

Heck arylation of allylic alcohols in molten salts

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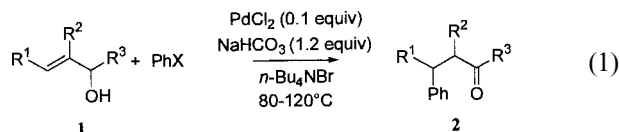
Abstract

The Heck coupling of ArX (X = I, Br) with allylic alcohols, carried out at 80–120 °C in molten *n*-Bu₄NBr using NaHCO₃ as base and PdCl₂ as catalyst without extra ligands, leads to the corresponding β-arylated carbonyl compounds. After extraction of the organic materials with diethyl ether, the ionic layer can be reused directly. © 2001 Published by Elsevier Science B.V.

Keywords: Heck reactions; Allylic alcohols; Molten ammonium salts; Recycling

1. Introduction

In the course of our studies devoted to Pd-catalyzed oxidations of alcohols [1–4], we have recently disclosed that anionic catalysts, [Pd₂X₆][*n*-Bu₄N]₂, can be obtained from PdCl₂ and *n*-Bu₄NX (X: Cl, Br) [5]. This led us to envisage the arylation of allylic alcohols through Heck reactions using such a catalyst in molten *n*-Bu₄NBr. Indeed, Heck reactions may involve Pd^{II}/Pd^{IV} catalytic cycles when particular Pd^{II}-catalysts are used [6–12], and the formation of β-arylated ketones from allylic alcohols [13,14] seems to be promoted by the presence of an ammonium salt as additive [15–22]. Furthermore, the use of ionic liquids as solvents is presently undergoing a new springtime although they have been known since the beginning of the last century.¹ Recent reports concerning Heck reactions with α,β-unsaturated esters, styrene and vinyl ethers in phosphonium, 1-butyl-3-methylimidazolium or other ammonium salts [28–35] urge us to present the results we have obtained with allylic alcohols (Eq. (1)).



2. Results and discussion

Initial experimentation was undertaken in tetra-*n*-butyl ammonium bromide using 3-methyl-3-buten-2-ol (**1a**, R¹ = H, R² = R³ = Me), iodobenzene, sodium bicarbonate and catalytic amounts of palladium chloride, the mixture being heated at 80 °C for 6 h (Eq. (1), Table 1, run 1A). Although the melting point of *n*-Bu₄NBr is 103 °C, a melt was thus obtained. After cooling to room temperature, the resulting solid was carefully triturated with hexane to extract the organic compounds from which ketone **2a** (R¹ = H, R² = R³ = Me) was isolated in 74% yield after evaporation of the solvent and chromatography. The phenylation was repeated with the recovered solid and a fresh mixture of **1a** and iodobenzene: a lower conversion was obtained and the yield of **2a** dropped to 50%. Further recycling led to a dramatic decrease in the conversion (run 3A). We noted that the extraction of **2a** from the mixture was more effective when using diethyl ether as solvent rather than hexane (run 1B). The recycling process was then examined by adding a batch of NaHCO₃ for each new run: better results were obtained but, nevertheless,

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¹ For recent reviews, see Refs. [23–27].

Table 1
Use and reuse of PdCl₂ and *n*-Bu₄NBr in the reaction of iodobenzene with **1a**^a


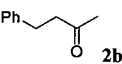
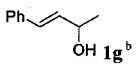
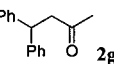

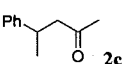

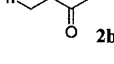
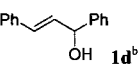
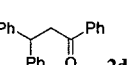
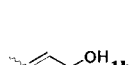
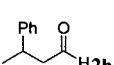

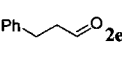

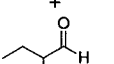

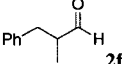
Protocol ^a	Run 1		Run 2		Run 3		Run 4	
	C (%) ^b	Y (%) ^c	C (%) ^b	Y (%) ^c	C (%) ^b	Y (%) ^c	C (%) ^b	Y (%) ^c
A	100	74	65	50	25	12	–	–
B	100	89	89	61	75	58	–	–
C	100	90	95	68	93	63	92	63

^a **A**: run 1 was carried out at 80 °C for 6 h using **1a** (1 mmol), iodobenzene (1 mmol), NaHCO₃ (1.2 mmol), PdCl₂ (0.1 mmol) and *n*-Bu₄NBr (1.5 g); runs 2–4 were carried out with the recovered solid without additive. **B**: run 1 as under **A** conditions; addition of NaHCO₃ (1.2 mmol) for runs 2–4. **C**: as under **B** conditions except for the reaction temperature and the reaction time which were 120 °C and 24 h, respectively. **A**: hexane was used for extractions; **B** and **C**: diethyl ether was used for extractions.

^b C: conversion of **1a**.

^c Y: isolated yield of **2a**.

Table 2
Use and reuse of PdCl₂ and *n*-Bu₄NBr in the reaction of iodobenzene with **1b–1h** under conditions of protocol **C** (see Table 1)

Substrate	Product	Yield % ^a	Substrate	Product	Yield %
		71 ^{a1}			33
		57 ^{a2}			27
		58			35
		62 ^{a3}			14
		52			

^aYields of reactions carried out using recycled Pd-catalyst and *n*-Bu₄NBr: ^{a1}77, 76, 76 and 69; ^{a2}63, 59, 56

and 54%; ^{a3}64, 68, 62 and 59%.

^bReaction time: 36 h.

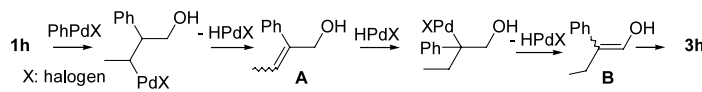
^cReaction time: 8 h.

the conversion dropped with each cycle (runs **2B** and **3B**). However, an increase in both the reaction time and temperature led to improved results (runs **2C–4C**).

Since the chemical yields of **2a** thus obtained were superior to those previously reported under conventional Heck conditions, i.e. in DMF as solvent [36], Protocol **C** was extended to alcohols **1b–1h** (Table 2). Alcohols **1b–1f** were regioselectively β-phenylated giving carbonyl compounds **2b–2f** with fair yields. The reaction with **1g** and **1h** was in contrast less selective. Indeed, the isomerization of the double bond of **1g** leading to the corresponding ketone (**2b**) was a competitive reaction while **1h** underwent non-regioselective phenylation. The formation of **3h** indicates that the HPdX species, which were produced in situ by β-H

elimination, added back to the initially formed α-adduct (**A**) rather than reacting with the base; this addition followed by a second β-H elimination results in the isomerization to the enol (**B**) giving then the aldehyde (Scheme 1) [13,14,37]. The formation of **2b** from **1g** could also be due to a 1,2-addition/elimination sequence of HPdX on **1g**.

Since iodobenzene is relatively expensive, we examined the treatment of **1a** with bromobenzene and chlorobenzene. No reaction was observed with PhCl at 120 °C and increasing the temperature to 150 °C produced a complex mixture. With PhBr, **1a** yielded 65% of **2a** in 4 h at 120 °C; interestingly, the decrease of the amount of PdCl₂ to 0.05 equivalents led to the same chemical yield (reaction time: 6 h). The use of solely

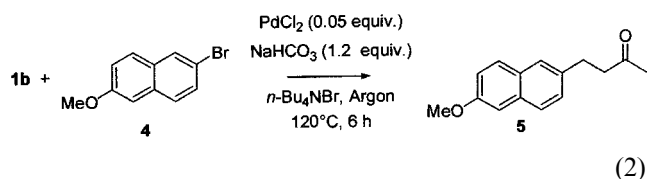


Scheme 1.

0.01 equivalents of the catalyst required a long reaction time (24 h, 56% yield).

A drawback of the above procedures is the formation of sodium halides which remain trapped in the ammonium salt. This led us to employ benzoic anhydride instead of phenyl halides because (i) this arylating agent does not require the presence of a base [38] and (ii) we expected an easy removal of the byproduct, PhCO_2H , from the ammonium salt [30]. Furthermore, it has been shown that the Heck reaction of double bonds with benzoic anhydride under classical conditions requires the addition of halide salts such as *n*- Bu_4NBr [38]. However, this protocol was unsuccessful: a mixture of **1a**, $(\text{PhCO})_2\text{O}$, *n*- Bu_4NBr and catalytic amounts of PdCl_2 reacted slowly at 120 °C giving 20% conversion of **1a** after 72 h with the appearance of small amounts of **2**, butyl benzoate and 3-(2-methyl-1-butenyl) benzoate. In fact, these two esters were also produced when the experiment was repeated in the absence of the Pd-catalyst.

The success of the reaction with PhBr prompted us to attempt the single-step synthesis of nabumethone (**5**), a nonsteroidal antiinflammatory drug [39,40] (Eq. (2)). Using a 1:1 ratio of **1b** and 2-bromo-6-methoxynaphthalene (**4**), **5** was isolated in 74% yield.



3. Conclusions

Molten tetra-*n*-butyl ammonium bromide is a good medium for the Heck reaction using allylic alcohols as substrates and palladium chloride as catalyst.² The system, which does not require phosphine ligands, remains stable for several reaction runs. As we previously suspected for Pd-catalyzed oxidations [1], the ammonium salt apparently stabilizes the catalytic species.

4. Experimental

¹H- and ¹³C-NMR (250 and 63 MHz) spectra were

² Since the submission of the present article, similar observations have been reported [41].

obtained in a Bruker AC 250 spectrometer using TMS as internal standard and CDCl_3 as solvent.

4.1. Typical procedure

Palladium chloride (18 mg, 0.1 mmol) and tetra-*n*-butylammonium bromide (1.5 g) were heated at 120 °C for 10 min in a round-bottomed flask under an Ar atmosphere. To this homogeneous mixture, cooled to around 80 °C, was successively added the allylic alcohol (1 mmol), the aryl halide (1 mmol) and NaHCO_3 (101 mg, 1.2 mmol). After 24 h at 120 °C, the mixture was cooled and extracted with Et_2O (3×10 ml). The solid phase is thus ready for use in a new run. The organic phase was evaporated under reduced pressure and the residue was purified by chromatography.

The NMR data of the isolated compounds—**2b** [42], **2c** [43], **2d** [44], **2e** [45], **2f** [44], **2g** [44], **2h** [43], **3h** [46], butyl benzoate [47] and 3-(2-methyl-1-butenyl) benzoate [48]—were in agreement with literature.

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