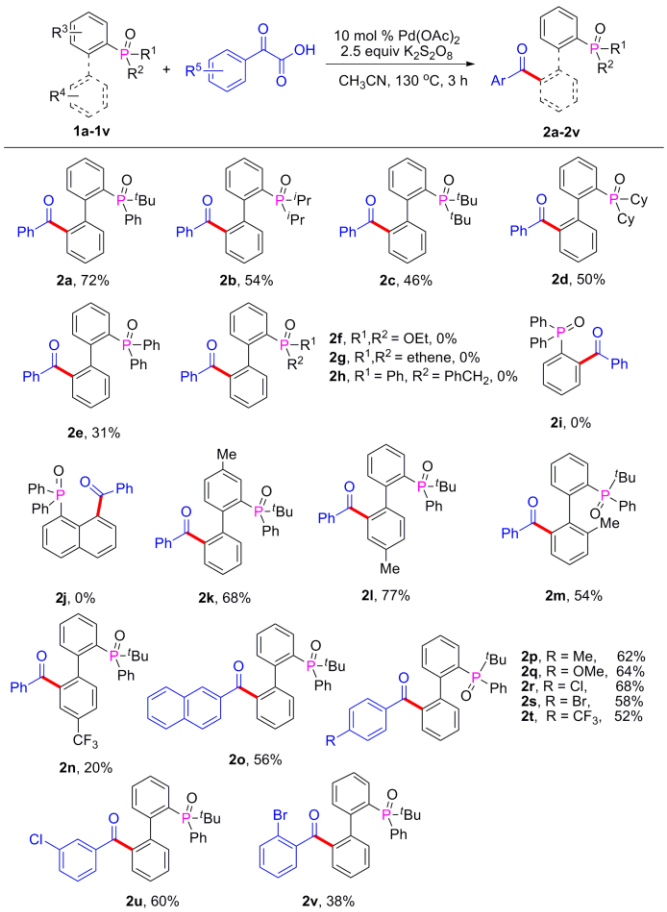


Entry	Cat. (mol %)	Oxidant (equiv)	Solvent	T (°C)	Yield [%]*b*
1	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (2.5)	CH_3CN	100	65
2	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (2.5)	DCE	100	n.r.
3	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (2.5)	CH_3NO_2	60	22[c]
4	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (2.5)	Diglyme	60	35[c]
5	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (2.5)	DME	60	29[c]
6	$Pd(OAc)_2$ (10)	$(NH_4)_2S_2O_8$ (2.5)	CH_3CN	100	<5
7	$Pd(OAc)_2$ (10)	Oxone (2.5)	CH_3CN	100	55
8	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2.5)	CH_3CN	100	n.r.
9	$Pd(OAc)_2$ (10)	Ag_2O (2.5)	CH_3CN	100	n.r.
10	$Pd(TFA)_2$ (10)	$K_2S_2O_8$ (2.5)	CH_3CN	100	22
11	$Pd(NO_3)_2$ (10)	$K_2S_2O_8$ (2.5)	CH_3CN	100	38
12	$PdCl_2$ (10)	$K_2S_2O_8$ (2.5)	CH_3CN	100	<5
13	$Pd(acac)_2$ (10)	$K_2S_2O_8$ (2.5)	CH_3CN	100	29
14	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (2.5)	CH_3CN	120	71
15	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (2.5)	CH_3CN	130	72
16	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (3.0)	CH_3CN	120	68
17	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (2.0)	CH_3CN	120	62
18	$Pd(OAc)_2$ (5)	$K_2S_2O_8$ (2.5)	CH_3CN	120	58
19		$K_2S_2O_8$ (2.5)	CH_3CN	120	n.r.

[a] Reaction conditions: 1a (0.3 mmol), phenylglyoxylic acid (0.6 mmol), catalyst, and oxidant in dry CH_3CN (3 mL) for 3 h under air atmosphere unless otherwise noted; [b] Isolated yield; [c] 12 h.

With the optimized reaction conditions in hand, we first examined the scope of subtrates by changing the phosphate directing group (Table 2). In addition to 2-(*tert*-butyl(phenyl)phosphoryl)-biphenyl, 2-(diisopropylphosphoryl)biphenyl, 2-(di-tert-butylphosphoryl) biphenyl, 2-(dicyclophosphoryl)biphenyl and 2-(diphenylphosphoryl)biphenyl were also compatible with this reaction and afforded the desired products in moderate yields (Table 2, **2a**-**2e**). However, when diethyl biphenyl-2-ylphosphonate was used, no product was detected (**2f**). Furthermore, other phosphates such as triphenylposphine oxide, naphthyl diphenylposphine, styrylphosphine oxide and phenethylphosphine oxide did not work at all (**2g**-**2j**). These results illustrated that the seven-memebered cyclopalladium pretransition state may play a critical role in this transformation. Next, we further investigated the scope of various substituted α-oxocarboxylic acids and 2-(*tert*-butyl(phenyl)phosphoryl)biphenyl derivaties. The steric effect and electronic effect were obvious in the reactions; the methyl group was located on the *para*-position of t*ert*-butyl(phenyl)phosphine oxide, the higher yield of **2l** was obtained than the methyl group was located on the *ortho*-position of **2m**. Furthermore, the biphenyl possessing electon-donating groups such as **2k** and **2l** gave higher yields than those with electron-withdrawing groups of **2n**. As for the phenylglyoxylic acids, substituents such as the methyl-, methoxyl-, chloro-, bromo-, trifluoromethyl groups at the *para*- or *meta*-position of the α-oxocarboxylic acids were well tolerated and afforded the corresponding ketones in moderate to good yields and the electronic effect was insignificant (**2o**-**2u**). However, when the substituent at the *ortho*-position, the electronic effect was evident and the yield of product (**2v**) decreased obviously. Meanwhile, α-keto acids with a naphthyl moiety could also participate in the reaction and provide the product in moderate yield (**2o**). Unfortunately, couplings with alkylglyoxylic acids did not give the desired products. It should be noted that the reaction gave the monoacylation products selectively in all cases.

Table 2. Pd(II)-catalyzed C-H Acylation of Various Substrates [a,b]

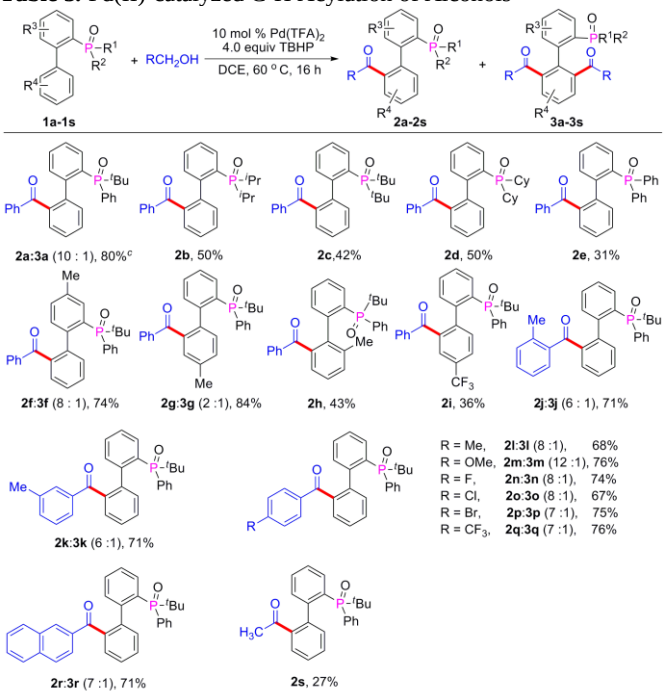


[a] All the reactions were carried out in the presence of 0.3 mmol of 1a-1t, in 3 mL CH_3CN at 130 ℃. [b] Isolated yield.

Some reports of the acylation with alcohols [8h,u,w] also encouraged us to carry out our reactions using cheaper and readily available benzyl alcohols. Firstly, we chose 2-(*tert*-butyl(phenyl)phosphoryl)biphenyl and benzyl alcohol as our template substrates to proceed the acylation under the previous standard conditions (Table 1, entry 15). However, only trace amount of product was obtained. This result urged us to screen different oxidants and solvents again, the desired product of 2a was obtained in moderate yield by using TBHP as oxidant and DCE as solvent (Table S1, entries 2-7). Meanwhile, bisacylated compound of 3a was also observed. The catalyst screening shown that $Pd(TFA)_2$ was the best choice and the yield of acylated product was improved to 70% (Table S1, entries 8-10). Reducing the temperature was very helpful and the acylated product was obtained in 80% yield with a 10 : 1 ratio of 2a and 3a at 60 ℃ (Table S1, entries 11-12). Then the direct acylation of biphenyl with different directing groups were investigated with benzyl alcohol and the corresponding products afforded in moderate yields with good regioselectivity (Table 3, **2b**-**2e**). The examination of different substituted 2-(*tert*-

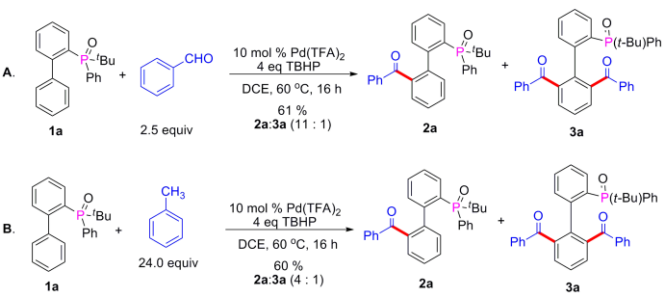
butyl(phenyl)phosphoryl) biphenyl derivaties indicated that the electronic and steric effect are very evident (Table 2, **2f**-**2i**), such as **2h** and **2i** were obtained in low yields. The electron-donating groups can increase the reactivity of 2-(*tert*-butyl(phenyl) phosphoryl)biphenyl. Next, we also evaluated the scope of different kinds of primary alcohols. To our delighted, the reactions with benzylic alcohols bearing electron-donating groups and electron-withdrawing groups at the aromatic ring proceeded to give the desired products in good yields accompanying with a small amount of the bisacylated compounds and the steric effect was also unconspicuous (Table 3, **2j**-**2r**). It's very interesting that the aliphatic alcohols such as ethyl alcohol were also compatible with this reaction in spite of the yield of **2s** was relative low.

Table 3. Pd(II)-catalyzed C-H Acylation of Alcohols [a,b]



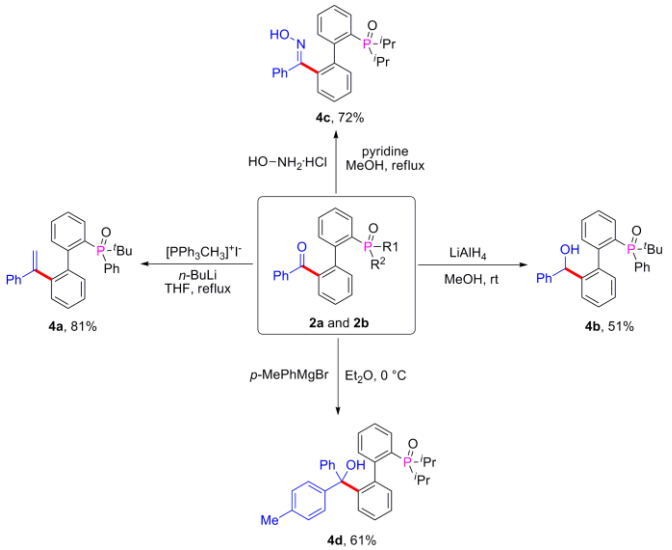
[a] All the reactions were carried out in the presence of 0.3 mmol of 1a-1s in 1.5 mL DCE at 60 ℃ under air atmosphere. [b] Isolated yield.

Inspired by these impressive progress, we further selected the toluene and benzaldehyde as the acylation reagents and wished to expand its wide application of acylations. As we expected, the acylated reactions really occurred and the monoacylated and bisacylated products were obtained in good yields with 11:1 and 4:1 ratios of 2a and 3a respectively (Scheme 2).



Scheme 2. Pd-catalyzed acylation of 2-phosphorylbiphenyl with toluene and benzaldehyde

We all knew that the carbonyl moiety is a very important synthon and can be transformed into different functional groups under appropriate conditions. In order to show the utility of our chemistry, we selected several acylated products and made derivatizations (Scheme 3). By using the product of **2a**, we could transform the carbonyl group into olefin (**4a**) in 81% yield by Wittig reaction[11] and alcohol (**4b**) in 51% yield by Lithium chloride hydrogen reduction.[12] In addition, we used the **2b** as starting material, which could be converted into benzophenone oxime (**4c**) in 72% yield by treating with hydroxylamine hydrochloride.[13] We could also obtain the tertiary alcohol **4d** in 61% yield by the reaction of the ketone on the aryl Grignard regent.[14]



Scheme 3. Transformations of acylated products into other compounds.

Conclusions

In conclusion, we have developed a novel R2(O)P-directed Pd(II)-catalyzed C-H acylation to synthesis various substituted 2'-phosphorylbiphenyl-2-acyl compounds. This method provided a simple and efficient pathway for the preparation of diverse biaryl ketones. Notebly, we simultaneously achieved the reaction using different acylation reagents, which offered a possibility to select according to the properties of products and substrates.

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Notes and references

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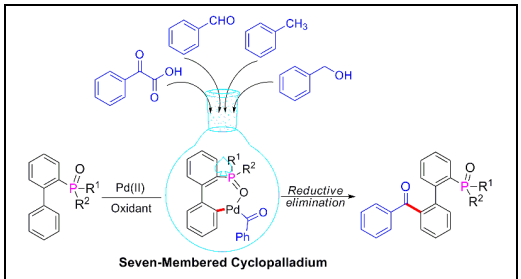

A novel method of Pd(II)-catalyzed C-H acylation of 2-phosphorylbiphenyl with α-oxocarboxylic acids, aldehyde, alcohol and toluene is performed.