

One single catalyst, Pd(OAc)₂, for two sequential very different steps: allylic alcohol oxidation–Heck reaction. Access to functionalised α,β -unsaturated ketones†

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A single addition of the catalyst, Pd(OAc)₂, was realised to mediate two transformations as different as allylic alcohol oxidation under O₂ and C–C bond formation of the Heck type, to give substituted α,β -unsaturated ketones without intermediate purification.

According to current synthetic requirements, effective and environmentally benign procedures are particularly welcome. Among them, tandem or sequential reactions are especially interesting because they limit the amount of solvent used by reducing the number of costly workups as well as purification procedures and are less time-consuming.¹ In numerous cases, a transition metal catalyst presents in the reaction mixture, is efficient in one of the consecutive steps, but acts as a spectator in the other steps.² Much more interesting are transition metal catalysed syntheses which rely on a single catalyst for several steps.³ This has been reported for tandem reactions as different as cross metathesis–intramolecular hydroarylation with Ru,⁴ deprotection–heterocyclisation with Pd⁵ or Sonogashira–heteroannulation with Pd/C.⁶ With this in mind, we have developed a strategy for a rapid construction of functionalised α,β -unsaturated ketones starting from allylic alcohol and using 3% Pd(OAc)₂ added in the first step and able to mediate two transformations as different as the oxidation of allylic alcohols and the Heck reaction.

In the course of our study on green methods for organic transformations, we published a selective method for the oxidation of allylic alcohols using oxygen with a catalytic amount of Pd(OAc)₂ and Et₃N.⁷ With these results in hand, we examined the possibility of performing a second reaction, catalysed by Pd(OAc)₂ but without addition of more palladium. The Heck reaction seemed to be a good candidate (Fig. 1).⁸

First of all we had to adjust our reaction conditions as the Heck reaction was usually described in polar solvent. Dimethylacetamide (DMA) instead of the mixture THF–toluene

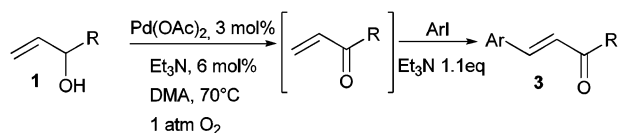


Fig. 1 Sequential allylic alcohol oxidation–Heck reaction.

initially used in the oxidation procedure turned out to be a good solvent. The first step, the oxidation, was thus performed at 70 °C and was finished after around 4 h. Then, the halogenated derivative and 1.1 equiv. of Et₃N were added and the reaction mixture was heated for four additional hours. After addition of water, extraction with diethyl ether and column chromatography on silica, the product was obtained with good isolated yields (41–60% for the two consecutive reactions, 64–77% for each separately). It is noteworthy that the Heck reaction was performed under air atmosphere.

Different sources of Pd(II) have been tested: with PdCl₂ and PdCl₄Na₂, 20 h were needed for the overall oxidation of product **1a** instead of 2 h with Pd(OAc)₂ but the Heck reaction with **2a** was finished in 6 h, leading to the same products. With PdCl₂(PPh₃)₂ no oxidation occurred. Pd(OAc)₂ was chosen for the rest of our study.†

In the case of aryl bromide, no reaction occurred even though triphenylphosphine was added in the second step. When 25% of *n*Bu₄NI was added, only 10% of bromobenzene was converted into product **3a**. When 1 equiv. or 2 equiv. *n*Bu₄NI–bromobenzene was added, no reaction occurred. Several iodoaryl compounds have been tested with success. Results are displayed in Table 1.§

In the case of disubstituted aryl iodides, whatever the nature of the second group (electron donating group, entry 3 or electron withdrawing group, entry 4) good isolated yields were obtained. In the case of a diiodo aromatic compound, two Heck reactions were performed which shows the great reactivity of our palladium, which has thus realised three steps. The lack of reactivity of bromine derivatives in our conditions makes it possible to limit the reaction to the carbon bearing an iodo atom (entry 6) with the possibility of performing other chemistry on the bromine site. Aniline derivatives were also used with success, leading to potential precursors of indoles (entry 7).⁹ Finally, our conditions are also compatible with different protecting groups such as silyl (entry 10) or benzyl (entry 11), leading to polyfunctionalised compounds.

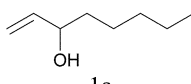
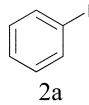
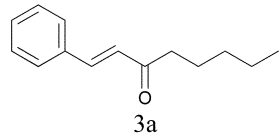
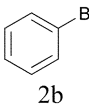
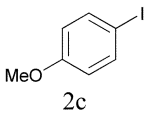
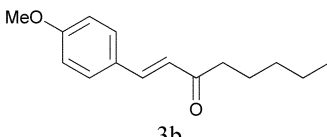
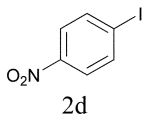
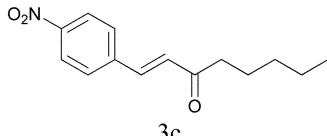
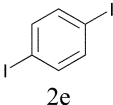
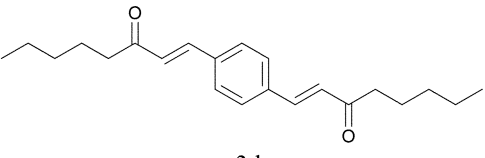
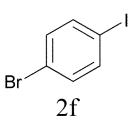
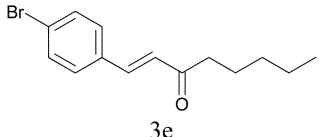
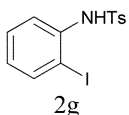
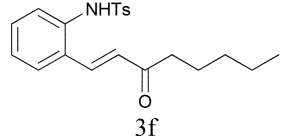
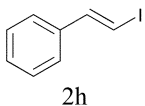
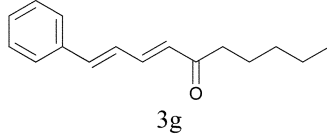
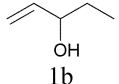
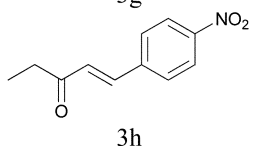
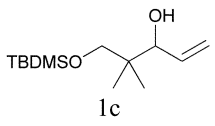
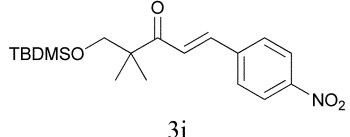
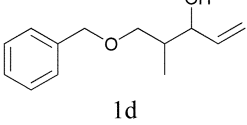
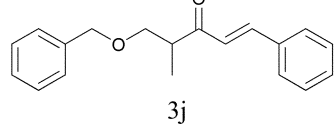
In conclusion, we have shown that it is possible to use one single amount of catalyst to perform in a one-pot sequential

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† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b810538c

Table 1 Scope of Pd-catalysed allylic alcohol oxidation–Heck reaction sequence

Entry	1	2	Product 3	Isolated Yield (%)
1	 1a	 2a	 3a	61
2	1a	 2b	3a	0
3	1a	 2c	 3b	55
4	1a	 2d	 3c	59
5	1a	 2e	 3d	60
6	1a	 2f	 3e	64
7	1a	 2g	 3f	41
8	1a	 2h	 3g	60
9	 1b	2d	 3h	57
10	 1c	2d	 3i	53
11	 1d	2a	 3j	50

way two reactions as different as alcohol oxidation and C–C bond formation. This provides a rapid access from allylic alcohols to valuable α,β -unsaturated ketones with a great variety of possible structures, which is highly useful for the purpose of molecule library syntheses.

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Notes and references

‡ General procedure: 3% Pd(OAc)₂ and 6% Et₃N were added to a 1 M solution of alcohol **1** in DMA and heated under stirring at 70 °C for the appropriate amount of time (generally 4 h) under an atmosphere of O₂. The reaction was monitored by TLC. When all the alcohol was oxidized, the O₂ balloon was removed and 1.1 equiv. of Et₃N and 1.1 equiv. of the halogenoaryl compound were added. The reaction mixture was allowed to stir at 70 °C under air atmosphere without special precautions until completion. After diethyl ether–water extraction, column chromatography on silica made it possible to obtain the product with good isolated yields.

§ All the analytical data of these substances (Table 1) are in accordance with the literature (see supplementary information†).

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