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Palladium-Catalyzed Cross-Coupling of Aryl or Vinyl Iodides with Ethyl Diazoacetate

Cheng Peng, Jiajia Cheng, and Jianbo Wang*

Beijing National Laboratory of Molecular Sciences (BNLMS), Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China

Received April 30, 2007; E-mail: wangjb@pku.edu.cn

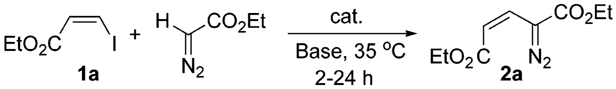
Palladium catalyzed cross-coupling reaction has been developed into one of the most powerful methods for the formation of C−C bonds.[1] Recently, remarkable progress has been made in the Pd-catalyzed cross-coupling reactions with carbon nucleophiles derived from active methylene compounds,[1d] ketones,[2] esters,[3] amides,[4] and nitriles.[5] Hydrazones have also been applied in this type of reactions as acyl anion nucleophiles.[6] In connection with our interest in the chemistry of diazo compounds as nucleophiles,[7] we have conceived that α-diazocarbonyl compounds, which are commonly used as carbene precursors,[8] may be utilized as carbon nucleophiles in Pd-catalyzed coupling reactions. Diazo carbon bears a partial negative charge and thus has considerable nucleophilicity;[9] however, to the best of our knowledge, diazo compounds have not been directly used as partners in Pd-catalyzed cross-coupling reactions.[10] This may be attributed to the general belief that diazo decomposition should occur readily upon complexation with transition metals.[8,11] Herein we report that ethyl diazoacetate (EDA) undergoes efficient Pd-catalyzed cross-coupling with aryl or vinyl iodides. Moreover, carbonylation occurs prior to the coupling if the reaction is carried out under an atmosphere of CO.

An initial attempt to couple EDA with ethyl (*Z*)-3-iodopropenoate (**1a**) using Et_3N as base and $Pd(OAc)_2$ as catalyst in CH_2Cl_2 resulted in rapid diazo decomposition (Table 1, entry 1). $Pd_2(dba)_3$ also decomposed EDA (entry 2). To our delight, with $PdCl_2(PPh_3)_2$ the reaction afforded cross-coupling product, albeit in low yield (entry 3). The yield could be slightly improved by $Pd(PPh_3)_4$ (entry 4). Other reaction parameters were then screened with this catalyst. Increasing the catalyst loading could further improve the yield (entry 5). The reaction seemed more favored in polar solvents such as MeCN, DMF, and acetone, but MeOH and DMSO resulted in diminished yields (entries 10, 11). Inorganic bases of Cs_2CO_3, K_2CO_3 were found unsuitable in this reaction (entries 12, 13). The introduction of 1 equiv of *n*-Bu_4NBr as additive significantly improved the reaction (entry 15).[12] However, Pd(0) catalyst containing more electron-rich phosphine ligands were found not effective in this reaction (entries 16, 17).

Moreover, it was noteworthy that without Pd(0) catalyst no coupling product could be observed (entry 18). This experiment rules out the possibility of a conjugate addition−elimination mechanism for the formation of **2a**.[13]

A series of vinyl iodides were then subjected to the optimized reaction conditions (Table 1, entry 15). The reaction gave cross-coupling products in moderate to good yields (Table 2). The strong electron-withdrawing substituent at the double bond was found necessary for this reaction since the reaction with *β*-iodo styrene gave no cross-coupling product. Besides, it was noted that the reaction proceeded with retention of configuration at the double bond.

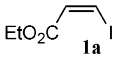
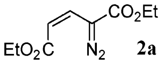
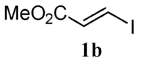
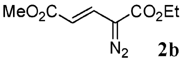
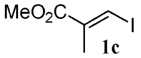
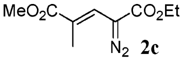
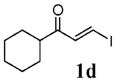
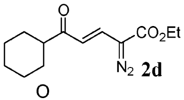
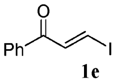
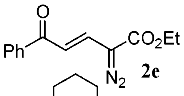
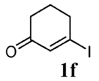
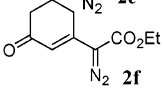
Table 1. Pd-Catalyzed Cross-Coupling of Iodide **1a** with EDA



entry	catalyst (mol %)	solvent	base	yield (%)[a]
1	$Pd(OAc)_2$ (2.5)	CH_2Cl_2	Et_3N	*b*
2	$Pd_2(dba)_3$ (2.5)	CH_2Cl_2	Et_3N	*b*
3	$PdCl_2(PPh_3)_2$ (2.5)	CH_2Cl_2	Et_3N	27
4	$Pd(PPh_3)_4$ (2.5)	CH_2Cl_2	Et_3N	41
5	$Pd(PPh_3)_4$ (5)	CH_2Cl_2	Et_3N	62
6	$Pd(PPh_3)_4$ (5)	MeCN	Et_3N	70
7	$Pd(PPh_3)_4$ (5)	DMF	Et_3N	66
8	$Pd(PPh_3)_4$ (5)	$Me_2C{=}O$	Et_3N	79
9	$Pd(PPh_3)_4$ (5)	Et_2O	Et_3N	47
10	$Pd(PPh_3)_4$ (5)	MeOH	Et_3N	40
11	$Pd(PPh_3)_4$ (5)	DMSO	Et_3N	40
12	$Pd(PPh_3)_4$ (5)	MeCN	Cs_2CO_3	26
13	$Pd(PPh_3)_4$ (5)	MeCN	K_2CO_3	*c*
14	$Pd(PPh_3)_4$ (5)	MeCN	DBU	*c*
15	$Pd(PPh_3)_4$ (5)/*n*-Bu_4NBr	$Me_2C{=}O$	Et_3N	86
16[d]	$Pd_2(dba)_3$ (2.5)/dppb (5)/*n*-Bu_4NBr	$Me_2C{=}O$	Et_3N	11
17	$Pd_2(dba)_3$ (2.5)/${}^tBu_3P$ (5)/*n*-Bu_4NBr	$Me_2C{=}O$	Et_3N	trace
18	*n*-Bu_4NBr[e]	$Me_2C{=}O$	Et_3N	*c*

[a] Isolated yield. [b] Diazo decomposition occurred rapidly to give a complex mixture. [c] **2a** was not detected. [d] dppb = 1,4-bis(diphenylphosphino)butane. [e] No Pd catalyst.

Table 2. $Pd(PPh_3)_4$-Catalyzed Cross-Coupling of Vinyl Iodides **1a**−**f** with EDA[a]

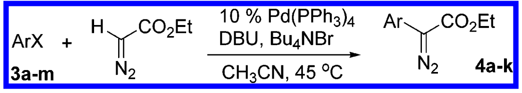
entry	iodide **1a-f**	product	time (h)	yield (%)[b]
1	 **1a**	 **2a**	2	86
2	 **1b**	 **2b**	2	75
3	 **1c**	 **2c**	2	88
4	 **1d**	 **2d**	3	55
5	 **1e**	 **2e**	1	48
6	 **1f**	 **2f**	4	78

[a] Reaction conditions: **1** (1 equiv), EDA (2.5 equiv), Et_3N (1.5 equiv), *n*-Bu_4NBr (1equiv), $Pd(PPh_3)_4$ (5 mol %), in acetone at 35 °C. [b] Isolated yield after column chromatography.

Next we conceived to extend the coupling reaction to aryl halides. However, when the above reaction conditions were applied to iodobenzene, the expected cross-coupling product was not obtained. After screening the reaction conditions, we found that by replacing Et_3N with DBU, the above optimized conditions could be successfully applied to the coupling reaction with aryl iodides (Table 3).

10.1021/ja073010+ CCC: $37.00

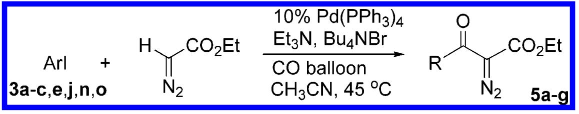
Table 3. Pd(PPh$_3$)$_4$-Catalyzed Cross-Coupling Reaction of Aryl Halides with EDA



entry	halide (**3**, ArX)	reacn time (h)	**4**, yield (%)[a]
1	**3a**, C_6H_5I	12	**4a**, 80
2	**3b**, *p*-$CH_3C_6H_4I$	14	**4b**, 77
3	**3c**, *m*-$CH_3C_6H_4I$	11	**4c**, 75
4	**3d**, *p*-ClC_6H_4I	5	**4d**, 74
5	**3e**, *p*-BrC_6H_4I	5	**4e**, 80
6	**3f**, 3,5-$Br_2C_6H_3I$	8	**4f**, 75
7	**3g**, *p*-$CH_3O_2CC_6H_4I$	13	**4g**, 76
8[b]	**3h**, *p*-$NO_2C_6H_4I$	8	**4h**, 96
9	**3i**, *p*-$CH_3OC_6H_4I$	17	**4i**, 39
10	**3j**, *o*-ClC_6H_4I	72	**4j**, trace
11	**3k**, *o*-BrC_6H_4,I	72	**4k**, trace
12	**3l**, C_6H_5Br	24	**4a**, trace
13[b]	**3m**, *p*-$NO_2C_6H_4Br$	10	**4h**, 19

[a] Isolated yield after column chromatography. [b] Reaction run using 5 mol % Pd(PPh$_3$)$_4$ and 1.5 equiv of Et$_3$N.

Table 4. Pd(PPh$_3$)$_4$-Catalyzed Carbonylation of CO with Iodides and EDA



entry	iodide (**3**, Ar)	reacn time (h)	**5**, yield (%)[a]
1	**3a**, C_6H_5	11	**5a**, 62
2	**3b**, *p*-$CH_3C_6H_4$	12	**5b**, 66
3	**3c**, *m*-$CH_3C_6H_4$	12	**5c**, 43
4	**3e**, *p*-BrC_6H_4	13	**5d**, 51
5	**3j**, *o*-ClC_6H_4	24	**5e**, trace
6	**3n**, 1-naphthyl	11	**5f**, 60
7	**3o**, *trans*-PhCH=CH	11	**5g**, 59

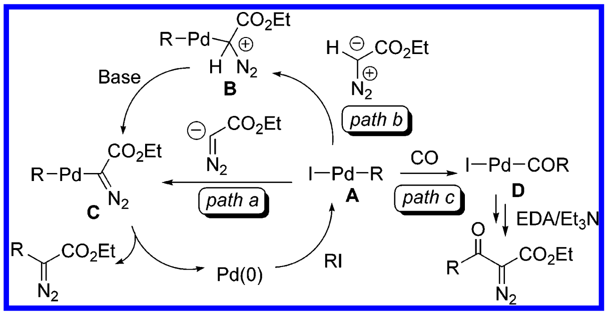
[a] Isolated yield after column chromatography.

The reaction occurred smoothly with meta and para substituted aryl iodides to afford the corresponding aryl diazoacetate. The contrasting results obtained with *p*-NO$_2$ and *p*-MeO substituted substrates indicated significant influence of electronic effects on the reaction (entries 8, 9). On the other hand, the reactions with ortho substituted aryl iodides failed to afford the corresponding coupling products, which revealed that the reaction was also affected by steric hindrance (entries 10, 11). It was also noted that aryl bromides were less reactive in this reaction (entries 12, 13).

Encouraged by the results with vinyl and aryl iodides, we further investigated the carbonylation with CO in this cross-coupling process. After optimizing the reaction conditions, we found that Et$_3$N was the suitable base for this purpose. Typical results are summarized in Table 4. The carbonylation followed by cross-coupling afforded β-keto α-diazocarbonyl compounds in moderate yields. The slightly diminished yields as compared with direct coupling reaction were attributed to the decreased reactivity of the catalyst under this condition, which resulted in long reaction time and incomplete reaction. Again, ortho substituted aryl iodide afforded only trace amount of coupling product (entry 5).

The reaction mechanism for this reaction is shown in Scheme 1. Oxidative addition of Pd(0)L$_n$ with aryl or vinyl iodide affords the Pd(II) intermediate **A**. Substitution of the iodo by diazo anion, which is derived from deprotonation of EDA, provides the intermediate **C** (path *a*). Alternatively, EDA coordinates to Pd(II) intermediate **A** to form complex **B**, from which proton is removed by base to afford **C** (path *b*).[14] Remarkably, nitrogen extrusion, which is a very facile process for transition metal-complexed diazo compounds,[8,11] does not occur from complex **B**. Finally reductive elimination of the intermediate **C** gives the cross-coupling product and regenerates the catalyst. In the presence of CO, prior to the reaction with EDA the CO insertion occurs from intermediate **A** to afford **D**, from which reaction with EDA/Et$_3$N followed by reductive elimination leads to β-keto α-diazocarbonyl compounds (path *c*).

Scheme 1. Mechanistic Rationale



In summary, α-diazocarbonyl compound has been utilized for the first time as cross-coupling partner in Pd-catalyzed reaction. The reaction provides a novel approach to introduce diazo functionality to organic compounds.

Acknowledgment. The project is generously supported by NSFC (No. 20225205, 20390050) and the Ministry of Education of China (Cheung Kong Scholars Program).

Supporting Information Available: Experiment procedure and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA073010+