

Direct allylic substitution of allyl alcohols by carbon pronucleophiles in the presence of a palladium/carboxylic acid catalyst under neat conditions

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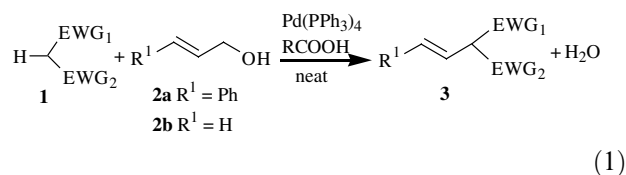
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Abstract—The reaction of allylic alcohols with carbon pronucleophiles in the presence of the Pd(PPh₃)₄/carboxylic acid combined catalytic system, under neat conditions (without an organic solvent or without water as the solvent) enabled the direct allylation of the pronucleophiles, giving the corresponding allylated products in high yields.

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Palladium catalysed allylic alkylation of active methylene compounds such as β-ketoesters and malonates (the Tsuji–Trost reaction) is a reliable and widely used method for C–C bond formation.¹ In general, the method involves the use of allylic acetates, carbonates, halides, phosphates, NR₂ etc.² However, the direct use of allylic alcohols is not well exploited because of the poor capability of the hydroxyl group to serve as a good leaving group.³ Some efforts have been made in this direction by the use of activators, which coordinate with the hydroxyl group thereby increasing its leaving group ability.⁴ As a part of our continuing interest on palladium catalysed C–C bond formation, we recently reported an entirely different approach, using the hydrocarbonation of alkynes in the presence of the Pd(PPh₃)₄/carboxylic acid combined catalytic system,⁵ which serves as an alternative allylation procedure to the existing methods. While researching the applicability of this combined catalytic system, we found that heating a mixture of cinnamyl alcohol with 1.2 equiv of diethyl malonate in the presence of Pd(PPh₃)₄ (5 mol%) and acetic acid (10 mol%) in 1,4-dioxane at 100 °C gave the monoallylated product in excellent yield. While the work was in progress in our laboratory, a similar report

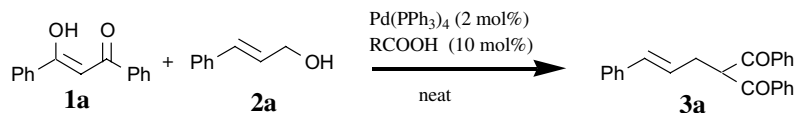
appeared in the literature⁶ based on the same concept in which the authors studied several acid sources and concluded that 1-adamantanecarboxylic acid (1-Ad-COOH) and lauric acid in water were the best. We were excited with these results as they may open a new insight into palladium chemistry in water. The novelty of the concept led us to test the ability of this catalytic system in an iterative fashion. Unfortunately, during these studies, we found that in the present reaction there is no need for a specific carboxylic acid or water as a solvent; the direct allylation of pronucleophiles **1** with allylic alcohols **2** takes place, without an organic solvent and without water as the solvent, in the presence of a catalytic amount of Pd(PPh₃)₄/carboxylic acid under neat conditions (Eq. 1).



In one set of experiments, we carried out the reaction of dibenzoylmethane with cinnamyl alcohol with Pd(PPh₃)₄ and 1-AdCOOH in water at 70 °C for 30 min as per the literature procedure (Table 1, entry 1). A similar result was obtained with lauric acid as an additive in water (entry 2). In another experiment, the same reaction was performed with acetic acid and benzoic acid as the additive under neat conditions at 70 °C for

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Table 1. Effect of carboxylic acids on Pd-catalysed allylic substitution of **2a** with **1a**

Entry	Acid	Solvent	Conditions	Yield ^a
1	1-AdCOOH	Water	70 °C, 30 min	30
2	Lauric acid	Water	70 °C, 30 min	30
3	Acetic acid	Neat	70 °C, 30 min	31
4	Benzoic acid	Neat	70 °C, 30 min	28
5	1-AdCOOH	Neat	70 °C, 30 min	33
6	Acetic acid	Neat	100 °C, 30 min	95(91) ^b
7	Acetic acid	1,4-Dioxane	100 °C, 12 h	98(90) ^b

^a NMR yield.^b Isolated yield.

30 min (entries 3 and 4). The rates of these two sets of reactions (followed by ¹H NMR) were found to be almost identical. With 1-AdCOOH as the additive, the reaction also proceeded at the same rate under neat conditions (entry 5). As shown in entry 6, the reaction was heated to 100 °C in the presence of acetic acid to obtain full conversion. The reaction proceeded well in an organic solvent such as 1,4-dioxane however it took longer (entry 7). The above observations unequivocally confirmed that there was no specific role for either water as a solvent or a particular carboxylic acid. Although Kobayashi et al. studied several carboxylic acids and found that 1-AdCOOH or lauric acid gave the best result in water, the experimental results obtained in our laboratory are quite different. Perhaps, the difference is due to whether the reaction was carried out in water or

under neat conditions. It is reasonable that the acid having a more hydrophobic⁷ nature tends to remain in the organic phase and hence catalyses the reaction more effectively. On the other hand, a hydrophilic acid tends to remain in the water at high temperatures and is not available for the reaction in the organic phase hence the reaction rate is slow. Although the authors of Ref. 6 reported the reaction in water, the reaction must proceed in the organic phase because neither the catalyst nor substrate is soluble in water. Some representative examples of direct allylic alkylation using Pd(PPh₃)₄/acetic acid under neat conditions are summarised in Table 2.

After standardisation of the catalytic system we then applied this catalytic system to various pronucleophiles.

Table 2. Pd(PPh₃)₄/acetic acid catalysed allylic substitution of allyl alcohols with C-nucleophiles under neat conditions

Entry	1	2	Pd(PPh ₃) ₄ (mol%)	Conditions	Product 3	Yield ^a (%)
1	1a	2b	2	80 °C/30 min	3b	81
2		2a	5	100 °C/10 min	3c	95
3	1b	2b	5	100 °C/10 min	3d	61 ^b
4		2a	2	80 °C/1.5 h	3e	95
5	1c	2b	2	80 °C/1.5 h	3f	63 ^c
6		2a	5	100 °C/2 h	3g	98
7	1d	2b	5	100 °C/2 h	3h	94
8		2a	5	100 °C/5 h	3i	85
9		2a	0.5	80 °C/30 min	3j	71 ^d
10		2a	2	100 °C/10 min	3k	98
11	1g	2b	2	80 °C/15 min	3l	96

^a Isolated yield.^b 30% of diallylated product was isolated.^c 21% of diallylated product was isolated.^d Yield refers to diallylated product.

As shown in entry 1, allylation of dibenzoylmethane **1a** with allyl alcohol **2b** proceeded smoothly to give the monoallylated adduct **3b** in good yield. The monoallylation of diethyl malonate with cinnamyl alcohol also proceeded smoothly to give **3c** in excellent yield. However, when allyl alcohol was employed as the substrate, monoallylated product **3d** was isolated in 61% yield with the formation of the diallylated product in 30% yield. The reaction of **1c** and **1d** with cinnamyl alcohol and allyl alcohol gave the corresponding monoallylated products in good yields (entries 4–7). However the less reactive substrate **1e** took 5 h for the completion of the reaction (entry 8). In the case of Meldrum's acid **1f**, diallylated product **3j** was obtained (entry 9). The five-membered cyclic β -keto ester **1g** on reaction with **2a** and **2b** gave the products **3k** and **3l**, respectively, in excellent yields (entries 10–11).

In conclusion, we have discovered that the palladium catalysed allylic substitution of pronucleophiles with allyl alcohols proceeds under neat conditions. We have also shown that there is no need for water as a solvent⁸ or a long-chain fatty acid; even acetic acid works well for the present reaction.

General procedure for the allylation of pronucleophiles with allyl alcohols. The preparation of **3a** is representative. To a mixture of dibenzoylmethane **1a** (200 mg, 0.90 mmol) and cinnamyl alcohol **2a** (188 mg, 1.34 mmol) were added Pd(PPh₃)₄ (52 mg, 0.046 mmol) and acetic acid (6 mg, 0.090 mmol) and the mixture was heated at 100 °C for 30 min. The gummy material thus obtained was purified through a short column of silica gel using hexane/EtOAc=9:1 as a eluent to give **3a** (275 mg) in 91% yield.

Acknowledgements

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- The present reaction conditions, the allylation under neat conditions, produced 1 equiv of water after completing the reaction. It is not clear at present whether the water generated during the reaction progress is essential or not for promoting the allylation. All we can say here is that water is not needed as a solvent.