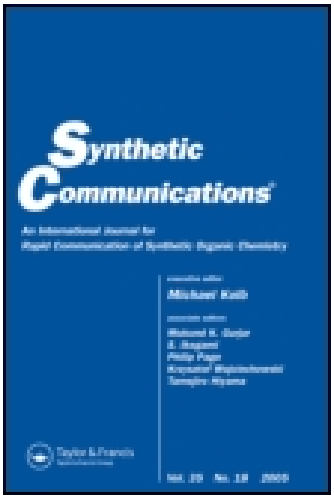

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Palladium-Catalyzed Allylation of α-Nitroacetates with Propynes

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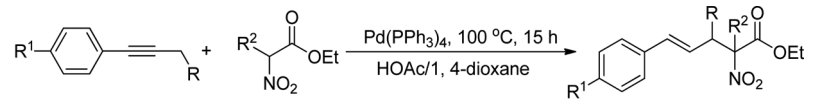
GRAPHICAL ABSTRACT



R^1 = MeO, CH_3CO etc.
R = H, OCH_3, OCH_2Ph etc.

R^2 = CH_3, Et, $PhCH_2$ etc.

25-95%

Abstract *A novel way to synthesize allylated α-nitroacetates under Pd catalysis has been described. Reactions of propynes with diverse α-nitroacetates in the presence of a catalytic amount of* $Pd(PPh_3)_4$ *and HOAc in 1,4-dioxane afforded the corresponding allylated products in good yields. Compared with other known methods, this method of synthesizing allylated α-nitroacetates generated no waste and needed neither a stoichiometric amount of base nor a leaving group.*

Keywords α-Nitroacetate; allylation; Pd catalysis; propynes; Tsuji–Trost reaction

INTRODUCTION

The palladium-catalyzed allylic alkylation (Tsuji–Trost reaction) has been widely recognized as one of the most powerful methods for the construction of carbon–carbon bonds.[1] Typically these allylic alkylations are carried out with an allylic electrophile, a pronucleophile, and a stoichiometric amount of base to react with the pronucleophile to generate the real nucleophile ($^-$Nu). Though highly efficient, like most other cross couplings, a leaving group (-X) is liberated in the reaction and some type of salt was formed as the by-product, thus limiting the overall atom economy. To overcome this problem, Kadota et al. have shown that the palladium-catalyzed allylation reactions can be performed by reacting a propyne derivative with methylmalononitrile in the presence of a catalytic amount of AcOH [Scheme 1, Eq. (1)].[2] Not only were the allylated products obtained with excellent

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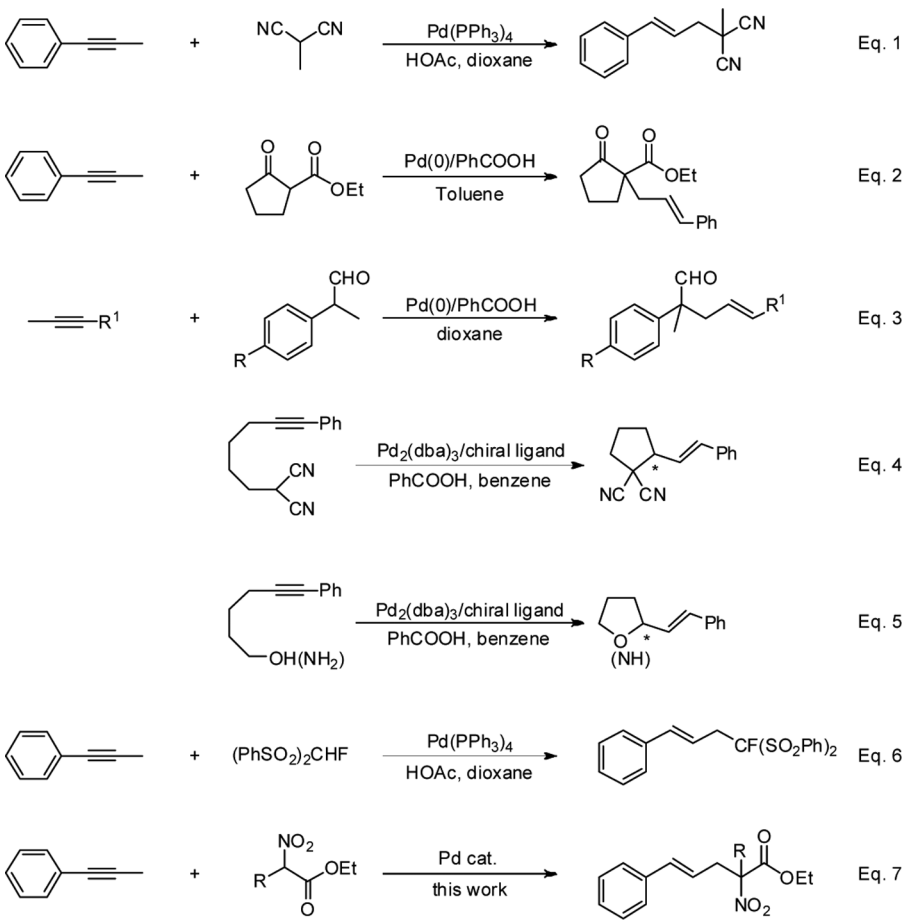


Scheme 1. Pd-catalyzed allylation of pronucleophiles with alkynes.

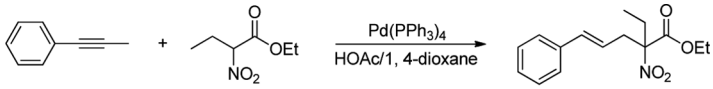
regioselectivities, but also the reaction can be adapted to an intramolecular version to afford cyclic products. More importantly, the reaction was achieved with 100% atom efficiency, which means no waste was generated in the process. They also showed that the same type of allyation can be extended to pronucleophiles such as cyanoesters and disulfonylmethanes. Later on, by using a different ligand in combination with a catalytic amount of benzoic acid, they also demonstrated that ketoesteres [Eq. (2)],[3,4] phenyl amines, and simple aldehydes [Eq. (3)][5] can also participate in this type of allylation reactions. Even more impressively, when a suitable chiral ligand was used together with the Pd catalyst, they were able to use malononitriles [Eq. (4)], alcohols [Eq. (5)], and amines as the pronucleophiles as well.[6] In addition, they were also able to synthesize heterocycles and carbocycles in good to excellent enantioselectivites (ees).[6] Building upon these results, Ni and Hu recently also reported that fluorine-containing sulfones can be used to serve as pronucleophiles to allylate propyne derivatives [Eq. (6)].[7] Based on their results, Yamamoto

believed that these reactions go through hydropalladation–dehydropalladation–rehydropalladation of the propyne to give a π-allylpalladium intermediate, which subsequently react with the pronucleophile to give the desired allylated product. Inspired by these results, we wondered if other nucleophiles can also be used to participate in this type of allylation. Herein we report that in the presence of Pd catalyst and a catalytic amount of AcOH, nitroacetate can also be used to react with propynes to give allylated nitroacetates [Eq. (7)].[8]

RESULTS AND DISCUSSION

2-Substituted nitroacetates constitute a class of valuable intermediates for the synthesis of a large variety of organic compounds, particularly for the synthesis of amino acids.[9–11] They are frequently prepared from the parent nitroacetates by the classical alkylation procedure, the S_N2 reaction.[9,10] Among the various alkylations, allylation stands out from the rest because allylations are much more favorable and generally can be run under relatively mild conditions. Inspired by Yamamoto's results and the fact that nitroacetates can also be used to participate in the classical Tsuji–Trost reaction,[12,13] we attempted to use propyne to allylate nitroacetates under Yamamoto's condition. At the outset of our study, we decided to use the reaction of 1-phenyl-1-propyne (**1a**) with ethyl 2-nitrobutanoate (**2a**) as our model reaction. When we treated 1-phenyl-1-propyne with 1 equiv of ethyl 2-nitrobutanoate in the presence of $Pd(PPh_3)_4$ (10 mol%) and acetic acid (50 mol%) in dioxane at 80 °C for 12 h, much to our delight, the desired product (E)-ethyl 2-ethyl-2-nitro-5-phenylpent-4-enoate (**3a**) was isolated in 53% yield (Table 1, entry 1). It should be noted that the addition took place on the propargyl position only and the stereochemistry of the double was exclusively E, based on the large coupling constant observed for the two olefinic hydrogens. When the temperature was elevated to 100 °C, the yield was increased to 77% (Table 1, entry 2). In contrast, the reaction was rather sluggish when the reaction was run at 60 °C (Table 1, entry 3). When the Pd source was switched to either $Pd(OAc)_2$ or $Pd_2(dba)_3$, **3a** was only isolated in <10% yield (Table 1, entries 4 and 5). The use of $PdCl_2(PPh_3)_2$ instead of $Pd(PPh_3)_4$ also led to much lower yield (Table 1, entry 6). These results showed the use of Pd(0) catalyst in combination with a ligand is essential for achieving good yield. Next we tried to examine the reaction using other solvents. Unfortunately, the use of solvents such as CH_3CN, dimethylsulfoxide (DMSO), and dimethylformamide (DMF) all resulted in disappointing yields (Table 1, entries 7–9). Moreover, increasing the amount of acetic acid in the reaction did not affect the yield much (Table 1, entries 10 and 11). On the other hand, lowering the amount of AcOH used led to much lower yield of **3a** (Table 1, entries 12 and 13). In addition, we found that when AcOH was substituted with benzoic acid, the reaction of **1a** with **2a** only gave **3a** in 23% yield (Table 1, entry 14) We also found that no product was formed when no acetic acid was added to the reaction mixture (Table 1, entry 15). Control reaction also indicated no reaction took place in the absence of Pd catalyst (Table 1, entry 16). On the basis of these results, we decided to run the reaction in 1,4-dioxane at 100 °C for 15 h with propyne (1 equiv), nitroacetate (1 equiv), $Pd(PPh_3)_4$ (10 mol%), and acetic acid (50 mol%) under a balloon of nitrogen as our standard condition.

Table 1. Reaction condition optimization[a]



1a 2a 3a

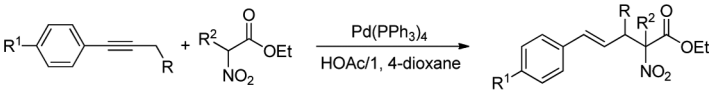
Entry	Pd catalyst	Solvent	Acid (equiv)	Temperature (°C)	Yield (%)[b]
1	$Pd(PPh_3)_4$	Dioxane	HOAc (0.5)	80	53
2	$Pd(PPh_3)_4$	Dioxane	HOAc (0.5)	100	77
3	$Pd(PPh_3)_4$	Dioxane	HOAc (0.5)	60	16
4	$Pd(OAc)_2$	Dioxane	HOAc (0.5)	100	9
5	$Pd_2(dba)_3$	Dioxane	HOAc (0.5)	100	4
6	$PdCl_2(PPh_3)_2$	Dioxane	HOAc (0.5)	100	24
7	$Pd(PPh_3)_4$	CH_3CN	HOAc (0.5)	100	45
8	$Pd(PPh_3)_4$	DMSO	HOAc (0.5)	100	33
9	$Pd(PPh_3)_4$	DMF	HOAc (0.5)	100	25
10	$Pd(PPh_3)_4$	Dioxane	HOAc (0.7)	100	75
11	$Pd(PPh_3)_4$	Dioxane	HOAc (1.0)	100	73
12	$Pd(PPh_3)_4$	Dioxane	HOAc (0.1)	100	21
13	$Pd(PPh_3)_4$	Dioxane	HOAc (0.3)	100	39
14	$Pd(PPh_3)_4$	Dioxane	PhCOOH (0.5)	100	23
15	$Pd(PPh_3)_4$	Dioxane	—	100	Trace
16	—	Dioxane	HOAc (0.5)	100	Trace

[a]Unless specified otherwise, all reactions were carried out under a balloon of nitrogen by treating **1a** (1 equiv) with **2a** (1 equiv), $Pd(PPh_3)_4$ (10 mol%) in dioxane (3 mL) at 100 °C for 15 h.
[b]Isolated yields.

With the optimized protocol in hand, we next set out to explore the scope and limitation of the reaction. We first tried to test the allylation reaction on the 2-unsubstituted 2-nitroacetate. When we treated ethyl 2-nitroacetate with 1-phenyl-1-propyne under our standard condition, we found that both mono-allylated and diallylated products were formed in 65% yield with a ratio of 2.2/1. Because the selectivity is rather poor, we focused our study using 2-substituted 2-nitroacetates to avoid the diallylation problem and the results are summarized in Table 2. As we expected, the reaction worked satisfactorily for various substituted 1-phenyl-1-propynes and nitroacetates. From the table, we can see substituents such as methoxy and ethoxy were well tolerated on the benzene ring (Table 2, entries 3–10). Gratifyingly, we found that substrates with electron-withdrawing groups such as acetyl and pentanoyl on the benzene ring also reacted satisfactorily, affording the desired products in 65–78% yields (Table 2, entries 11–18). In addition, the substituent on the α-carbon of 2-nitroacetates can also be replaced by different groups such as methyl, n-butyl, and benzyl groups, affording the desired allylated products in good yields. From the table, we do see slightly better yields were obtained with electron-donating groups such as methoxy or ethoxy groups than electron-withdrawing groups. We can also see a gradual yield drop as the substituent size on the α-carbon of 2-nitroacetates was increased. This is probably due to the increasing steric hindrance on the reaction site.

To see whether propargyl ether and amine derivatives are suitable substrates, we synthesized substrates bearing methoxy, benzyloxy, and dimethylamino groups

Table 2. Pd-catalyzed allylation of ethyl 2-nitroacetates with 1-phenyl-1-propynes[a]



1 2 3

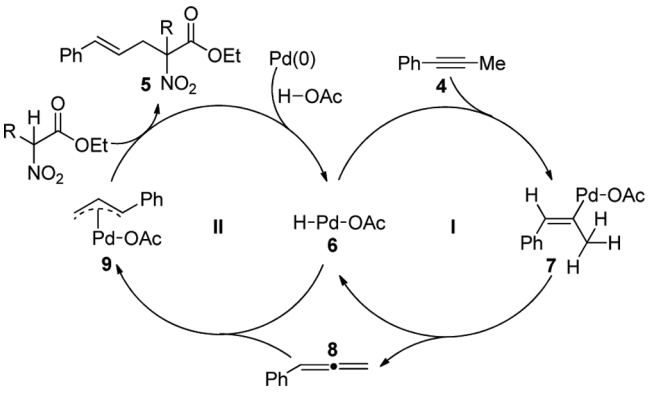
Entry	Substrate	Product	Yield (%)[b] (dr)[c]	Entry	Substrate	Product	Yield (%)[b] (dr)[c]
1	R=H R^1=H R^2=CH_3	**3b**	82 (—)	12	R=H R^1=CH_3CO R^2=C_2H_5	**3m**	70 (—)
2	R=H R^1=H R^2=n-C_4H_9	**3c**	87 (—)	13	R=H R^1=CH_3CO R^2=n-C_4H_9	**3n**	69 (—)
3	R=H R^1=MeO R^2=CH_3	**3d**	80 (—)	14	R=H R^1=CH_3CO R^2=$PhCH_2$	**3o**	67 (—)
4	R=H R^1=MeO R^2=C_2H_5	**3e**	87 (—)	15	R=H R^1=n-C_4H_9CO R^2=CH_3	**3p**	72 (—)
5	R=H R^1=MeO R^2=n-C_4H_9	**3f**	84 (—)	16	R=H R^1=n-C_4H_9CO R^2=C_2H_5	**3q**	78 (—)
6	R=H R^1=MeO R^2=$PhCH_2$	**3g**	90 (—)	17	R=H R^1=n-C_4H_9CO R^2=n-C_4H_9	**3r**	76(—)
7	R=H R^1=EtO R^2=CH_3	**3h**	80 (—)	18	R=H R^1=n-C_4H_9CO R^2=$PhCH_2$	**3s**	71(—)
8	R=H R^1=EtO R^2=C_2H_5	**3i**	92 (—)	19	R=OCH_3 R^1=H R^2=CH_3	**3t**	39 (1.7:1)
9	R=H R^1=EtO R^2=n-C_4H_9	**3j**	89 (—)	20	R=OCH_3 R^1=H R^2=C_2H_5	**3u**	35 (1.1:1)
10	R=H R^1=EtO R^2=$PhCH_2$	**3k**	95 (—)	21	R = OCH_2Ph R^1=H R^2=CH_3	**3v**	27 (1:1)
11	R=H R^1=CH_3CO R^2=CH_3	**3l**	68 (—)	22	R = OCH_2Ph R^1=H R^2=C_2H_5	**3w**	25 (1.1:1)

[a]All reactions were carried out under dry nitrogen atmosphere using 10 mol% $Pd(PPh_3)_4$ and 50 mol% HOAc in dioxane (3 mL) at 100 °C for 15 h.

[b]Isolated yields.

[c]The diastereomeric ratios were determined from the ^{1}H NMR spectra of the isolated product mixtures.

on the 3-position of 1-phenyl-1-propyne accordingly. Under the standard reaction conditions, propargyl amine derivative failed to react with **2a**. This might be because the amine has reacted with AcOH to form the corresponding ammonium salt, thus shutting down the isomerization reaction pathway (see the mechanism discussion part). On the other hand, propargyl ether derivative did react with **2a** to deliver the desired products **3t**–**3w** in 25–39% yields (Table 2, entries 19–22). From the



Scheme 2. Possible mechanism for the Pd(0)/HOAc-catalyzed allylation of α-nitroacetates with propynes.

results, we do see yields are generally much lower than the parent alkynes, which might be due to the large steric hindrance imposed by the methoxy and benzyloxy groups. Additionally, the diastereomeric ratios observed are between 1:1 to 1.7:1, showing that the diastereoselectivities are quite poor.

Based on previous literature reports,[2–5,7] a plausible mechanism for this allylation was proposed and is illustrated in Scheme 2. The initial step would be hydropalladation of **4** with the hydridopalladium species **6** generated from Pd^0 and acetic acid (catalytic cycle **I**). The resultant vinyl palladium species **7** next underwent dehydrometallation to produce phenyl allene **8** and Pd-hydride **6**. Next, rehydropalladation of **8** with **6** would give the π-allylpalladium intermediate **9**, which subsequently reacted with nitroacetate to give the desired product **5** along with Pd(0) catalyst, thus completing the catalytic cycle **II**.

In summary, we have developed a novel way of synthesizing allylated 2-nitroacetates from 1-phenyl-1-propynes and ethyl 2-nitroacetates. By treating 1-phenyl-1-propynes and ethyl 2-nitroacetates with $Pd(PPh_3)_4$ and acetic acid in 1,4-dioxane at 100 °C for 15 h, a variety of allylated nitroacetates were synthesized in good yields. It is important to point out that this reaction requires neither a stoichiometric amount of base nor a leaving group. Detailed mechanistic investigation on this reaction is still ongoing and the results will be reported in due course.

EXPERIMENTAL

All solvents and reagents were purchased from the suppliers and used without further purification. ^1H NMR and ^{13}C NMR were recorded in $CDCl_3$ at room temperature on the Varian Inova-400 spectrometer (400 MHz ^1H) and Bruker spectrometer (400 MHz ^1H). The chemical-shift scale is based on internal tetramethylsilane (TMS). All reactions were carried out under a dry nitrogen atmosphere.

General Reaction Procedure

Acetic acid (14 μL, 0.5 mmol) was added to a mixture of 1-phenyl-1-propyne (**1a**, 1.0 mmol), ethyl 2-nitrobutanoate (**2a**, 1.0 mmol), and $Pd(PPh_3)_4$(116 mg,

0.1 mmol) in dry dioxane (3 mL), and the mixture was stirred at 100 °C for 15 h under a balloon of nitrogen. After cooling to room temperature, the reaction mixture was diluted with dichloromethane (25 mL) and water (25 mL). The aqueous layer was extracted with dichloromethane (3×25 mL) and washed with brine. The organic layers were combined, dried with $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 50:1) to afford the desired product (E)-ethyl 2-ethyl-2-nitro-5-phenylpent-4-enoate (**3a**) in 77% yield.

(E)-Ethyl 2-Ethyl-2-nitro-5-phenylpent-4-enoate (3a)[14]

Yield: 77%; yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz,) δ7.32–7.25 (m, 5H), 6.50 (d, $J = 15.6$ Hz, 1H), 5.96 (dt, $J = 15.6$ Hz, 7.4 Hz, 1H), 4.28 (q, $J = 6.4$ Hz, 2H), 3.15–3.04 (m, 2H), 2.36–2.20 (m, 2H), 1.28 (t, $J = 7.0$ Hz, 3H), 0.96 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.48, 136.38, 135.70, 128.56, 127.88, 126.34, 120.58, 96.18, 62.66, 37.07, 27.02, 13.90, 7.93; MS (m/z, %): 277 [M^+]; IR / cm^{-1}: 2939, 1749 (COO), 1608 (C=C), 1554 (NO_2).

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

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