Arylation of Allylic Alcohols in Ionic Liquids Catalysed by a Pd-Benzothiazole Carbene Complex

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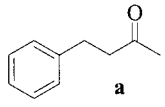
Keywords: Carbenes / Palladium / Homogeneous catalysis / Allylic alcohols / Ionic liquids

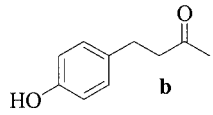
The reaction of aryl bromides with allylic alcohols catalysed by a Pd-benzothiazole carbene complex, in tetrabutylammonium bromide as solvent, leads principally to β-arylated carbonyl compounds.

β-Aryl ketones are useful intermediates for the synthesis of medicinal products such as **a**−**c**[1−3] and therefore the development of efficient synthetic methods is of significant interest.



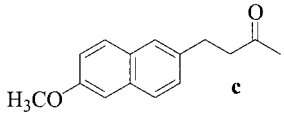
a

4-phenyl-2-butanone
(enzymatic inhibitor)



b

4-(4-hydroxyphenyl)-2-butanone
(precursor of anticancer agent)

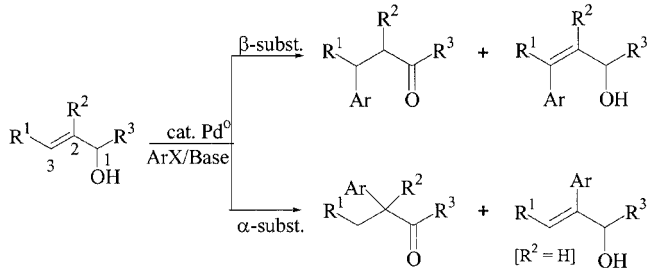


c

Nabumetone
(non stereoidal anti-inflammatory drug)

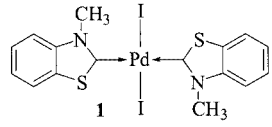
Pd-catalysed arylation of allylic alcohols has been applied by various authors for the synthesis of these compounds.[4−9] However, these arylation reactions were poorly regioselective as the reaction led to a mixture of carbonyl compounds and substituted allylic alcohols (Scheme 1).[10,11]

Beside this drawback, the choice of aryl halides and bases was limited to aryl iodides,[4,5,8] triflates,[11b] diazonium salts[9e] and weak bases, since aryl bromides, by requiring more harsh reaction conditions, led, in the case of arylation of primary allylic alcohols, to aldol reaction of the formed aldehydes. Moreover, toxic solvents as DMF or HMPA, phosphanes, high palladium concentrations[8] and ammonium salts as additive were found to be necessary.[7,9,10]



Scheme 1

Recently we reported[12] that the catalyst **1**, with benzothiazole carbenes as ligands,[13] efficiently catalyses the regioselective arylation of 3-hydroxy-2-methylene alkanoates (the Baylis−Hillman adducts) to β-aryl ketones in tetrabutylammonium bromide (TBAB) as solvent.



1

Beside the catalyst's stability towards heat and moisture, the reaction products could be extracted from the ionic liquid, thus allowing the recycling of both catalyst and ionic liquid. Though this reaction proved to be regioselective and suitable from an environmentally point of view, the choice of cheaper allylic alcohols as the olefinic reagent would be more convenient.

We report here the application of the Pd catalyst **1** for an efficient Heck reaction of aryl bromides and activated aryl chlorides with allylic alcohols in molten TBAB as solvent.[14]

As shown in Table 1, electron-rich and electron-poor aryl bromides reacted smoothly and selectively at the 3-position of the allylic alcohols to give, in the presence of 1 mol % of

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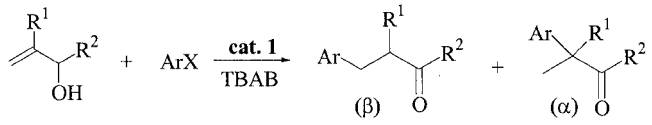
1 (based on aryl halide), 2 mol % of sodium formate as reducing agent for Pd^{II} and sodium bicarbonate as base, β-aryl ketones or aldehydes together with a small quantity of the positional isomers — the α-aryl-substituted carbonyl compounds. No unsaturated alcohols, aldol condensation products or palladium black deposition were observed. The efficiency of the reaction is much lower when replacing TBAB with either DMA or butylmethylimidazolium bromide $[bmim]^+ \cdot Br^-$ (runs 10,11).

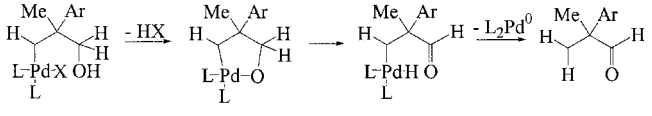
Table 1. Arylation of terminal allylic alcohols in TBAB catalysed by complex **1**[a]



Run	R^1	R^2	Ar	X	*t* (h)	Conv. (%)	Yields[b] (%)	β:α[b]
1	H	Me	Ph	Br	5	>99	87	95:5
2	H	C_2H_5	Ph	Br	5	95	88	95:5
3	H	C_2H_5	*p*-MeC_6H_4	Br	7	94	82	93:7
4	H	C_2H_5	*p*-$MeOC_6H_4$	Br	7	83	70	92:8
5	H	C_2H_5	*p*-$MeCOC_6H_4$	Cl	26	75	65	98:2
6	H	nC_5H_{11}	Ph	Br	5	94	85	95:5
7	Me	H	C_6H_5	Br	4	>99	94[c]	96:4
8	Me	H	4-MeC_6H_4	Br	5	>99	91[c]	94:6
9	Me	H	4-$MeOC_6H_4$	Br	5	>99	96[c]	90:10
10[d]	H	Me	Ph	Br	24	50	26[c]	90:10
11[e]	H	Me	Ph	Br	22	20	12	90:10

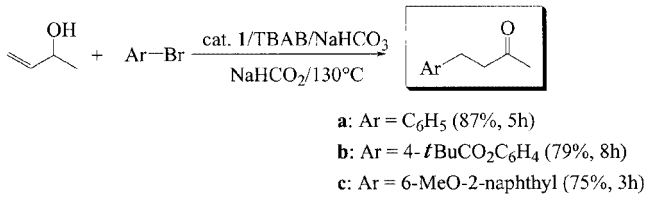
[a] Typical procedure: TBAB (3 g), allylic alcohol (6 mmol), catalyst **1** (1 mol %), HCO_2Na (2 mol %), aryl halide (5 mmol), $NaHCO_3$ (10 mmol), 130 °C. [b] Determined by GLC. [c] Isolated yields. [d] Solvent: $[bmim^+]\cdot Br^-$. [e] Solvent: DMA.

α-Alkyl-substituted alcohols (runs 7−9) also afforded α-alkyl-β-aryl-substituted propanals regioselectively, together with small quantities of α-alkyl-α-aryl-substituted propanals, the minor regioisomers, derived from the rearrangement of a five-membered chelate intermediate[4,11c] (Scheme 2).



Scheme 2

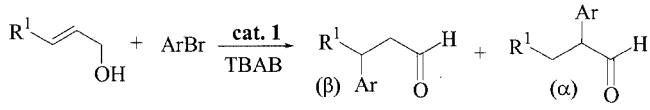
This procedure was extended to an efficient synthesis of compounds **a**−**c** by reaction of 3-buten-2-ol with the appropriate aryl bromide (Scheme 3). For compound **b**, as *p*-bromophenol is unreactive, it was necessary to protect the phenolic group by esterification with pivaloyl chloride before the C-C coupling process (see Exp. Sect.).



Scheme 3

The regioselectivity decreased when β-alkyl- or -aryl-substituted allylic alcohols were used (Table 2). For example, the reaction of cinnamic alcohol with *p*-bromotoluene gave (run 6) an equal mixture of 3,3- and 2,3-diphenylpropanal. Replacement of TBAB with $[bmim]^+ \cdot Br^-$ as solvent (run 7), in order to increase the regioselectivity, did not give better results, as reaction of crotyl alcohol with bromobenzene did not occur even after long reaction times.

Table 2. Regioselectivity in the arylation of allylic alcohols in TBAB catalysed by complex **1**[a]



Run	R^1	Ar	Arylated carbonyl compound Yields[b] (%)	*t* (h)	β:α[b]
1	Me	C_6H_5	63	4	70:30
2	Me	4-AcC_6H_4	94	4	64:36
3	Me	6-MeO-2-naphthyl	84[c]	6	70:30
4	*n*Pr	4-CNC_6H_4	93	4	68:32
5	Ph	C_6H_5	92	6	60:40
6	Ph	4-MeC_6H_4	75	16	50:50
7[d]	Me	C_6H_5	n.r.	23	−

[a] Reaction conditions as reported in Table 1. [b] Determined by GLC. [c] Isolated yield. [d] $[bmim]^+ \cdot Br^-$ as solvent.

The recycling of the catalyst and ionic liquid was then examined for the reaction of bromobenzene with 3-buten-2-ol, adding a new batch of sodium bicarbonate for each run. Unfortunately, the conversion dropped with each cycle (Figure 1), probably due to an increase in the amount of sodium bromide trapped in the ammonium salt which, by rendering the reaction medium more and more viscous, decreases the solubility and efficiency of the catalyst.

The stability of **1** in TBAB in a phosphane-free environment, despite the observed beneficial effects exerted by quaternary ammonium salts on the Heck reaction, cannot be ascribed to a single effect such as the high polarity or phase-transfer ability,[10e] but rather to a combination of several factors. For example, Reetz et al.[15] have found that reduction of a Pd salt in THF in the presence of tetraalkylammonium acetate or formate gives Pd nanoparticles stabilized by the large ammonium cation. Furthermore, Negishi et al.[16] and Amatore and Jutand,[17] have demonstrated that $Pd^0(PPh_3)_2$, the proposed catalyst in the Heck reaction, is unstable in the absence of halide or acetate ions, which

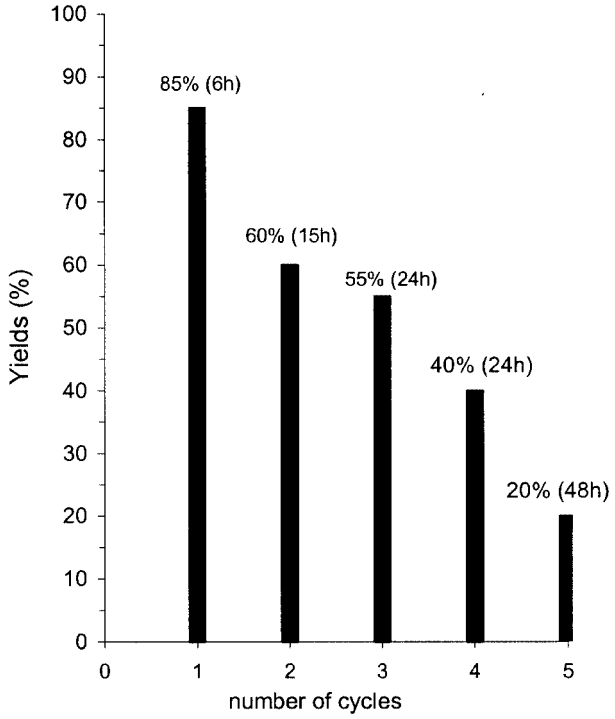


Figure 1. Recycling of catalytic system TBAB/**1**; reaction conditions: TBAB (3 g), bromobenzene (5 mmol), 3-buten-2-ol (6 mmol), $NaHCO_3$ (10 mmol), $NaHCO_2$ (0.1 mmol), catalyst **1** (0.05 mmol) at 130 °C; isolation of products by extraction with diethyl ether; the same quantities of reagents and base were added to the reaction mixture after each cycle

transform this complex into a more stable and catalytically active 16-electron anionic complex such as $[Pd(PPh_3)_2X]^-$. The stabilization of catalytic systems by halide salts has also been demonstrated by extension of the lifetime of the Herrmann palladacycle.[18] To explain some of the ionic liquid effects, we propose some considerations that could explain our results. The addition of sodium formate reduces[19] **1** to the underligated L_2Pd^0 complex, which, by reaction with TBAB, would afford an anionic and catalytically active 16-electron complex $[L_2Pd\ Br]^-\cdot NR_4^+$. This should not be surprising, since in TBAB the bromide ion, being poorly solvated, should be a good nucleophile for palladium. The stabilizing effect is exerted not only by the bromide ion, which is likely to enter the coordination shell of underligated L_2Pd^0 to give the anionic complex, but also by the large tetrabutylammonium cation. Indeed, the formation of a large $[L_2Pd\ Br]^-\cdot NR_4^+$ complex should impede the formation of clusters, and their growth into metal nanoparticles, by imposing a Coulombic barrier for collision. Besides this effect, interaction of the tetrabutylammonium cation with the bromide or iodide ligated to the palladium centre gives rise to the formation of ion pairs with a naked $L_2Pd^0\cdots Br^-\cdots NR_4^+$ moiety, which affords a more reactive palladium(0) complex.[17] Furthermore, the ammonium cation could electrostatically assist the polarisation or decomplexation of the bromide ion from the anionic, pentacoordinated Pd^{II} complex $[L_2PdArBr_2]^-\cdot NR_4^+$ deriving from oxidative addition with aryl bromides, which would render the Pd^{II} complex more electrophilic for a fast olefin insertion. This is conceivable since it has been calculated, for analogous Pd complexes with imidazol-2-ylidene carbenes as ligands, that the removal of bromide from the oxidative addition complex of aryl bromides is a strongly endothermic process.[20] In addition, we believe that the better performance of TBAB compared with $[bmim]^+\cdot Br^-$ (Table 1, run 10; Table 2, run 7) could be ascribed to the structural differences between the $[NBu_4]^+$ and $[bmim]^+$ cations. Indeed, the bulkiness of the tetrahedral ammonium ion, by forcing the bromide ion away from the cation, renders the anion more available for the catalyst activity. On the contrary, the planar $[bmim]^+$ cation, by binding the anion tightly,[21] would decrease its availability for the Pd catalyst. Similar behaviours were observed by us for different Heck reactions and this will be published in due course.

In conclusion, while some aspects of the catalytic cycle involving Pd-carbene complexes in ionic liquids are not well understood, our results show that complex **1**, in tetraalkylammonium bromide as solvent, is an efficient catalyst for carbon-carbon coupling processes.

Experimental Section

General Procedure for Reactions of Allylic Alcohols with Aryl Halides: The aryl halide (5 mmol), the alcohol (6 mmol), $NaHCO_3$ (10 mmol), $NaHCO_2$ (0.1 mmol) and the catalyst (0.05 mmol) were added, whilst stirring, to tetrabutylammonium bromide (3 g) at 130 °C. After the appropriate reaction time and product extraction with diethyl ether, the ammonium salt and the catalyst can be recycled. For compound **b**, *p*-bromophenol was protected by esterification with pivaloyl chloride in pyridine under conventional conditions before the C-C coupling process. The pivaloyl group was efficiently removed under basic conditions [NaOH, $MeOH/H_2O$ (20:1), 23 °C, 20 h, 87%, m.p. 82−83 °C (ethanol), ref.[22] 79−81 °C]. The reaction products were identified by comparison of their NMR and MS spectra with those reported in the literature.

Acknowledgments

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