Tetrahedron Letters,Vol.30,No.48,pp 6629-6632,1989
Printed in Great Britain

0040-4039/89 $3.00 + .00
Pergamon Press plc

SYNTHESIS OF ARYL-SUBSTITUTED ALDEHYDES AND KETONES VIA PALLADIUM-CATALYZED COUPLING OF ARYL HALIDES AND NON-ALLYLIC UNSATURATED ALCOHOLS

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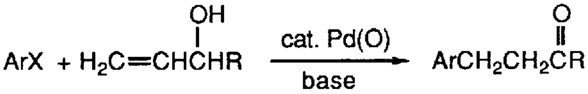
Summary. The palladium-catalyzed coupling of aryl halides and non-allylic unsaturated alcohols affords excellent yields of aryl-substituted aldehydes and ketones.

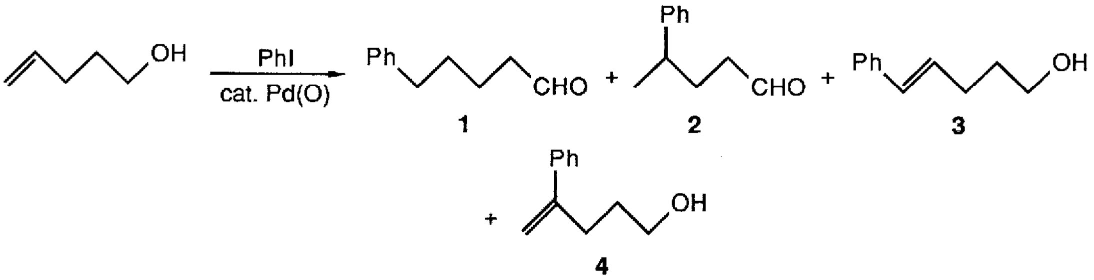
The palladium-catalyzed coupling of allylic alcohols and aryl halides under the right reaction conditions can afford high yields of aryl-substituted aldehydes or ketones (eq. 1).[1-13] The unique ability of



$$ArX + H_2C{=}CH\overset{OH}{\overset{|}{C}}HR \xrightarrow[\text{base}]{\text{cat. Pd(O)}} ArCH_2CH_2\overset{O}{\overset{\|}{C}}R \qquad (1)$$

palladium to migrate along carbon chains by palladium hydride elimination and subsequent readdition[14] suggested some time ago that analogous reactions with non-allylic unsaturated alcohols might afford long chain aldehydes or ketones. Unfortunately, previous efforts to effect such reactions have generally resulted in low yields and bad mixtures of carbonyl and aryl-substituted olefinic alcohol products.[9-13] For example, the reaction of iodobenzene and homoallylic alcohols commonly affords less than 50% of the desired carbonyl products and attempts to obtain carbonyl products from 9-decen-1-ol proved fruitless.[10] We now wish to report reaction conditions which routinely afford such carbonyl products in high yields, *even with long chain olefinic alcohols,* and with very little formation of the corresponding aryl-substituted olefinic alcohols.

A thorough examination of the reaction conditions required for the coupling of iodobenzene and 4-penten-1-ol lead to the following conclusions (eq. 2). Catalytic amounts (3%) of $Pd(OAc)_2$ give yields



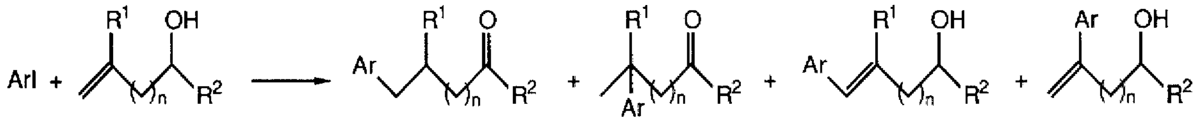
(2)

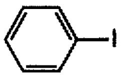
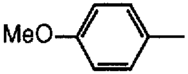
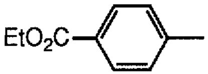
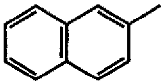
comparable to Pd(dba)$_2$ (dba = dibenzylidene acetone). Higher yields and faster reactions are obtained using DMF as the solvent and adding *n*-Bu$_4$NCl (2 equiv.). An added base is generally necessary and acetate bases are superior to bicarbonate, carbonate or organic amine bases. The nature of the cation in the acetate base is significant with yields increasing as follows: Li > Na > K > Cs. Despite the presence of chloride and lithium from *n*-Bu$_4$NCl and LiOAc, the addition of 1 equivalent of LiCl further increases the yield of carbonyl product. The addition of further LiCl however had little effect on the yield. Finally, the reactions can be run at room temperature (as opposed to 100-130°C used in all previous procedures[9-13]) although the longer the carbon chain the slower the reaction, and temperatures of 50°C become desirable when the carbon–carbon double bond and alcohol moieties are separated by more than three carbons. It is important to note that the yields *increase* as one reduces the number of equivalents of olefinic alcohol from 5 to 2 to 1 equivalent.

Using our best reaction conditions [3% Pd(OAc)$_2$, *n*-Bu$_4$NCl (1.0 mmol), LiOAc (1.25 mmol), LiCl (0.5 mmol), DMF (1 ml), aryl halide (0.5 mmol), olefinic alcohol (0.5 mmol), 4 days at room temperature], the reaction of iodobenzene and 4-penten-1-ol gives an 85% yield of aryl aldehydes **1** and **2** in an 83:17 ratio, and only 6% of the corresponding aryl olefins **3** and **4** are observed (ratio 92:8). The regioselectivity of the reaction is similar to that observed in previous reactions of homoallylic alcohols and varies little upon changing reaction conditions. The reaction conditions are sufficiently mild that no decomposition of the resulting aldehydes is observed.

Employing our best reaction conditions on a variety of aryl iodides and unsaturated alcohols routinely affords high yields of the corresponding aryl-substituted carbonyl products as shown in Table I. Unlike previous procedures, our reaction conditions actually give higher yields with increasing chain length (compare entries 1-4), with 10-undecen-1-ol giving over a 90% yield of the corresponding aldehyde (entries 4 and 5)! However, the rate of reaction is observed to decrease with increasing chain length (compare entries 1-3 and 4) or substitution of a vinylic hydrogen by a methyl group (entries 6 and 8) and a reaction temperature of 50°C is recommended in those cases. Substitution about the carbon-carbon

Table I. Synthesis of Aryl-Substituted Aldehydes and Ketones[a]


5 6 7 8

Entry	ArI	n	R^1	R^2	% Isolated yield **5** + **6** (**5**:**6**)	% Isolated yield **7** + **8** (**7**:**8**)
1		1	H	H	77 (84:16)	4 (100:0)
2		2	H	H	85 (83:17)	6 (92:8)
3		3	H	H	88 (82:18)	6 (94:6)
4		8	H	H	94 (89:11)[b]	—[c]
5		8	H	H	91 (88:12)[d]	—[c]
6		1	Me	H	69 (100:0)[e]	0
7		2	H	Me	87 (85:15)	4 (86:14)
8		2	Me	Me	79 (100:0)[f]	0
9		2	H	H	82 (82:18)	9 (93:7)
10		2	H	H	77 (76:24)	15 (90:10)
11		2	H	H	81 (84:16)	9 (91:9)
12		2	H	H	77 (80:20)	11 (95:5)

[a] For the general reaction procedure see text. [b] Reaction run 12 days. [c] Yield and ratio not easily determined. [d] Reaction run 3 days at 50°C. [e] Reaction run 3.5 days at 50°C. [f] Reaction run 4.5 days at 50°C.

double bond results in only a slight decrease in yield (compare entries 1 and 6, and 7 and 8), whereas increasing substitution about the alcohol group has no effect (compare entries 2 and 7) on yield.

A variety of aryl iodides have been successfully employed in these reactions (entries 9-12). Little change in yield or regioselectivity is observed in going from electron-rich to electron-poor aryl iodides, though a slight decrease in the amount of aryl olefin is evident.

The mechanism of this useful reaction undoubtedly involves arylpalladium generation and addition to the carbon-carbon double bond, palladium migration via reversible palladium hydride elimination and subsequent readdition, and eventual enol formation with regeneration of the palladium catalyst as described previously.[1,10,12]

In conclusion, we have been able to develop very mild reaction conditions which now afford excellent yields of aryl-substituted aldehydes or ketones from the palladium-catalyzed cross-coupling of aryl iodides and non-allylic unsaturated alcohols of substantial chain length.

Acknowledgment. Acknowledgment is made to the Donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. This work was initiated through the financial support of the National Institutes of Health (GM 24254).

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(Received in USA 31 August 1989)