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Pd-catalyzed domino carbonylative–decarboxylative allylation: an easy and selective monoallylation of ketones†

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In the presence of an allyl alcohol, α-chloroacetophenones undergo an allyloxycarbonylation reaction followed by *in situ* decarboxylative allylation to selectively afford the corresponding monoallylated ketones *via* a Pd-catalyzed domino sequence. The scope of the reaction was extended to substituted α-chloroacetophenones as well as various allyl alcohols.

Monoallylation of ketones remains challenging in organic synthesis. Direct allylation of enolates is not selective and normally results in mixtures of mono- and diallylated ketones.[1] The Stork enamine strategy is highly efficient, but requires the stoichiometric formation of an enamine, which may not be stable.[2] Pd-catalyzed allylation reactions have recently emerged, but the need for a special ferrocene-based ligand[3] makes these multi-step syntheses tedious.

To the best of our knowledge, palladium-catalyzed alkoxycarbonylation of α-chloroketones has been so far limited to the preparation of simple, saturated esters, using the required alcohol as the solvent.[4] We anticipated that, in the presence of an allyl alcohol, the resulting allyl β-ketoester could undergo *in situ* Pd-catalyzed decarboxylative allylation.[5] In such a case, a Pd(0) complex would catalyze the carbonylation step as well as the decarboxylative allylation in a *pseudo-domino type I* manner,[6] thereby selectively generating the desired monoallylated ketone *via* a doubly catalytic one-pot process. Scheme 1 shows the prospective overall mechanism of this new *pseudo-domino* sequence.[7] The desired path follows elementary steps from ***1*** to ***7*** incorporated in the two consecutive catalytic cycles sharing Pd(0). However, an accurate perusal at the possible undesired reactivities (Scheme 1, dotted paths) unveils the *caveat* that makes such a sequence challenging. First, an undesired nucleophilic substitution between allyl alcohol and the halide might generate the corresponding ether, thereby directly subtracting the two components of the reaction (step ***8***). Furthermore, premature protonation of the palladium complex deriving from oxidative addition of the halide may also take place, directly, or *via* its palladium enolate[8] (step ***9***). Finally, competitive oxidative addition of the alcohol to Pd(0) may, after β-elimination, generate acrolein, thereby consuming the alcohol (step 12).[9]

We first studied both steps separately. On the one hand, in MeOH and under a CO atmosphere (10 bar), α-chloroacetophenone **1a** provided the expected methyl β-ketoester **2**. Unfortunately, the reaction did not proceed at atmospheric pressure.[4f,g]

On the other hand, treatment of allyl β-ketoester **3** with catalytic $Pd(dba)_2/4PPh_3$ at 90 °C in allyl alcohol gave readily the allylated acetophenone **4a** in high yield (Scheme 2).

We next focused on the *pseudo-domino* process. Accordingly, we investigated the reactivity of **1a** in the presence of allyl alcohol, a base, a catalytic amount of a palladium complex, and under a CO atmosphere (Table 1).

Under the conditions suitable for the methoxycarbonylation reaction, neither allylated acetophenone **4a**, nor allyl β-ketoester **3** was observed (entry 1). Raising the temperature to 130 °C led to 11% isolated yield of allylated acetophenone **4a** (entry 2).

Use of a combination of $Pd(OAc)_2$ and PPh_3 (1 : 4) resulted in a slightly better yield (20%, entry 3). Raising CO pressure to 20 bar gave the desired product in 27% yield (entry 4). Although an increase in the catalyst loading to 5 mol% showed no improvement (25%, entry 5), further increase to 10 mol% Pd resulted in a doubled isolated yield (52%, entry 6). So far, allyl alcohol was used as the solvent (30 equiv.). Next, we reduced the amount of allyl alcohol to 15 equivalents, in the presence of an additional solvent, so as to keep the molarity constant. THF and DMF were less efficient, affording 39% and 3% yield of **4a**, respectively (entries 7 and 8), whereas toluene was suitable (57%, entry 9). Tributylamine as the base was as efficient as 1,8-bis(dimethylamino)naphthalene (DMAN) (54%, entry 10), yet, allowing an easier workup. A decrease in the amount of allyl alcohol to 6 equiv. led to the exclusive formation of acetophenone (entry 11). A ligand screening revealed that tri(2-furyl) phosphine (TFP) was the best one (76%, entry 12). Finally, the reaction proceeded with equal efficiency reducing the reaction time to 2 h (73%, entry 13). All electron-rich phosphines studied, but Xantphos, led to

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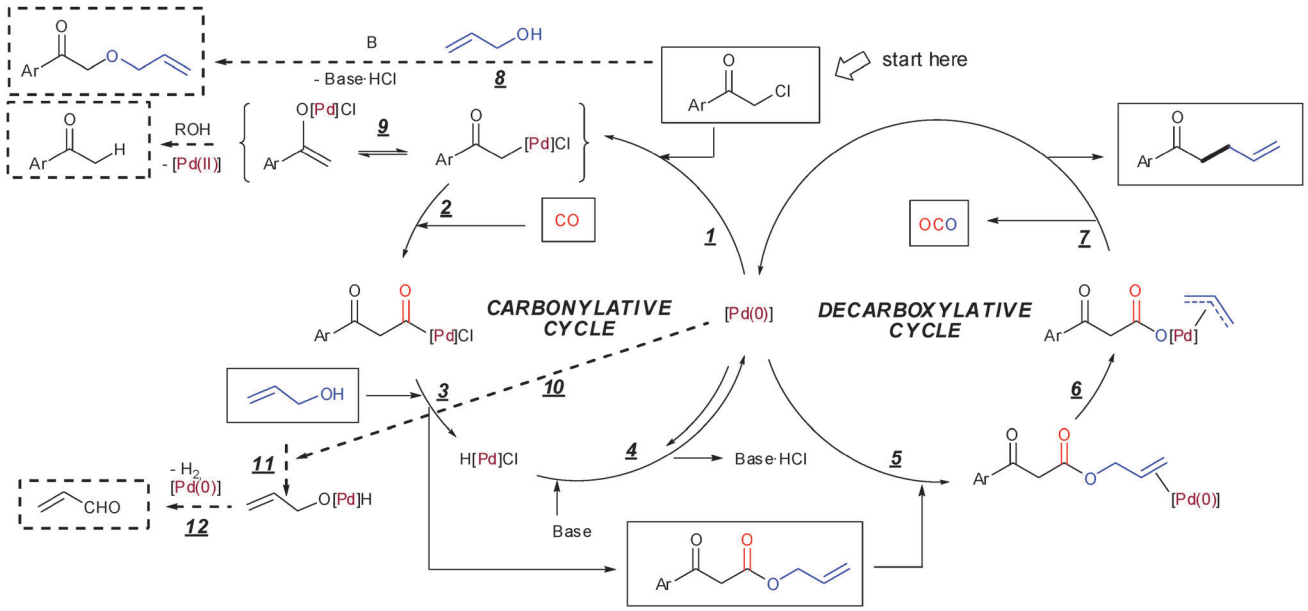
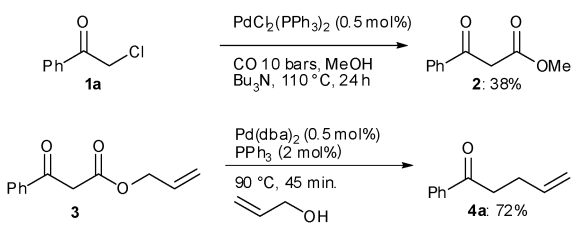


Scheme 1 Mechanism of the Pd-catalyzed carbonylative–decarboxylative allylation pseudo-domino sequence, and the possible side reactions.

unsatisfactory results.[10] Triethyl phosphite led to disappointing results, too (entry 14). Generating CO from methyl formate[11] was also not efficient.§

With these optimized conditions in hand (Table 1, entry 13), substituted acetophenones **1b–n** were tested as substrates (Scheme 3).

Monoallylated aryl ketones bearing an electron-withdrawing group at the *para* position were isolated in moderate to acceptable yields (**4b–e**, 31–65%). The reaction was equally successful for ketones bearing electron-donating groups at the *para* position (**4f–h**, 44–77%). An EWG or EDG group at the *meta* position was also well tolerated (**4i–j**, 37%). However, our procedure proved to be sensitive to steric hindrance. Allylated acetophenone **4k**, bearing chlorine atoms at *para* and *ortho* positions was obtained in a lower yield than allylated acetophenone **4c** bearing only the *para* chlorine atom (36% *vs.* 57%, respectively). Desyl chloride also furnished the desired monoallylated ketone, albeit in moderate yield (**4l**, 33%). α-Chloro cycloalkanones and α-chloroketones bearing β-hydrogen atoms led to mixtures of β-hydride elimination and/or reduction products. Finally, α-chloroacetophenone **1a** was reacted with substituted allyl alcohols. These alcohols were used as the solvent. Indeed, use of 15 equiv. of the desired alcohol in toluene led to unsatisfactory results. Monosubstitution at either the 2- or 3-position of the allylic motif was tolerated, affording the desired allylated ketones **4p–r** in good yields (51%, Scheme 4).

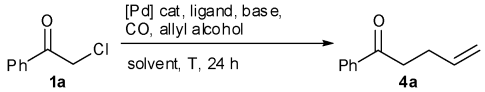


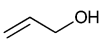
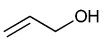
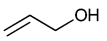
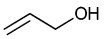
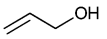
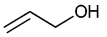
Scheme 2 Pd-catalyzed methoxycarbonylation and decarboxylative allylation, separately.

In the case of crotyl alcohol, mixtures of regioisomeric allylated acetophenones **4p** and **4q** were obtained. Worthy of note, in the case of methallyl alcohol, Xantphos revealed to be the ligand of choice.

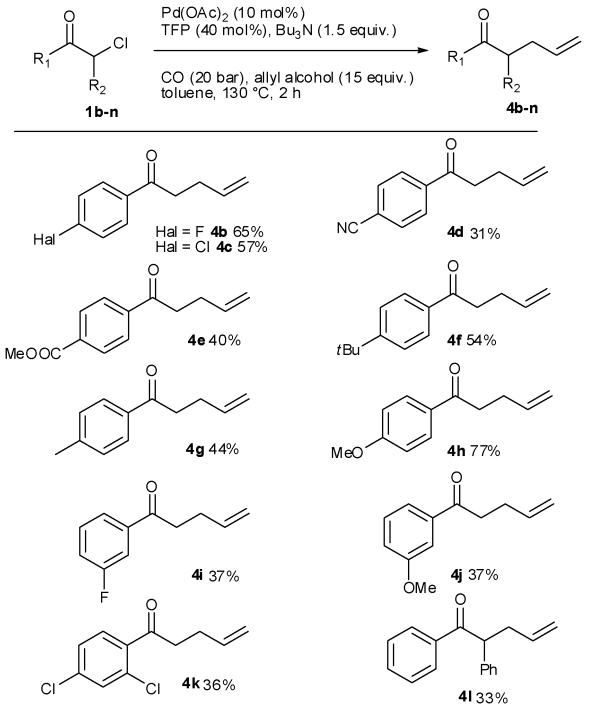
In conclusion, we have developed a synthetic protocol for the selective generation of γ,δ-unsaturated aromatic ketones

Table 1 Optimization of the reaction conditions for the domino sequence



Entry	[Pd][a]	Ligand	Base	Solvent[b]	T/ °C	P_{CO}/ bar	Yield[c] (%)
1	$PdCl_2(PPh_3)_2$	—	DMAN		100	10	0
2	$PdCl_2(PPh_3)_2$	—	DMAN		130	10	11
3	$Pd(OAc)_2$	PPh_3	DMAN		130	10	20
4	$Pd(OAc)_2$	PPh_3	DMAN		130	20	27
5	$Pd(OAc)_2$	PPh_3	DMAN		130	20	25
6	$Pd(OAc)_2$	PPh_3	DMAN		130	20	52
7	$Pd(OAc)_2$	PPh_3	DMAN	THF	130	20	39
8	$Pd(OAc)_2$	PPh_3	DMAN	DMF	130	20	3
9	$Pd(OAc)_2$	PPh_3	DMAN	Toluene	130	20	57
10	$Pd(OAc)_2$	PPh_3	Bu_3N	Toluene	130	20	54
11[d]	$Pd(OAc)_2$	PPh_3	Bu_3N	Toluene	130	20	0
12	$Pd(OAc)_2$	TFP[e]	Bu_3N	Toluene	130	20	76
13[f]	**$Pd(OAc)_2$**	**TFP**	**Bu_3N**	**Toluene**	**130**	**20**	**73**
14	$Pd(OAc)_2$	$P(OEt)_3$	Bu_3N	Toluene	130	20	0

[a] Entries 1–4: 0.5 mol%; entry 5: 5 mol%; entries 6–14: 10 mol%; in all cases, 4 equiv. of ligand with respect to [Pd] were used. [b] For allyl alcohol: 30 equiv. allyl alcohol. For other solvents: 15 equiv. allyl alcohol unless otherwise noted. [c] Isolated yields. The mass balance to 100% was essentially acetophenone. Traces of aldehydes were sometimes noticed. [d] 6 equiv. of allyl alcohol. [e] Tri(2-furyl)phosphine. [f] 2 h.



Scheme 3 Scope and limitations of the pseudo-domino sequence.[12]

starting from readily accessible α-chloroacetophenones. The method, which is based on a Pd-catalyzed carbonylative–decarboxylative allylation pseudo-domino process, was insensitive to the electronic properties of the substituents on the aromatic ring. As this new concept could be extended to substituted α-chloroacetophenones, further synthetic applications involving γ,δ-unsaturated aromatic ketones can be foreseen.

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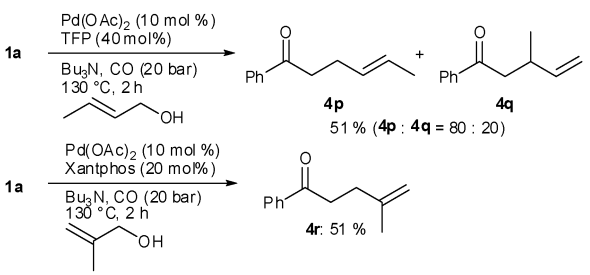

Scheme 4 Influence of the substitution pattern of the allyl alcohol.

Notes and references

§ Representative experimental procedure: an autoclave was charged with $Pd(OAc)_2$ (10 mol%), P(2-furyl)$_3$ (40 mol%), Bu_3N (1.5 equiv.), α-chloroketone (1.0 mmol), allyl alcohol (1 mL) and toluene (1.5 mL). The autoclave was purged with CO, sealed and pressurized to 20 bar and heated at 130 °C for 2 h. After cooling to r.t., pressure was released. The reaction mixture was diluted with ether (10 mL) and water (20 mL) was added. After extraction with Et_2O (3 × 20 mL), drying over $MgSO_4$ and concentration *in vacuo*, the residue was purified by column chromatography, affording the desired product.

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