Palladium-catalyzed reaction of allyl halides with α-diazocarbonyl compounds†

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The Pd(OAc)$_2$-catalyzed reaction between α-diazocarbonyl compounds and allyl bromides or chlorides leads to the formation of 1,3-diene derivatives.

π-Allylic palladium complexes are important intermediates in palladium-catalyzed reactions.[1] The π-allylic palladium complexes are electrophilic in character and react with various nucleophiles, such as amines, alcohols, and carbon nucleophiles. These Pd-catalyzed allylation reactions have found wide applications in organic synthesis. In particular, the reactions with carbon nucleophiles have developed into a valuable method for the formation of C–C bonds. The common carbon nucleophiles used in Pd-catalyzed allylation include anions or enolates derived from carbonyl compounds such as ketones, esters, and 1,3-dicarbonyl compounds.[2] In connection to our recent interest in the palladium-catalyzed reaction of diazo compounds,[3,4] we have conceived that it may be possible to use α-diazocarbonyl compounds as nucleophiles in the reaction of π-allylic palladium complexes. In this communication we report the palladium-catalyzed reaction of allylic halides with aryldiazoacetates and aryldiazoacetones, in which carbon double bonds are generated to afford 1,3-diene products (Scheme 1).

At the outset of this investigation, various Pd(0) and Pd(II) complexes were examined as the catalysts in the reaction of allyl bromide with methyl phenyldiazoacetate **1a** (Table 1). Two Pd(0) catalysts, Ph(PPh$_3$)$_4$ and Pd$_2$(dba)$_3$, were examined with Et$_3$N as base and MeCN as solvent. Ph(PPh$_3$)$_4$ was found to be not effective and the starting materials remained unchanged at 25 °C (entry 1). Pd$_2$(dba)$_3$ led to the formation of 1,3-diene **2a** in 45% yield (entry 2). Among four Pd(II) catalysts examined, Pd(PPh$_3$)$_2$Cl$_2$ was found to be not effective, while PdCl$_2$, Pd(PhCN)$_2$Cl$_2$ and Pd(OAc)$_2$ all gave **2a** in low to moderate yields (entries 3–6). The highest yield, of 77%, was obtained with Pd(OAc)$_2$ (entry 6). Rh$_2$(OAc)$_4$, CuOTf and CuI were examined under the similar reaction conditions and the reactions were found to lead to a complex mixture (entries 7–9).

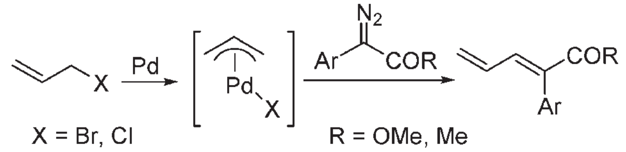
For comparison, the reaction was carried out in the absence of transition metal catalyst. No reaction occurred under such conditions (entry 10). After Pd(OAc)$_2$ was identified as the most efficient catalyst, the effect of base on this reaction was next examined. Bases such as K$_2$CO$_3$, Cs$_2$CO$_3$ and KOAc also led to the formation of diene **2a** in moderate yields (entries 11–13). However, no diene **2a** was detected when the organic base DBU was used (entry 14). The reaction under this condition resulted in a complex mixture. Finally, in the absence of base, no reaction occurred and the starting material was recovered unchanged (entry 15).

The optimized reaction conditions were then applied to a range of aryldiazoacetates and aryldiazoacetones **1a–n** (Table 2). Various substitutions on the aromatic ring could be tolerated, and moderate to good yields of the products **2a–n** were obtained. The stereoselectivity of the products was generally high. Moreover, it was noted that the ester moiety of the diazo compounds did not affect the reaction (entries 13, 14). It was also observed that diazo compounds other than aryldiazoacetates or aryldiazoacetones afforded the diene products in rather lower yields. The reaction with ethyl diazoacetate under identical conditions resulted in complex mixture.

Next, we examined the scope of allyl substrates. When the substituted allyl bromide was subjected to the above reaction with methyl phenyldiazoacetate **1a**, the reaction led to a low yield of the expected diene products. However, we were delighted to find that when the substituted allyl chloride was used, the reaction proceeded smoothly under the identical reaction conditions. As shown in Table 3, for a series of substituted allyl chlorides **3a–h**, the reaction gave the 1,3-diene products in moderate to good yields. It was noted that the allyl chlorides worked well with either alkyl or aryl substituents.

It should be mentioned that the formation of **4a–k** can not be attributed to ylide [2,3]-sigmatropic rearrangement–elimination mechanism.[5] Moreover, the same 1,3-diene product **2a** can be obtained under the identical conditions from the reaction of allyl carbonate **5** or allyl acetate **6** with methyl phenyldiazoacetate **1a**, albeit in low yields (Scheme 2).

Three plausible reaction pathways to account for the formation of dienes are considered as shown in Scheme 3. In all cases, the reaction is initiated by the reduction of Pd(II) to Pd(0) by the diazo compound, followed by the formation of π-allylpalladium complex **A**. In *path a*, the diazo substrate attacks the allyl ligand



Scheme 1 Pd-catalyzed reaction of allyl halides with diazo compounds.

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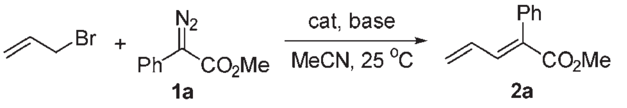
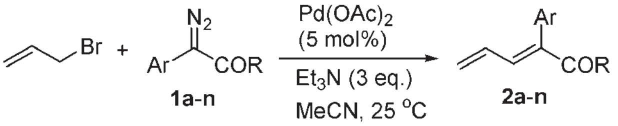
Table 1 Transition metal-catalyzed reaction of allyl bromide with methyl phenyldiazoacetate **1a**[a]



Entry	Cat. (mol%)	Base	Time/h	Yield (%)[b]
1	$Pd(PPh_3)_4$ (5)	Et_3N	12	0 (38)[c]
2	$Pd_2(dba)_3$ (5)	Et_3N	24	45
3	$PdCl_2(PPh_3)_2$ (5)	Et_3N	24	0 (54)[c]
4	$PdCl_2$ (5)	Et_3N	19	32
5	$Pd(PhCN)_2Cl_2$ (5)	Et_3N	20	55
6	$Pd(OAc)_2$ (5)	Et_3N	12	77
7	$Rh_2(OAc)_4$ (0.5)	Et_3N	11	0[d]
8	CuOTf (10)	Et_3N	24	0[d]
9	CuI (10)	Et_3N	24	0[d]
10	None	Et_3N	24	N.R.[e]
11	$Pd(OAc)_2$ (5)	K_2CO_3	12	61
12	$Pd(OAc)_2$ (5)	Cs_2CO_3	1	48[f]
13	$Pd(OAc)_2$ (5)	KOAc	9	55
14	$Pd(OAc)_2$ (5)	DBU	24	0
15	$Pd(OAc)_2$ (5)	None	24	N.R.[e]

[a] Reactions were carried out with 0.3 mmol of allyl bromide, 0.42 mmol of **1a**, and 0.9 mmol of Et_3N. [b] Yield of the isolated product after chromatography. [c] The reaction was run at 50 °C. [d] The reaction gave a complex mixture. [e] N.R.: no reaction, starting materials were recovered. [f] Starting materials disappeared after 1 h.

Table 2 $Pd(OAc)_2$-catalyzed reaction of allyl bromide with diazo compounds **1a–n**

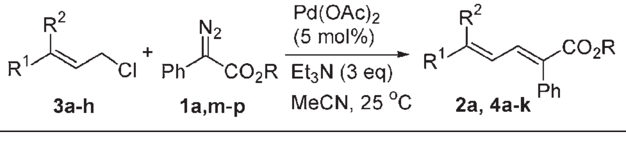


Entry	**1**, Ar, R	Time/h	**2**, Yield (%)[a]	*E* : *Z*
1	**1a**, C_6H_5, OMe	12	**2a**, 77	>20 : 1
2	**1b**, *p*-$CH_3C_6H_4$, OMe	12	**2b**, 77	5 : 1
3	**1c**, *p*-$CH_3OC_6H_4$, OMe	4	**2c**, 53	>20 : 1
4	**1d**, *m*-$CH_3OC_6H_4$, OMe	17	**2d**, 71	5 : 1
5	**1e**, *o*-ClC_6H_4, OMe	7	**2e**, 61	10 : 1
6	**1f**, *p*-ClC_6H_4, OMe	12	**2f**, 73	10 : 1
7	**1g**, *m*, *p*-$Cl_2C_6H_3$, OMe	22	**2g**, 50	10 : 1
8[c]	**1h**, C_6H_5, Me	8	**2h**, 55	>20 : 1
9[c]	**1i**, *p*-ClC_6H_4, Me	20	**2i**, 68	>20 : 1
10[cd]	**1j**, *m*-ClC_6H_4, Me	4	**2j**, 70	>20 : 1
11[cd]	**1k**, *p*-BrC_6H_4, Me	4	**2k**, 63	>20 : 1
12[cd]	**1l**, *m*,*p*-$Cl_2C_6H_3$, Me	4	**2l**, 60	>20 : 1
13	**1m**, C_6H_5, O(C_6H_4*o*-*O*-allyl)	4	**2m**, 77	>20 : 1
14	**1n**, C_6H_5, $O(C_6H_5)_2CH$	5	**2n**, 69	>20 : 1

[a] Yield of isolated product after chromatography. [b] Ratio was determined by GC-MS and ^1H NMR of the crude product. [c] Reaction run with 1 eq. of diazo compound and 3 eq. of allyl bromide. [d] Reaction was carried out at 60 °C.

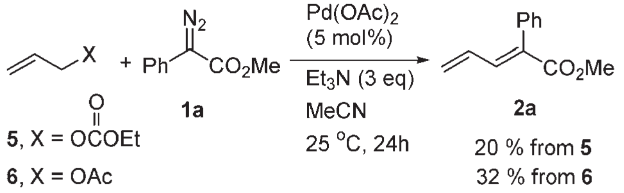
to afford intermediate **B** with the regeneration of Pd(0). Subsequent deprotonation and dinitrogen extrusion led to the formation of the 1,3-diene product. In the chemistry of the π-allylpalladium complex, it has been suggested that "soft" carbon centered nucleophiles, defined as those derived from conjugate acids whose $pK_a < 25$, usually attack the allyl ligand. On the contrary, "hard" carbon-centered nucleophiles, defined as those derived from conjugate acids whose $pK_a > 25$, attach themselves to the metal center of the π-allyl palladium complex, and the substitution occurs through subsequent transmetallation and reductive elimination.[1d] The pK_a values of the conjugate acids of diazoesters and diazoketones have been estimated to be between −5 and −2, respectively.[4a] Therefore, the α-diazocarbonyl compounds are categorized as "soft" nucleophiles, which will attack the allyl ligand. However, since the strong coordination ability of the diazo group toward transition metals, nucleophilic attack of the diazo substrate to palladium can not be strictly ruled out. In such case, intermediate **C** is generated, followed by reductive elimination to offer diazonium intermediate **B** and to regenerate Pd(0) catalyst (*path b*). The third possible pathway is the generation of a palladium carbene species **D** from **C** (*path c*). η^3–η^1 Interconversion leads to the η^1-allylpalladium complex **E**, from which migratory insertion[3b,6] occurs to afford intermediate **F**. β-Hydride elimination from **F** gives the diene product. Further extensive investigations will be required to distinguish these possible pathways.

Table 3 $Pd(OAc)_2$-catalyzed reaction of allyl chlorides **3a–h** with phenyldiazoacetates **1a, m–p**

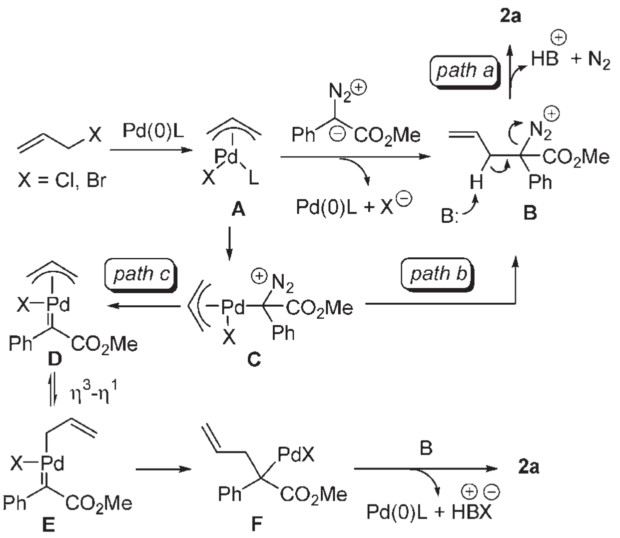


Entry	**3**, R^1, R^2	**1**, R	Time/h	Yield (%)[a]	*E* : *Z*[b]
1	**3a**, H, H	**1a**, Me	12	**2a**, 74	>20 : 1
2	**3b**, CH_3, H	**1a**, Me	11	**4a**, 63	10 : 1
3	**3c**, CH_3, CH_3	**1a**, Me	1	**4b**, 72	>20 : 1
4	**3d**, $-C_5H_{10}-$	**1a**, Me	2	**4c**, 71	>20 : 1
5	**3e**, C_6H_5, H	**1a**, Me	4	**4d**, 66	>20 : 1
6	**3f**, *p*-$CH_3C_6H_4$,H	**1a**, Me	14	**4e**, 57	>20 : 1
7	**3g**, *p*-ClC_6H_4, H	**1a**, Me	3	**4f**, 65	>20 : 1
8	**3h**, C_6H_5, C_6H_5	**1a**, Me	15	**4g**, 65	>20 : 1
9	**3e**, C_6H_5, H	**1m**, *o*-Allyl-*O*-C_6H_4	16	**4h**, 70	>20 : 1
10	**3e**, C_6H_5, H	**1n**, $(C_6H_5)_2CH$	16	**4i**, 60	>20 : 1
11	**3e**, C_6H_5, H	**1o**, *trans*-$C_6H_5CH{=}CHCH_2$	7	**4j**, 58	>20 : 1
12	**3e**, C_6H_5, H	**1p**, $CH_2{=}CHCH_2$	3	**4k**, 51	>20 : 1

[a] Yield of isolated product. [b] The ratio of *E* and *Z* isomers was estimated by GC-MS and ^1H NMR (300 MHz) of the crude product.



Scheme 2 The reaction of allyl carbonate **5** and acetate **6** with methyl phenyldiazoacetate **1a**.



Scheme 3 Possible reaction pathways.

In conclusion, a novel C=C double bond forming reaction between allyl halides and α-diazocarbonyl compounds was developed by using $Pd(OAc)_2$ as the catalyst under mild conditions. Further investigation on related Pd-catalyzed reactions of diazo compounds are ongoing in our laboratory.

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