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Aryl–aryl coupling via palladium-catalyzed C–P/C–H bond cleavage

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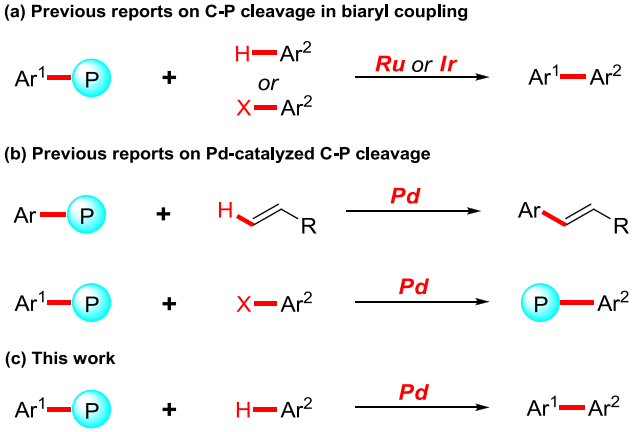
ABSTRACT

The first example of aryl–aryl coupling through palladium-catalyzed C–P/C–H bond cleavage with good functional group tolerance is disclosed. This work demonstrates the phosphines could be used as coupling partners in palladium-catalyzed aryl–aryl coupling.

1. Introduction

In the past several decades, transitional metal catalyzed[1] carbon (sp2)-carbon (sp2) cross-coupling reactions for building aryl–aryl scaffolds have been massively developed. In these reactions, phosphines have been commonly used as potent ligands,[2] due to their ability to accelerate the oxidative addition step and may also favor the transmetalation step.[3] In addition to their utilization as ligands, several reports suggested that phosphines could also be used as coupling partners providing aryl groups to substrates through C–P bond cleavage. For instance, it has been reported that ruthenium[4] or irinium[5] could cleave the C–P bond in triarylphosphines, which were used as aryl donors (Scheme 1a). Other than these expensive metals, the more cost-effective and commonly-used palladium has been reported to cleave the C–P bond in tetraphenylphosphonium salt giving alkenylated benzene in a Heck-type reaction (Scheme 1b).[6] Moreover, triarylphosphines has also been used as the phosphinating reagents in palladium-catalyzed phosphination for the preparation of various phosphine ligands (Scheme 1b).[7] Up to date,[8] few example of arylation of unpreactivated arenes or heteroarenes via palladium-catalyzed C–P bond cleavage, however, has been reported to the best of our knowledge (Scheme 1c).[9]

As a continuation of our previously works[10] on Pd(II)-catalyzed C(5)-H bond activation of azole-4-carboxylic derivatives,[11] we were originally focusing on the decarboxylative arylation.[3a,12] However, when we treated methyl oxazole-4-carboxylate (**1a**) with different benzoic acids under reaction conditions for decarboxylative arylation, only 5-phenyloxazole (**2a**) was obtained. We speculated that the phenyl group of **2a** was donated from triphenylphosphine (Ph_3P) rather than benzoic acids, suggesting this aryl–aryl coupling is realized via C–P bond cleavage. Recognizing the novelty of this process, here we report our findings about a new Pd-catalyzed aryl–aryl coupling reaction via C–P/C–H bond cleavage.



Scheme 1. Discovery of C–C coupling of heteroarenes with triarylphosphine as aryl donor.

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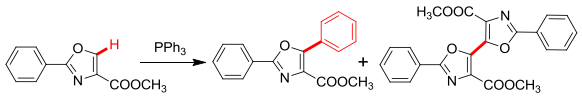
2. Results and discussion

Our initial investigation focused on the coupling of **1a** with Ph_3P as summarized in Table 1.[13] A preliminary trial using 1 equiv of Ph_3P without benzoic acid still afforded the C5-phenyl product **2a**, albeit in very low yield and most of **1a** was converted to homocoupling byproduct **3a** (entry 1). Subsequent screening on the additive revealed that the use of PivOH could remarkably increase the yield of the desired product **2a** to 42% (entry 2). Changing the reaction temperature, and the loading of Ag(I) and PivOH could generate **2a** in only moderate yield.[13] To our delight, screening on acidic additives indicated that the yield of **2a** could further rise to 70% while **3a** was not produced, when 2 equiv of TFA was used (entry 3). We then explored the reaction in various solvents, and found that NMP was the best choice (entry 4). Other palladium catalysts or other commonly used oxidants were shown to be less effective.[13] Changing loading of PPh_3 from 0.33 equiv to 1.5 equiv revealed that 0.66 equiv of PPh_3 showed no difference in the yield of **2a** but reacted faster, comparing to 1.5 equiv of PPh_3 (entries 5–10). This also suggested that at least two phenyl groups in one phosphine compound could be provided to the substrate, showing the promising efficiency of the triphenylphosphines as aryl donors. Replacing the PPh_3 with triphenylphosphine oxide provided no arylated product, which excluded the possibility that the C–P bond cleavage occurs on the phosphine oxide (entry 11). A control experiment without palladium catalyst showed that the palladium catalyst played an important role in this reaction (entry 12). Finally, the reaction conditions in entries 7 and 10 were selected for further investigation on the reaction scope.

Table 1
Optimization of reaction conditions[a]

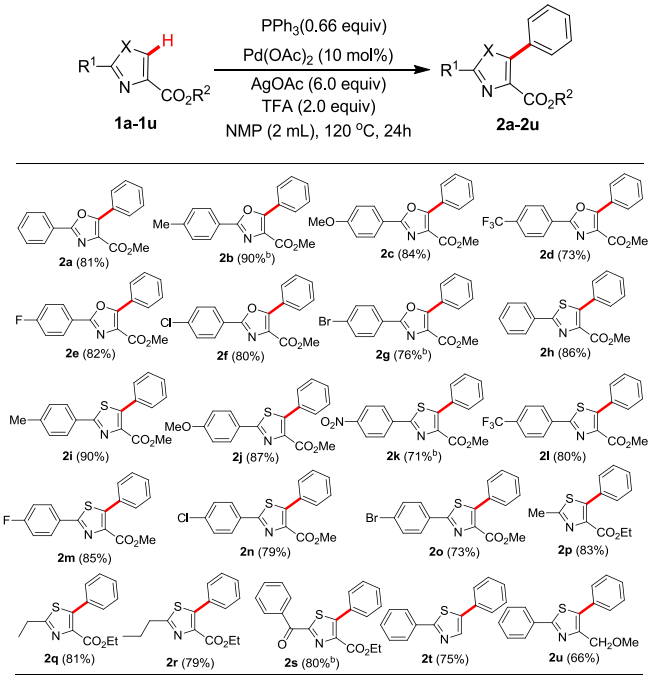


Entry	Ph_3P (equiv)	Additive (equiv)	Solvent	Yields (%) (**2a**/**3a**/**1a**)[b]
1	1	—	DMF	17/66/8
2	1	PivOH (2)	DMF	42/36/23
3[c]	1	TFA (2)	DMF	70/trace/23
4	1	TFA (2)	NMP	78/7/7
5	0.33	TFA (2)	NMP	52/40/0
6	0.5	TFA (2)	NMP	65/28/0
7	**0.66**	**TFA (2)**	**NMP**	**81/8/4**
8	1.2	TFA (2)	NMP	82/6/6
9	1.5	TFA (2)	NMP	72/6/17
10[d]	**1.5**	**TFA (2)**	**NMP**	**86/trace/7**
11[e]	1.5	TFA (2)	NMP	0/92/trace
12[d,f]	1.5	TFA (2)	NMP	0/0/95

[a] Reaction conditions: methyl 2-phenylthiazole-4-carboxylate **1a** (0.5 mmol), Ph_3P (1.5 mmol), $Pd(OAc)_2$ (0.05 mmol), AgOAc (3 mmol) and additive in DMF or NMP (2 mL) at 120 °C for 24 h.
[b] Isolated yields.
[c] Reacted at 140 °C.
[d] Reacted for 48 h.
[e] Ph_3P was replaced with triphenylphosphine oxide(Ph_3P=O).
[f] No palladium catalyst.

With the optimized conditions established, we first evaluated the coupling reactions of various azoles with PPh_3 as illustrated in Table 2, **2a**–**2u**.[14] Generally, both oxazole and thiazole substrates could afford the desired products in good to excellent yields. A wide range of substituents on azoles at C2 position were tolerated under these conditions. For 2-phenyloxazole substrates, electron-donating substitutions on phenyl group gave the corresponding products in excellent yields (**2b**, **2c**), while trifluoromethyl and halogen groups slightly declined the yields (**2d**–**2g**). It is noteworthy that the tolerance of chloro and bromo substituents might provide an opportunity for further synthetic functionalization. Similar patterns were observed on 2-phenyl substituted thiazoles (**2h**–**2o**). In addition, 2-alkyl or 2-carbonylsubstituted substrates could be phenylated in good yields (**2p**–**2s**) and the arylation of 2-phenylthiazole occurred selectively at C5-position (**2t**). Notably, 2-phenyl-4-methoxymethyl thiazole could also be phenylated to afford the corresponding product (**2u**) in moderate yield under the optimized conditions, while it was not efficiently arylated with unpreactivated benzene via double C–H cleavage.[10a]

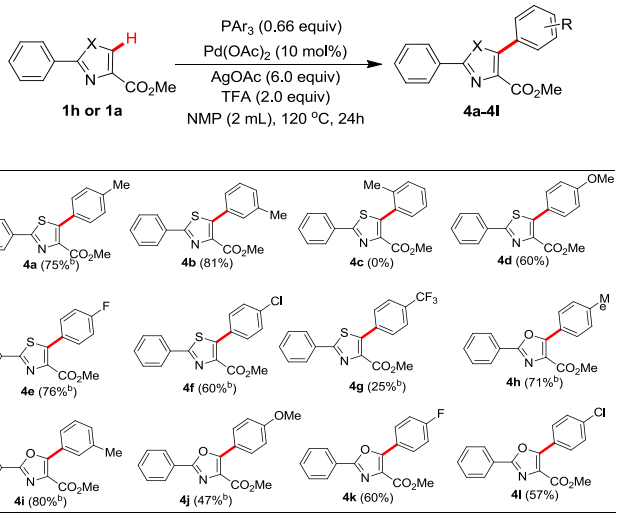
Table 2
Scope of azoles[a]



[a] Reaction conditions: azole (0.5 mmol), Ph_3P (0.33 mmol), $Pd(OAc)_2$ (0.05mmol), AgOAc (3 mmol) and TFA (1 mmol) in NMP (2 mL) at 120 °C for 24 h. Isolated yields. [b]1.5 equiv of Ph_3P was used, and reacted for 48 h.

Next, the effective conditions were extended to a variety of substituted triarylphosphines as illustrated in Table 3.[15] To our

Table 3
Scope of triarylphosphines[a]



[a] Reaction conditions: azole (0.5 mmol), Ar_3P (0.33 mmol), $Pd(OAc)_2$ (0.05mmol), AgOAc (3 mmol) and TFA (1 mmol) in NMP (2 mL) at 120 °C for 24 h. Isolated yields. [b]1.5 equiv of Ar_3P was used, reacted for 48 h.