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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Received (in Cambridge, UK) 20th June 2008, Accepted 19th August 2008
First published as an Advance Article on the web 30th September 2008
DOI: 10.1039/b810538c

A single addition of the catalyst, $Pd(OAc)_2$, was realised to mediate two transformations as different as allylic alcohol oxidation under O_2 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 Pd[5] 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 Et_3N.[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]

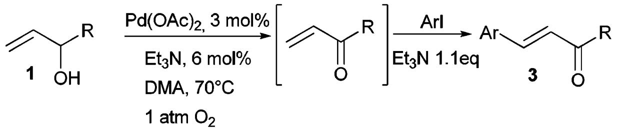

Fig. 1 Sequential allylic alcohol oxidation–Heck reaction.

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 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 Et_3N 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 $PdCl_2$ and $PdCl_4Na_2$, 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 $PdCl_2(PPh_3)_2$ 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 nBu_4NI was added, only 10% of bromobenzene was converted into product **3a**. When 1equiv. or 2 equiv. nBu_4NI–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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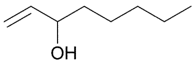
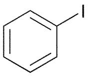
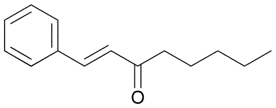
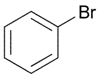
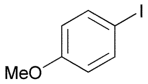
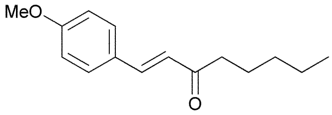
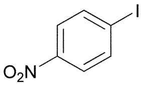
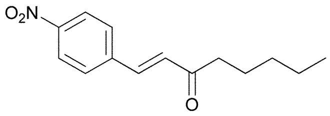
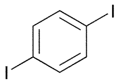
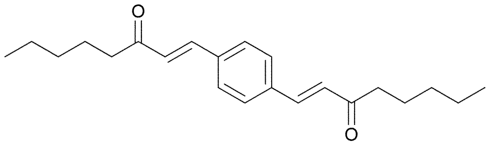
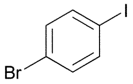
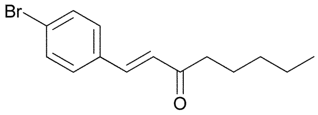
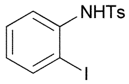
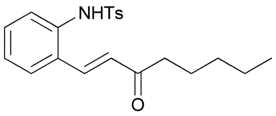
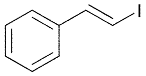
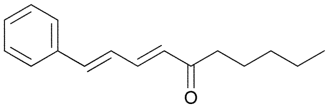
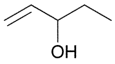
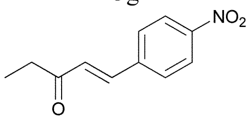
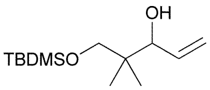
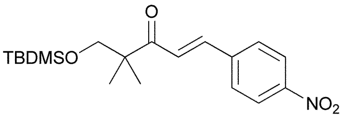
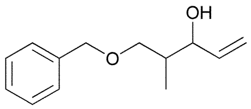
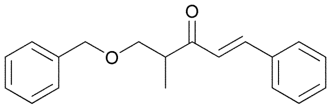
† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b810538c

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.

Acknowledgment is made to the "Ministère Français de l'Education Supérieure et de la Recherche" for financial support (F. Batt) and to Prof. O. Piva for scientific discussions.

Notes and references

‡ General procedure: 3% $Pd(OAc)_2$ and 6% Et_3N 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 O_2. The reaction was monitored by TLC. When all the alcohol was oxidized, the O_2 balloon was removed and 1.1 equiv. of Et_3N 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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