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Decarboxylative allylation of arylglyoxylic acids with allyl alcohol

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ABSTRACT

A decarboxylative allylation of arylglyoxylic acids with allyl alcohol has been developed. In the presence of catalytic amounts of $Pd(dba)_2$ and PPh_3, the substrates are in an esterification equilibrium with the allyl arylglyoxylates, which are continuously decarboxylated to give α,β-unsaturated ketones along with CO_2 and water as the only byproducts.

1. Introduction

Within the last decade, decarboxylative cross-coupling reactions have evolved into effective tools for C–C and C–heteroatom bond formation [1,2]. This reaction concept compares favourably to traditional cross-coupling reactions in that it involves using easily available carboxylic acids as carbon nucleophiles in place of organometallic reagents. Decarboxylative allylations, in which allyl esters of activated carboxylic acids extrude CO_2, are particularly efficient [3]. Carroll was the first to describe the thermal rearrangement of allyl β-ketocarboxylates into the corresponding γ,δ-unsaturated ketones [4]. Tsuji [5] and Saegusa [6] disclosed a catalytic version of the Carroll reaction which proceeds under mild, neutral conditions. This concept was extended to various other substrates and led to synthetic maturity by Tunge [7], Stoltz [8] and others [9]. However, in all these cases, the substrates employed are esters of carboxylic acids that decarboxylate with the formation of highly stabilized carbanions such as enolate, benzyl [10], α-cyano [6], or nitronate species [9a] (Scheme 1).

The first example of a decarboxylative allylation of non-activated allyl carboxylates was the Pd/phosphine-catalyzed conversion of arylglyoxylic acid allyl esters to allyl ketones, which immediately isomerize to give the α,β-unsaturated ketones [11]. The decarboxylation of the arylglyoxylates leads to an intermediate formation of synthetic equivalents to unstable acyl anion equivalents and is promoted by tri(*p*-tolyl)phosphine. These are then allylated within the coordination sphere of the palladium.

We have also shown that the allyl ester substrates can be generated *in situ* from arylglyoxylic acids and diallyl carbonate [12]. Liu et al. have recently disclosed the decarboxylative allylation of silver benzoates with allyl halides in the presence of a complex palladium/copper catalyst system, which is another example of a catalytic allylation of non-activated carboxylic acids [13].

In continuation of our search for concepts for the activation of carboxylic acids for catalytic coupling reactions [14], we herein present the decarboxylative allylation of arylglyoxylic acids with allyl alcohol as a new, sustainable allylation method. In this intermolecular C–C-bond forming process, the allyl ester substrates are generated *in situ* via esterification, so that CO_2 and water are the only byproducts.

2. Results and discussion

A combination of an esterification process and a decarboxylative coupling of the resulting allyl ester should be possible following the mechanistic hypothesis outlined in Scheme 2. Upon mixing an arylglyoxylic acid **1** with allyl alcohol **2**, at least small quantities of the allyl ester should form in a reversible esterification. Once formed, the allyl esters should oxidatively add to the palladium(0) species **A** with formation of an allylpalladium(II) α-oxocarboxylate

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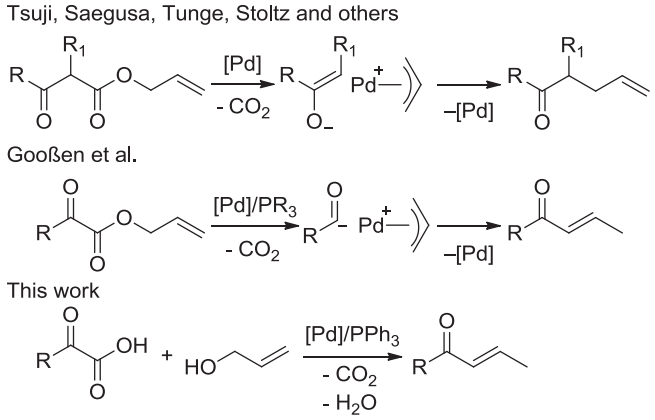
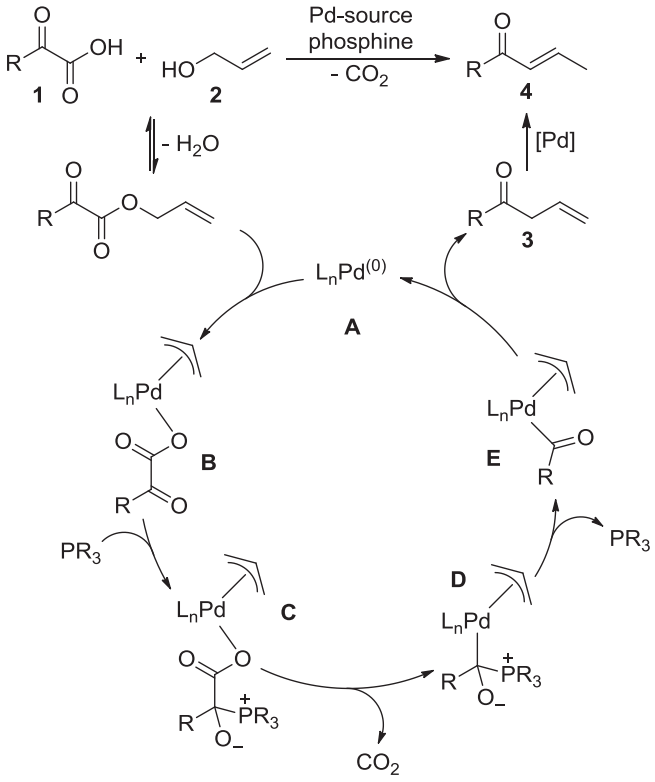


Scheme 1. Decarboxylative allylations.

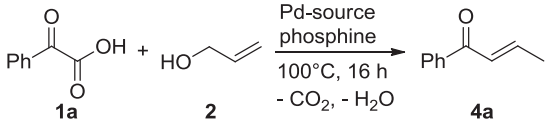
complex **B**. The phosphine should then add to the carbonyl group of the arylglyoxylate (**C**), promoting the extrusion of CO_2 with the formation of the acyl palladium complex **D**. In a reductive elimination step, the allylketone **3** would be released, regenerating the initial palladium(0) complex **A**. The product would then immediately isomerize to the stabilized (*E*)-configured α,β-unsaturated ketone (**4**).

In search for an effective catalyst system, we used phenylglyoxylic acid and allyl alcohol as the model reaction and evaluated various palladium complexes in combination with several phosphines [11,12]. Under the optimal reaction conditions for the conversion of preformed allyl esters ($Pd(dba)_2/P(pTol)_3$, toluene, 100 °C, 16 h), only protodecarboxylation of the phenlglyoxylic acid was observed (Table 1, entry 1). A screening of various solvents revealed that 1,4-dioxane was uniquely effective for the desired process. Whereas in this solvent, product **4a** was obtained in an encouraging 50% yield (entry 2), product formation was observed neither in less polar nor in strongly polar solvents (entries 3–7). Among the palladium precursors tested, the Pd(0) complex $Pd(PPh_3)_4$ gave the best result (entry 8), and almost no conversion was achieved for palladium(II) complexes (entries 9–11). The screening of various phosphines revealed that simple PPh_3 is the most active cocatalyst, with optimal donating ability and steric demand (entries 12–18). This is an interesting finding, since for other protocols $P(pTol)_3$ was by far the most effective phosphine cocatalyst. Using a catalyst generated *in situ* from 5 mol% $Pd(dba)_2$ and 35 mol% of PPh_3, the desired product was finally obtained in 89% yield when stirring a mixture of the phenylglyoxylic acid and 1.5 equivalents of allyl alcohol in 1,4-dioxane at 100 °C for 16 h (entry 19).



Scheme 2. Proposed mechanism of the decarboxylative allylation.

Table 1
Optimization of the reaction conditions.[a]



Entry	Pd source	Phosphine	Solvent	Yield [%][b]
1	$Pd(dba)_2$	$P(pTol)_3$	Toluene	0
2	$Pd(dba)_2$	$P(pTol)_3$	1,4-Dioxane	50
3	$Pd(dba)_2$	$P(pTol)_3$	Anisole	0
4	$Pd(dba)_2$	$P(pTol)_3$	Diglyme	0
5	$Pd(dba)_2$	$P(pTol)_3$	NMP	0
6	$Pd(dba)_2$	$P(pTol)_3$	DMF	0
7	$Pd(dba)_2$	$P(pTol)_3$	DMSO	0
8	$Pd(PPh_3)_4$	$P(pTol)_3$	1,4-Dioxane	79
9	$PdCl_2$	$P(pTol)_3$	1,4-Dioxane	0
10	$Pd(OAc)_2$	$P(pTol)_3$	1,4-Dioxane	23
11	$Pd(acac)_2$	$P(pTol)_3$	1,4-Dioxane	29
12	$Pd(dba)_2$	PPh_3	1,4-Dioxane	84
13	$Pd(dba)_2$	$P(p\text{-}F\text{-}C_6H_4)_3$	1,4-Dioxane	64
14	$Pd(dba)_2$	$P(p\text{-}OMe\text{-}C_6H_4)_3$	1,4-Dioxane	0
15	$Pd(dba)_2$	$P(o\text{-}Tol)_3$	1,4-Dioxane	0
16	$Pd(dba)_2$	$P(fur)_3$	1,4-Dioxane	0
17	$Pd(dba)_2$	PCy_3	1,4-Dioxane	0
18	$Pd(dba)_2$	JohnPhos	1,4-Dioxane	0
19[c]	$Pd(dba)_2$	PPh_3	1,4-Dioxane	89

[a] Reaction conditions: phenylglyoxylic acid (**1a**) (0.50 mmol), allyl alcohol (**2**) (0.75 mmol), Pd-source (5 mol%), ligand (30 mol%), 4 mL solvent, 100 °C, 16 h.
[b] Yields were determined by GC analysis, with *n*-tetradecane as an internal standard.
[c] 35 mol% PPh_3.

Having thus found an efficient reaction protocol, we next investigated the scope of the new transformation. As can be seen from the examples in Table 2, various aromatic and heteroaromatic glyoxylic acids were converted in good yields into the corresponding α,β-unsaturated ketones. Several functional groups, e.g., methoxy-, chloro- and fluoro-groups were tolerated. The reaction is not yet applicable to alkylglyoxylic acids, to particularly sterically demanding aromatic substrates such as mesitylglyoxylic acid, and to arylglyoxylic acids bearing strongly electron-withdrawing substituents such as nitro-groups in *para*-position.

3. Conclusion

In conclusion, a decarboxylative cross-coupling of arylglyoxylic acids with allyl alcohol was developed. It constitutes the first example of a C–C bond forming reaction starting from carboxylic acids and alcohols. The simplicity of the catalyst system, which is