Synthetic Methods

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Synthesis of Aryldiazoacetates through Palladium(0)-Catalyzed Deacylative Cross-Coupling of Aryl Iodides with Acyldiazoacetates**

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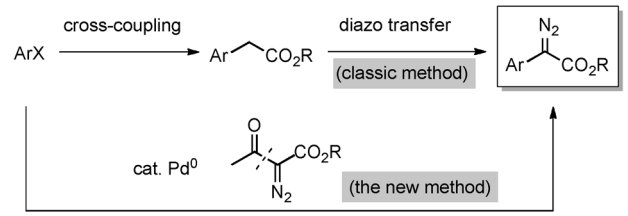
Abstract: *Palladium(0)-catalyzed deacylative cross-coupling of aryl iodides and acyldiazocarbonyl compounds can be achieved at room temperature under mild reaction conditions. The coupling reaction represents a highly efficient and general method for the synthesis of aryldiazocarbonyl compounds, which have found wide and increasing applications as precursors for generating donor/acceptor-substituted metallocarbenes.*

α-Diazo compounds have found wide applications because of their diverse reactivities.[1] In particular, the aryldiazoacetates have been extensively explored as the precursors for generating donor/acceptor-substituted metallocarbenes, which show excellent reactivity and selectivity in various transformations.[2,3] To access aryldiazoacetates, diazo-group-transfer reactions from an azide to arylacetates represents the classic method and has been extensively practiced (Scheme 1).[4] However, this important method



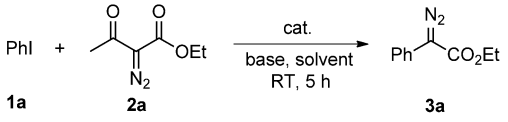
Scheme 1. Different strategies for the synthesis of aryldiazoacetates.

suffers two major drawbacks: 1) The arylacetates bearing various substituents are not readily available. Both traditional methods such as the reaction of benzyl Grignard reagents with CO_2, or modern transition-metal-catalyzed coupling reactions requires rigorous or forced reaction conditions,[5] and thus the functional-group tolerance is rather limited; 2) The yield of diazo transfer may be drastically affected by the azide, the base, and the solvent depending on the electronic nature of the aryl substituents.[6] In view of the importance of aryldiazoacetates and the drawbacks of the existing method, the development of alternative general methods to synthesize aryldiazoacetates and related diazo compounds is highly desirable.

We have previously reported palladium(0)-catalyzed cross-coupling of aryl iodides with ethyl diazoacetate (EDA).[7,8] The reaction represents a straightforward synthesis of aryldiazoacetates. However, the protocol we reported previously is less efficient in that a high loading of the palladium(0) catalyst and excess amount of EDA are required. Moreover, the substrate scope is limited. As a result, the reaction is not practically useful as a synthetic method for aryldiazoacetates. Herein we report a deacylative cross-coupling of aryliodides with acyldiazoacetates for the synthesis of aryldiazoacetates (Scheme 1). The deacylative approach is highly efficient and can be carried out at room temperature with low palladium(0) catalyst loading, and it shows a much wider substrate scope. In addition, this reaction uses relatively stable diazo compounds as the coupling partners (acyldiazoacetates versus EDA). This deacylative coupling approach can also be extended to the synthesis of acyldiazophosphates and aryldiazoketones.

At the outset of this study, phenyl iodide (**1a**) and acyldiazoacetate (**2a**) were employed as the model substrates to study the coupling reaction (Table 1). In the presence of

Table 1: Optimization of the reaction conditions.[a]



1a **2a** **3a**

Entry	Cat. (mol%)	Base (equiv)	Solvent	Yield [%][b]
1	$[Pd(PPh_3)_4]$ (5)	LiO*t*Bu (1.2)	toluene	trace
2	$[Pd(PPh_3)_4]$ (5)	NaOMe (1.2)	toluene	6
3	$[Pd(PPh_3)_4]$ (5)	NaOMe (1.2)	MeOH	17
4	$[Pd(PPh_3)_4]$ (5)	NaOMe (1.2)	EtOH	31
5	$[Pd(PPh_3)_4]$ (5)	NaOMe (1.2)	EtOH	45
6	$[Pd(PPh_3)_4]$ (5)	NaOMe (1.2)	EtOH	63
7	$[Pd(PPh_3)_4]$ (5)	NaOH (3.0)	EtOH	86
8	$[Pd(PPh_3)_4]$ (5)	KOH (3.0)	EtOH	79
9	$[Pd(PPh_3)_4]$ (1.5)	NaOH (3.0)	EtOH	85 (68)[c]
10	none	NaOH (3.0)	EtOH	n.r.

[a] All the reactions were carried out with **1a** (0.25 mmol), **2a** (0.3 mmol) in 1 mL solvent under room temperature for 5 h. [b] Yield of isolated product. [c] The yield within the parentheses refers to a gram-scale experiment. n.r. = no reaction.

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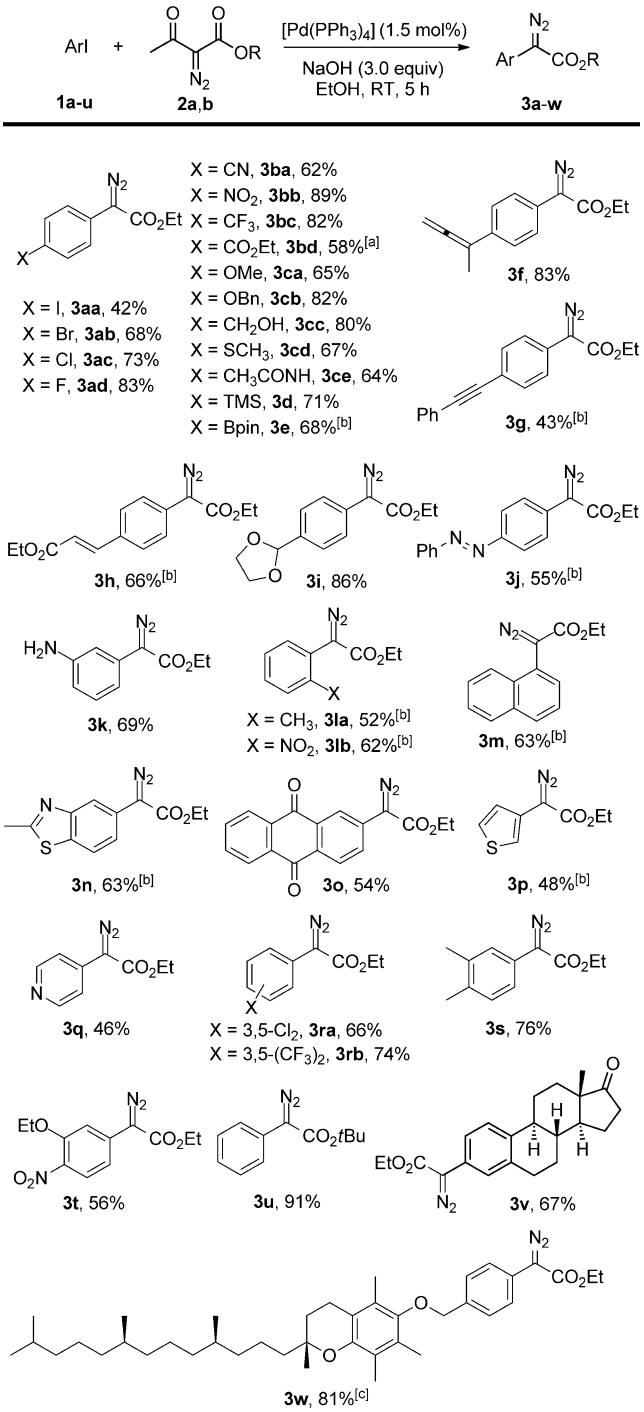
5 mol% $[Pd(PPh_3)_4]$, 1.2 equivalents of LiO*t*Bu, and toluene, only a trace amount of the desired product **3a** was detected (Table 1, entry 1). The reaction was slightly improved when NaOMe was used as the base instead of LiO*t*Bu (entries 2–4). Further improvement was observed by increasing the amount of NaOMe and using EtOH as the solvent (entries 4–6). Further experiments indicated that a significant increase of the yield could be achieved with either KOH or NaOH as the base (entries 7 and 8). Moreover, the palladium(0) catalyst loading could be reduced to 1.5 mol% without compensation of the yield (entry 9). A scale-up experiment under these reaction conditions with 10 mmol of **1a** afforded 1.3 grams of **3a** (68%). Finally, a control experiment indicated that no reaction occurred in the absence of the palladium(0) catalyst (entry 10).

With the optimized reaction conditions (Table 1, entry 9), we proceeded to survey the substrate scope with a series of aryl iodides as shown in Scheme 2. First, we found that the halogen substituents tolerate the reaction (**3aa**–**ad**). The aryl iodides bearing electron-withdrawing groups (**3ba**–**bd**) and electron-donating groups (**3ca**, **3cd**) are all suitable substrates, thus affording the corresponding products in good yields. It was noteworthy that aryl iodides with sensitive substituents, such as TMS and Bpin groups, are also suitable substrates for the reaction (**3d**, **e**). Unsaturated substituents, such as allene, alkyne, and vinyl groups, also tolerate the reaction conditions (**3f**–**h**). In addition, the reactions of the aryl iodides bearing azo and acetal substituents worked well under the standard reaction conditions, thus affording the corresponding products **3i** and **3j** in moderate yields. Remarkably, unprotected hydroxy and amino groups tolerate this transformation (**3cc**, **3k**). For the aryl iodides bearing *ortho* substituents, including NO_2 and bulky CH_3, increased loading of the palladium(0) catalyst was required presumably for facilitating the oxidative addition of the iodide substrate to the palladium(0) catalyst.

In the case of polycyclic substrates, such as 1-iodonaphthalene, 5-iodo-2-methylbenzothiazole, and 2-iodoanthraquinone, the desired products **3m**–**o** (Scheme 2) could also be formed in moderate yields. Substrates bearing a pyridine and thiophene moiety also gave the corresponding products **3p** and **3q**, albeit in slightly diminished yields. Next, we proceed to explore the coupling reaction with multisubstituted aryl iodides. As shown by the results, the coupling reaction all proceeded well to give the corresponding products in good yields (**3ra**, **3rb**, **3s**, **3t**). When the ethyl group is displaced by bulky *tert*-butyl group in the diazoester, the corresponding product **3u** is also obtained in excellent yield. Finally, aryl iodides containing estrone and tocopherol moieties could also smoothly undergo the reaction to give the corresponding products in good yields (**3v**, **w**).

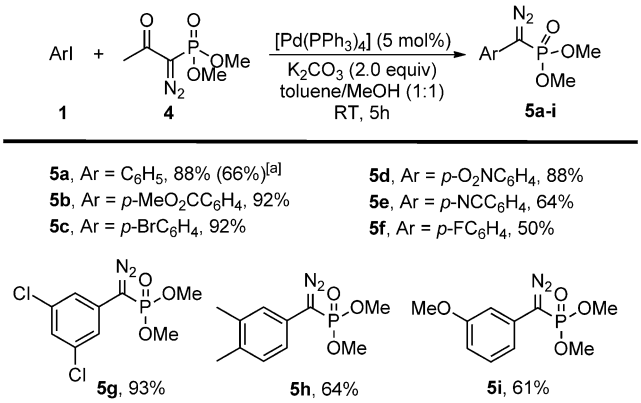
Next, we expanded this coupling reaction to aryl iodides and the acyldiazophosphate **4**. As shown in Scheme 3, the cross-coupling reactions proceeded smoothly under slightly modified reaction conditions. Thus, with K_2CO_3 as the base and a 1:1 mixture of toluene and MeOH as the solvent, the aryl iodides bearing both electron-withdrawing and electron-donating groups all worked well to give the corresponding products in moderate to good yields. A scale-up experiment



Scheme 2. Scope of the coupling reaction of acyldiazoacetate with aryl iodide. If not otherwise noted, the reactions were carried out with the aryl iodides **1a**–**u** (0.25 mmol), acyldiazoacetate **2a**,**b** (0.3 mmol), $[Pd(PPh_3)_4]$ (1.5 mol%), NaOH (3.0 equiv) in EtOH (1 mL) for 5 h at room temperature. All the yields refer to products isolated after column chromatography. [a] The substituent X in the substrate is CO_2Et. [b] Used $[Pd(PPh_3)_4]$ (5 mol%). [c] To enhance the solubility, petroleum ether (0.5 mL) was added. TMS = trimethylsilyl.

was also carried out with 6 mmol of **1a** under the same reaction conditions, thus affording 0.9 grams of **5a** (66%).

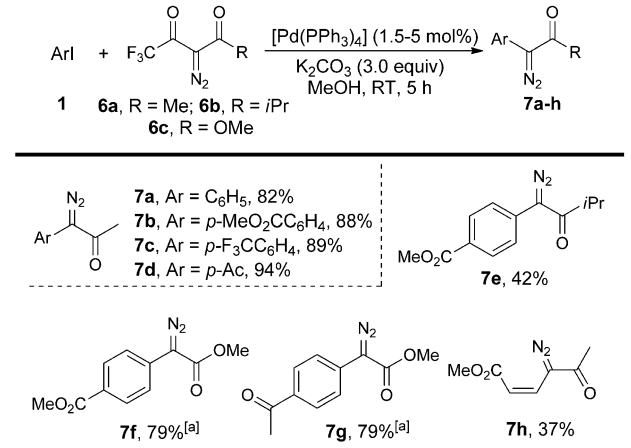
Encouraged by the above results, we proceeded to further apply this coupling reaction for the synthesis of aryldiazoke-



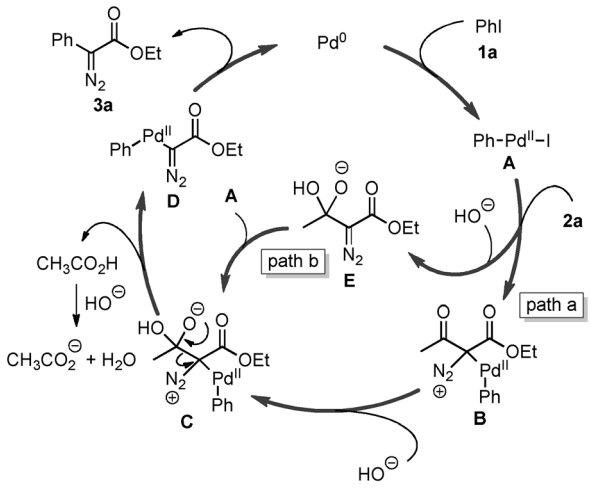
Scheme 3. Scope of the coupling reaction of acyldiazophosphate with aryl iodide. All the reactions were carried out with **1** (0.2 mmol), **4** (0.25 mmol), $[Pd(PPh_3)_4]$ (5 mol%), K_2CO_3 (2.0 equiv) in a mixed solvent of toluene (0.5 mL) and MeOH (0.5 mL) at room temperature for 5 h. All the yields refer to products isolated after column chromatography. [a] The yield within the parentheses refers to the scale-up experiment.

tones. The palladium(0)-catalyzed cross-coupling of **1a** with 3-diazopentane-2,4-dione under the same reaction conditions shown in Scheme 2 was found to not be efficient. Trifluoroacyldiazoketones were then proven to be good coupling partners because of the activation effect of the trifluoromethyl group.[9] As summarized in Scheme 4, aryldiazoketones (**7a–e**) could be prepared under slightly modified reaction conditions with K_2CO_3 as the base and MeOH as the solvent. Notably, the reaction with *p*-acylphenyl iodide gave the corresponding coupling product **7d**, while the corresponding reaction with **2a** in NaOH/EtOH system failed. It is also noteworthy that vinyldiazoketone could also be obtained, albeit in low yield (**7h**).

Based on our previous studies and our understanding of palladium-catalyzed reaction of diazo compounds,[1n,7,10]



Scheme 4. Scope of the coupling reaction of trifluoroacyldiazoketones with aryl iodides. If not otherwise noted, the reactions were carried out with **1** (0.3 mmol), **6** (0.25 mmol), $[Pd(PPh_3)_4]$ (5 mol%), K_2CO_3 (3.0 equiv) in MeOH (1 mL) at room temperature for 5 h. All the yields refer to the isolated products. [a] $[Pd(PPh_3)_4]$ (1.5 mmol%) were used. The reactions were carried out with **1** (0.25 mmol) and **6c** (0.3 mmol).



Scheme 5. Proposed reaction mechanism.

a plausible reaction mechanism is proposed as shown in Scheme 5. First, oxidative addition of phenyl iodide to the palladium(0) catalyst affords the intermediate **A**, which coordinates to diazo substrate to generate the intermediate **B**. Nucleophilic attack by hydroxide anion then generates the intermediate **C** (path a). Alternatively, the acyldiazoacetate **2a** may be first activated through nucleophilic attack of hydroxide anion to give **E**. Then **A** coordinates to **E** to give **C** (path b). Subsequently, deacylation from **C** gives the intermediate **D**,[11] from which reductive elimination affords the deacylative coupling product and regenerates palladium(0) catalyst.

Since ethyl diazoacetate (EDA) can be formed through the base treatment of **2a**,[1e] an alternative pathway involving the in situ generation of EDA followed by the coupling of EDA with **1a** may be operative.[7] However, a control experiment indicates that the palladium(0)-catalyzed reaction of **1a** with EDA under the standard reaction conditions resulted in the formation of **3a** in only trace amount, thus indicating that EDA is not the intermediate for this reaction.

In summary, we have developed a highly efficient deacylative cross-coupling, which can serve as a new method for the synthesis of acyldiazocarbonyl compounds and aryldiazophosphates.[12] This coupling reaction use easily available starting materials and proceeds at room temperature and tolerates various functional groups. It is thus expected that this reaction will find wide applications for the synthesis of diazo compounds.

Experimental Section

General procedure for the reaction of ethyl 2-diazo-3-oxobutanoate and aryl iodides. $[Pd(PPh_3)_4]$ (4.3 mg, 1.5 mol%, or 14.4 mg, 5 mol%), NaOH (30.0 mg, 0.75 mmol), and the aryl iodide **1a–u** (0.25 mmol) were suspended in ethanol (1.0 mL) in a 10 mL microwave tube under N_2. Ethyl 2-diazo-3-oxobutanoate (**2a**; 46.8 mg, 0.30 mmol) was then added, and the resulting solution was stirred at room temperature for 5 h. The mixture was filtered through a short path of silica gel (eluting with ethyl acetate), and the filtrate was evaporated in vacuo to remove the volatile compounds. The

crude residue was further purified by silica gel column chromatography to give the diazo products as shown in Scheme 2.

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