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THE EFFECT OF THALLIUM (I) SALTS ON PALLADIUM CATALYSED TANDEM CYCLISATION-ANION CAPTURE PROCESSES.

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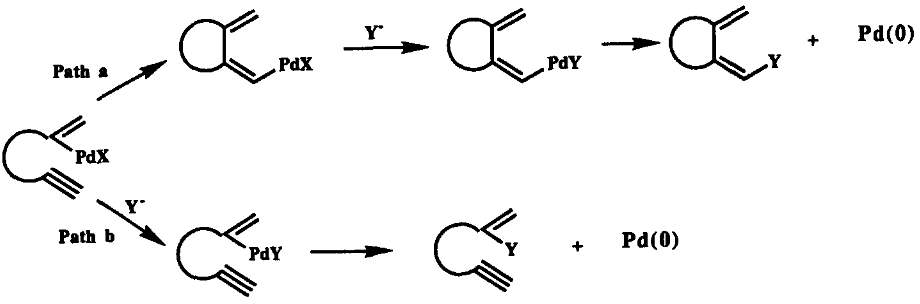
Summary The effect of the addition of 1 mol. of various additives [NEt_4Cl, Ag(I) and Tl(I) salts] on selectively suppressing direct capture processes has been studied for hydride ion transfer (from formate) and phenyl transfer (from PhZnCl). The additives can promote cyclisation-anion capture at the expense of direct capture with Tl(I) salts being especially useful although in one case NEt_4Cl promotes direct capture. The addition of Tl(I) formate diverts the cyclisation-hydride ion capture process into a new reaction channel in one case.

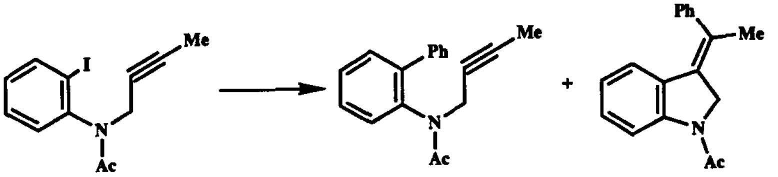
We have recently developed a flexible and synthetically powerful palladium catalysed tandem cyclisation-anion capture process whereby a vinyl- or aryl- palladium halide cyclises regio- and stereospecifically onto a proximate alkene, alkyne or diene moiety and the resulting alkyl, vinyl-, or π-allylpalladium species is intercepted by an "anion" transfer agent. The tandem process has recently been extended to bis-cyclisation-anion capture processes thereby creating two new rings with subsequent transfer of a suitable "anion".[1] Typical transfer agents include formate ion (H^- source),[2] organo-zinc,[3] -tin(IV)[4] and -boron derivatives,[3] and C-, O- and N-centred nucleophiles.[5]

The successful realisation of these processes is predicated on the cyclisation rate(s) being significantly faster than the rate of direct anion capture by the initial vinyl- or aryl-palladium species (e.g. Scheme, path a versus path b). In most instances studied so far the necessary rate difference is present and little, if any, direct capture is observed. Nevertheless there are some processes where substantial amounts of direct capture are observed and it was anticipated that this might pose more serious problems when rings larger than 5- or 6-membered were being formed or when more complex polycyclisation-anion capture-processes were being developed. Additives were therefore sought that allowed manipulation of the various reaction rates.

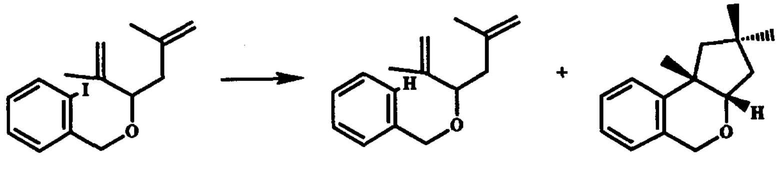
Two types of additives, tetralkylammonium chlorides,[6,7] and silver nitrate or carbonate,[8] have been found to increase the rates of Pd(0) catalysed reactions,[9] with silver salts additionally suppressing alkene isomerisation.[10] We initially selected the cyclisation-anion capture (1) → (3),[3] using phenylzinc chloride as the anion transfer reagent, and studied the effect of additives on the process (Table).



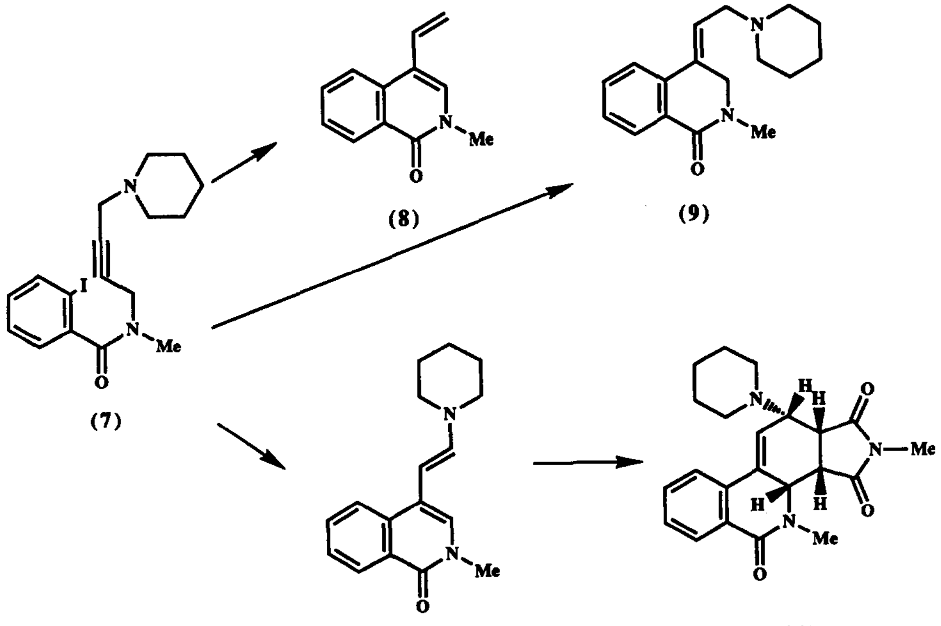
Scheme



(1) (2) (3)



(4) (5) (6)



(7) (8) (9) (10) (11)

The tandem cyclisation-anion capture process (1) → (3) was carried out for 1h and all the additives increased the amount of (3) at the expense of the direct capture product (2) (Table).

Table Effect of Additives on Rate and Product Distribution of the Cyclisation-Anion Capture Process (1) → (3).[a]

Additive	Product Ratio[b,c]		
	(1)	(2)	(3)
--	3	1	1
NEt_4Cl	1.8	1	2.5
Ag_2CO_3	2	1	2.6
Tl_2CO_3	--	1	1.9
$AgNO_3$	--	1	2.0
$TlNO_3$	--	1	2.3

a. Reaction carried in dry THF at 0-5°C for 1h. using the additive (1 mol), PhZnCl(3 mol), and 10 mol% $Pd(OAc)_2$ together with 20 mol% PPh_3. The PhZnCl in Et_2O was added via a syringe over 5 min to a stirred mixture of the other reagents in THF.

b. Ratios calculated from integrals of the ^1H n.m.r. spectra of the crude products. At 100% conversion the combined yields of (2) and (3) are ca. 60%.

c. The apparent rate differences may be misleading due to a competing conversion of PhZnCl to biphenyl.

The effect of additives on the polycyclisation-hydride capture process (4) → (6) was studied next. The reactions were carried out in boiling acetonitrile using 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, sodium formate (1.5 mol) and additive (1 mol). In the absence of any additive the reaction was slow and after 36h the product comprised a 4:1 mixture of (6) and (4) respectively together with a minor amount of an as yet unidentified product. When tetraethylammonium chloride was added the reaction was complete in 3h but gave a 2:3 mixture (70%) of (5) and (6), i.e. the additive promoted direct capture in this case. In contrast, heating for 6h with silver nitrate gave a 3.5:1 mixture of (6) and (4) respectively, whilst heating for 6h in the presence of $TlNO_3$ gave a 4.6:1 mixture of (6) and (4) together with a minor amount of an as yet unidentified product.

Interestingly it also proved possible to divert a cyclisation-anion capture process into a new reaction channel by appropriate choice of additive. Thus (7) cyclises to (8) [10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, MeCN, 80°C] in poor yield (30%) in the presence of formic acid (1 mol) (H^- source). When sodium formate (1.5 mol) is used in place of formic acid and tetraethylammonium chloride (1 mol) is added the product (33%) consists of ca 1:2 mixture of (8) and (9). The latter expected anion capture product becomes the sole product (53%) when silver carbonate or thallium (I) nitrate are the additives. However, when thallium (I) carbonate is the additive the reaction product is (10) and this can be trapped as the Diels-Alder adduct (11) [70% from (7)] by addition of N-methylmaleimide to the cooled reaction mixture and keeping at 25°C for 5h. Replacing both the sodium formate and the thallium (I) carbonate by thallium formate (1 mol) also gives (10).

The effect of additives on these and other cyclisation-anion capture processes is under active study[11].

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5. Grigg, R.; Sridharan, V., Sukirthalingam, S., and Worakun, T., *Tetrahedron Letters*, 1989, 30, 1139-1142.
6. The use of tetraalkylammonium halides to promote Heck reactions was introduced by Jeffrey, see e.g. Jeffrey, T., *Synthesis*, 1987, 70-71 and earlier papers.
7. Grigg, R.; Stevenson, P., and Worakun, T., *Tetrahedron*, 1988, 44, 2033-2048.
8. Karabelas, K.; Westerlund, C., and Hallberg, A., *J. Org. Chem.*, 1985, 50, 3896-3900; Karabelas, K.; Hallberg, A., *ibid*, 1986, 51, 5286-5290; *idem, ibid*, 1989, 54, 1773-1776.
9. In our hands use of silver salts frequently slows the rate of palladium catalysed tandem cyclisation-anion capture processes. Others have noted silver salts exert only a limited effect on some reaction rates: e.g. Nilsson, K.; Hallberg, A., *J. Org. Chem.*, 1990, 55, 2464-2470.
10. Abelman, M.M.; Overman, L.E., *J. Am. Chem. Soc.*, 1988, 110, 2328-2329; see also Larock, R.C.; Gong, W.H.; *J. Org. Chem.*, 1989, 54, 2047-2050.
11. Tl(I), Ag(I) and R_4N^+ are all large cations which form insoluble or easily aggregateable iodides. All are thus expected to effect anion exchange on the intermediate organopalladium(II) iodides. Anion bridged species Pd-X-M [M = Tl(I) or Ag(I)] may also be important.

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