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CYCLOPALLADATED IMINES IN SYNTHESIS : THE PREPARATION OF UNSYMMETRICAL STILBENES AND 3-ARYLISOQUINOLONES

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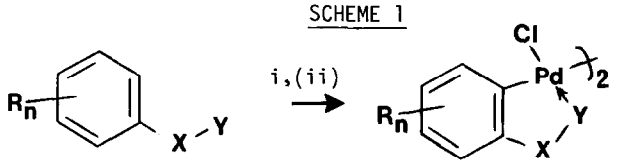
SUMMARY: A series of cyclopalladated t-butylimines of aromatic aldehydes were reacted with styrene to give o-formylstilbenes in high yield. The N-methylimines of these were converted to 3-aryl-N-methyl-isoquinolones by oxidation with mercuric acetate.

Cyclometallation is a powerful tool for regiospecific substitution in functionalised aromatics.[1-3] It has been exploited principally with the main group metals, particularly lithium.[2,3] Although cyclometallation with transition metals is commonly described in the literature,[1,4,5] exploitation of the complexes in synthesis remains undeveloped. Palladium is particularly effective in cyclometallation reactions[5] and the varied, well investigated organic chemistry of the metal[6,7] indicates a considerable potential in synthesis.

Cyclopalladation is observed with a variety of substrates[1,4,5,8,9] (Scheme 1). The choice of X and Y in Scheme 1 will be dictated by the needs of the subsequent elaboration, but because of its versatility in synthesis,[10] we have examined the use of the imine group, which acts as

SCHEME 1



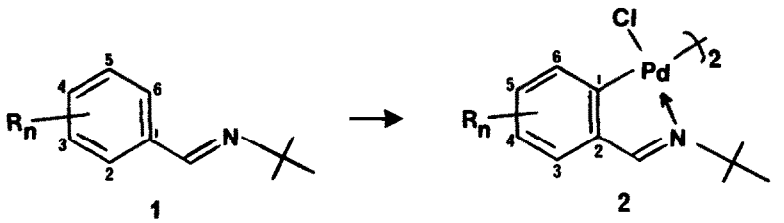
i, PdZ_2L_2; (ii, NaCl); X = C, N; Y = N, (O), S; Z = OAc, Cl, L = PhCN, Cl.

a masked aldehyde function, in the synthesis of unsymmetrical 2-formyl stilbenes. These compounds are not readily accessible by conventional means[11-13] and yet represent attractive intermediates in the synthesis of heterocycles (see below), and other systems.

Cyclopalladation of a series of aryl t-butyl imines (1)(Scheme 2), was conveniently carried out with palladium chloride (0.8 equiv) and sodium acetate[14] (15 equiv) in glacial acetic acid at 60-80° under a nitrogen atmosphere. The results are given in Table 1.

The palladations all occurred in high yield in the normal position for electrophilic aromatic substitution. Notably, however, the 3-methoxy-imine gave only the 4-methoxy complex. Presumably interaction between a 6-substituent and the palladium ligand in the square planar complex inhibits the formation of this isomer.

SCHEME 2



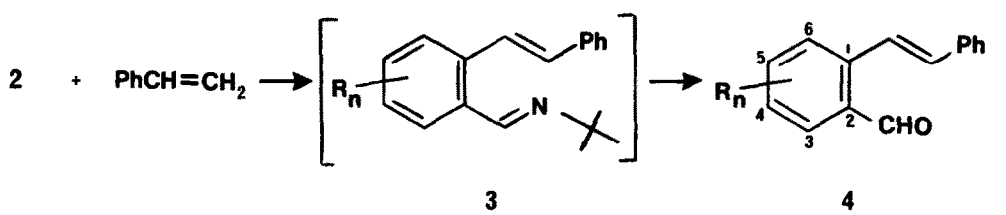
1 2

TABLE 1

Substrate (1, R =)	Product† (%) (2, R =)	
H	H	(95)
4-Cl	5-Cl	(88)
4-MeO	5-MeO	(95)
3-MeO	4-MeO	(96)
2-MeO	3-MeO	(81)
3,4-$(MeO)_2$	4,5-$(MeO)_2$	(89)

We have examined the reaction of these complexes with styrene[15,16] (Scheme 3). The reaction conditions which proved to be most effective were: complex (1 equiv) in trifluoroacetic acid/acetic acid (∿ 1:5) at 5^0, treated with styrene (5 equiv) and allowed to warm to room temperature during 24 h. Aqueous work up gave the stilbene aldehydes (Table 2).

SCHEME 3



† All new compounds have correct microanalyses and expected spectroscopic properties.

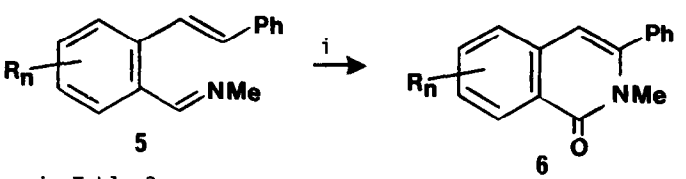
TABLE 2

Complex (2, R =)	Stilbene (%)
H	(90)
5-Cl	(85)
5-MeO	(75)
4-MeO	(81)
3-MeO	(67)
4,5-$(MeO)_2$	(91)

Again, yields were high with no pronounced electronic effect from the substituents. We have not examined substituent effects on the styrene, but results from similar reactions[17] show a tolerance of a wide range of functional groups. The nmr spectra of stilbenes 4 indicate the presence of only the trans isomer (J_{trans} = 16 Hz).

With the ready availability of stilbene aldehydes, we sought a route to 3-arylisoquinoline derivatives, a class of compounds which are difficult of access by conventional routes.[18,19] First the aldehydes were converted to the N-methylimine derivatives (5). These were reacted without purification (Scheme 4), with mercuric acetate (2 equiv) in toluene at reflux for 2-6 h. The products {for R = H, M^+ 235, ν_{max} 1645 cm^{-1}, δ ($CDCl_3$) 3.41 (3H, s, N-Me), 6.42 (1H, s, H-4)} are formulated as (6) on the basis of the spectral evidence and by identity with reported data where possible.

SCHEME 4



5 6

i, $Hg(OAc)_2$, PhMe

The results are given in Table 3.

TABLE 3

Stilbene aldehyde (4, R =)	Isoquinolone (%) (6, R =)	
H	H	(43)
5-Cl	6-Cl	(41)
5-MeO	6-MeO	(59)
4-MeO	7-MeO	(32)
3-MeO	8-MeO	(33)
4,5-$(MeO)_2$	6,7-$(MeO)_2$	(62)

The yields at this stage are only moderate, but the brevity of the synthesis makes this a particularly convenient route to the isoquinolones. Further application of these intermediates is in hand.

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