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Palladium-catalyzed allylation and deacylative allylation of 3-acetyl-2-oxindoles with allylic alcohols

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ABSTRACT

The Pd-catalyzed allylation of 3-acetyl-2-oxindoles with allyl alcohol is performed using 3 mol% of $Pd(dba)_2$, rac-BINAP and BINOL phosphoric acid as catalytic mixture. This procedure allows the in situ synthesis of 3-allyl-2-oxindole by adding Triton B to the reaction mixture. The deacylative allylation of 3-acetyl-3-methyl-2-oxindoles with allylic alcohols is carried out with 3 mol% of $Pd(OAc)_2$, dppp and 1.5 equiv. of LiO*t*Bu as base affording the corresponding 3,3-disubstituted 2-oxindoles in good yields. Both methodologies can be combined for the preparation of unsymmetrical 3,3-diallylated 2-oxindoles such as compound **7**. The DaA must be carried out in the absence of oxygen in order to avoid the competitive formation of 3-alkyl-3-hydroxy-2-indoles. The later compounds can be easily obtained by deacylative oxidation of 3-alkylated 3-acetyl-2-oxindoles with LiOEt at rt under air.

1. Introduction

Pd-catalyzed allylation of nucleophiles with allylic alcohols is a direct methodology for the formation of C–C bonds.[1] Allylic alcohols are commercially available compounds and their direct use avoids the preparation of their derivatives, normally acetates, carbonates and phosphates, to generate the corresponding π-allyl Pd electrophilic intermediates. Due to the poor leaving group ability of the OH group it has to be activated by means of Lewis or Brønsted acids or by forming in situ the corresponding esters. Alternatively, two main strategies can be used for the Pd-catalyzed allylation of active methylene derivatives: (a) decarboxylative allylation (DcA)[2] of allyl esters and (b) deacylative allylation (DaA)[3] with allylic alcohols of acylated substrates (Scheme 1). Intramolecular DcA requires an anion stabilizing group for the decarboxylative metalation of the starting allyl esters, which has to be previously formed by transesterification with Otera's catalyst[4] ($XR_2SnOSnR_2X$) using a large excess of the allylic alcohol. Intermolecular deacylative metalation needs the introduction of the acetyl or a carboxylate group, which react with the alcoholate under basic conditions generating, in situ, the acetate or carbonate, respectively. This DaA takes place in THF or DMSO at 60 °C and has been studied with α-nitro and α-cyano ketones, 1,3-diketones, and α-cyanoacetates.

3,3-Disubstituted 2-oxindoles are important class of heterocyclic compounds occurring in natural alkaloids and biologically active compounds,[5] for instance the alkaloid horsfiline[6] and also esermethole,[7] which is an intermediate for the synthesis of acetylcholinesterase inhibitors physostigmine and phenserine[8] (Fig. 1). This family of compounds have been synthetized from 3-allyl-3-methyloxindoles. The Pd-catalyzed prenylation and geranylation of 3-substituted 2-oxindoles has been performed with the corresponding allylic carbonates of the monoalkylated oxindole.[9] The resulting compounds are synthetic intermediates of flustramides A and B with skeletal and smooth muscle relaxant activity.

For the Pd-catalyzed synthesis of 3-allyl-2-oxindoles, two alternative methodologies have been described: (a) one intramolecular process based on the Meerwein–Eschenmoser Claisen rearrangement of 2-allyloxyindoles[10]; (b) direct allylic alkylation of oxindoles with simple allylic alcohols co-catalyzed by $Pd(OAc)_2$/

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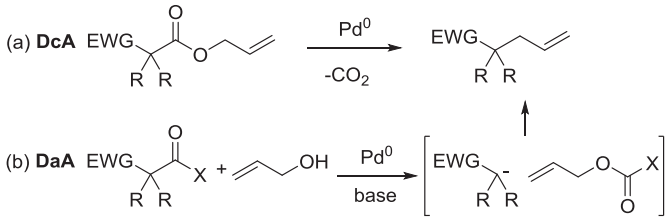


Scheme 1. Pd-Catalyzed allylation of active methylene compounds by DcA and DaA.

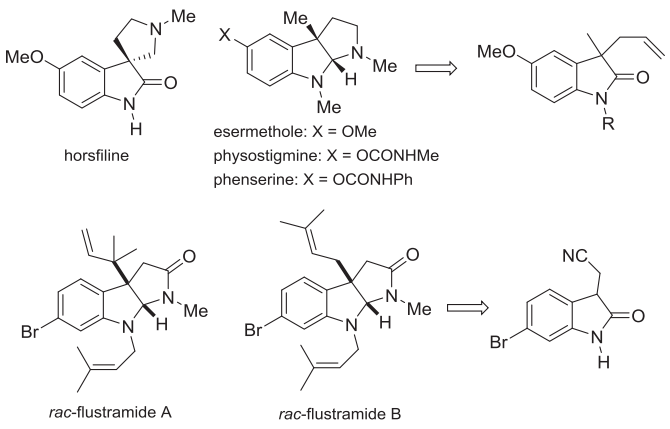
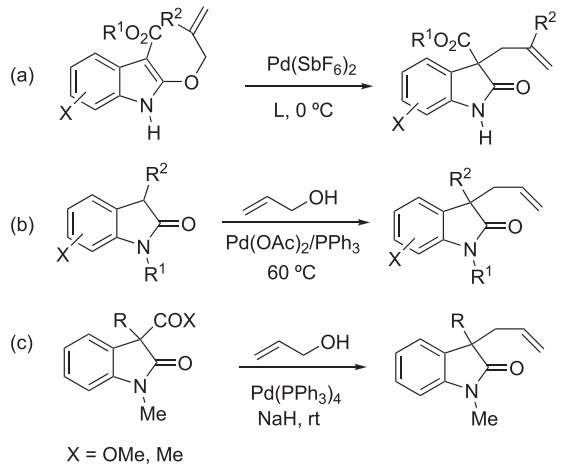


Fig. 1. Biologically active 3,3-disubstituted oxindoles.

Ph_3P and $PhCO_2H$[11a]; and c) the DaA of 3-acyl-2-oxindoles with allylic alcohols[11b] (Scheme 2).

We have recently described the synthesis of 3,3-disubstituted 2-oxindoles by deacylative alkylation of 3-acetyl-2-oxindoles with alkyl halides and electrophilic alkenes under basic conditions.[12] Independently, Bisai and co-workers published a palladium-catalyzed allylation of 3-acetyl-2-oxindoles during the elaboration of this manuscript.[11b] Herein, we report our findings about the synthesis of 3,3-disubstituted 2-oxindoles by Pd-catalyzed direct allylation of 3-acetyl-2-oxindoles and by deacylative allylation. The main objectives of this study are: a) evaluate the possible palladium-catalyzed monoallylation of 3-acetyl-1-methyl-2-oxindole **1a**; b) study the DaA using similar conditions from 3-acetyl-1,3-methyl-2-oxindole (**4a**); c) the oxidation of heterocycles **4** under a mild process avoiding oxidizing agents.



Scheme 2. Synthesis of 3-allyl-2-oxindoles by Pd-catalyzed methodologies.

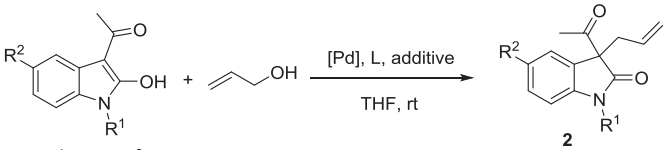
2. Results and discussion

Initially studies about the allylation of 3-acetyl-1-methyl-2-oxindole (**1a**)[12] were performed with allyl alcohol in the presence of different additives (Table 1). The selection of the *N*-methylated structure obeyed to this arrangement is present in many natural compounds (Fig. 1). Using the Tamaru reaction conditions for the allylation of active methylene compounds,[13] 3 mol% of $Pd(OAc)_2$ and 1,3-bis(diphenylphosphino)propane (dppp), in the presence of triethylborane (60 mol%), gave compound **2aa** in 99% isolated crude yield (Table 1, entry 1). In order to diminish the amount of additive 3 mol% of *p*-toluenesulfonic acid (TsOH) was employed instead of Et_3B affording **2aa** in only 3% yield (Table 1, entry 2). Next, $Pd(dba)_2$ was employed instead of $Pd(OAc)_2$ without success (Table 1, entry 3). However, by changing the dppp ligand by *rac*-BINAP product **2aa** was obtained in 66% yield (Table 1, entry 4). Using *rac*-BINOL phosphoric acid instead of TsOH gave a 98% of product **2aa** (Table 1 entry 5). These reaction conditions: 3 mol% of $Pd(dba)_2$/*rac*-BINAP// *rac*-BINOL phosphoric acid in THF at rt, were used for the allylation of 3-acetyl-2-oxindoles **1b** and **1c** providing the corresponding allylated compounds **2ba** and **2ca** in 61 and 89% yield, respectively (Table 1, entries 6 and 7). To the best of our knowledge, this is the first palladium-catalyzed allylation of 3-acetyl-1-methyl-2-oxindoles with allyl alcohol.

The synthesis of 3-allyl-1-methyl-2-oxindole (**3ab**) was carried out by in situ addition of a solution of benzyltrimethylammonium hydroxide (Triton B) (40% in MeOH) (1 equiv) followed by addition of AcOH (0.85 mL) in 61% yield (Scheme 3). Attempts to prepare this compound by allylation of *N*-methyl-2-oxindole with allyl bromide and Triton B as base gave the corresponding 3,3-diallylated 2-oxindole.[12] Therefore, this one-pot procedure can be used for the synthesis of 3-monoallylated oxindoles instead of using LiHMDS at −78 °C during the allylation of *N*-alkyloxindole or sodium hydride at different temperatures.[14]

Next, the Pd-catalyzed deacylative allylation of 3-acetyl-1,3-methyl-2-oxindole (**4a**) was attempted. The reaction conditions study was carried out with compound **4a**[12] and hex-2-en-1-ol (Table 2). Using $Pd(OAc)_2$ and dppp (3 mol%) as catalysts and KO*t*Bu (1.1 equiv) as base in THF, after 15 h at rt under Ar atmosphere, a 3:1 mixture of **5ab** and also the oxidized 3-hydroxy-1,3-

Table 1
Pd-Catalyzed allylation of 3-acetyl-2-oxindoles.[a]



1a: R^1 = Me, R^2 = H
1b: R^1 = Me, R^2 = OMe
1c: R^1 = Bn, R^2 = OMe

Ent.	Cat (3 mol%)	Ligand (3 mol%)	Additive (mol%)	**2**	Yield (%)[b]
1	$Pd(OAc)_2$	dppp	Et_3B (60)	**2aa**	99
2	$Pd(OAc)_2$	dppp	TsOH (3)	**2aa**	3
3	$Pd(dba)_2$	dppp	TsOH (3)	**2aa**	–
4	$Pd(dba)_2$	*rac*-BINAP	TsOH (3)	**2aa**	66
5	$Pd(dba)_2$	*rac*-BINAP	(BINOL)PO_2H (3)[c]	**2aa**	98 (96)
6	$Pd(dba)_2$	*rac*-BINAP	(BINOL)PO_2H (3)[c]	**2ba**	91 (61)
7	$Pd(dba)_2$	*rac*-BINAP	(BINOL)PO_2H (3)[c]	**2ca**	99 (89)

[a] Reaction conditions: **1** (0.3 mmol), allyl alcohol (0.45 mmol), Pd (3 mol%), ligand (3 mol%), additive (see column), THF (1.5 mL), 60 h.
[b] Isolated crude yield. In parenthesis, yield after flash chromatography.
[c] Racemic (BINOL)PO_2H was employed.