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Decarboxylative allylation of arylglyoxylic acids with allyl alcohol

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Dedicated to Professor Wolfgang A. Herrmann on the occasion of his 65th birthday.

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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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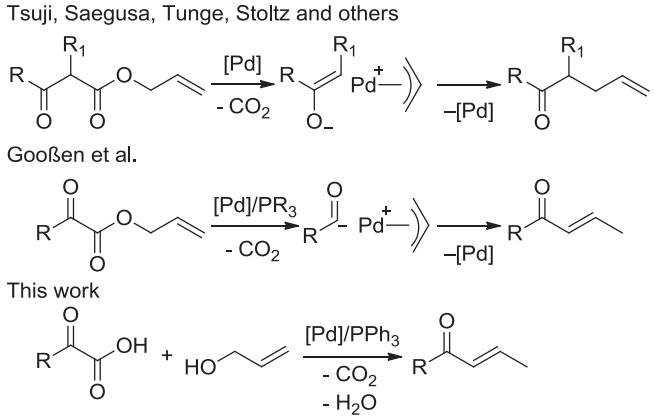
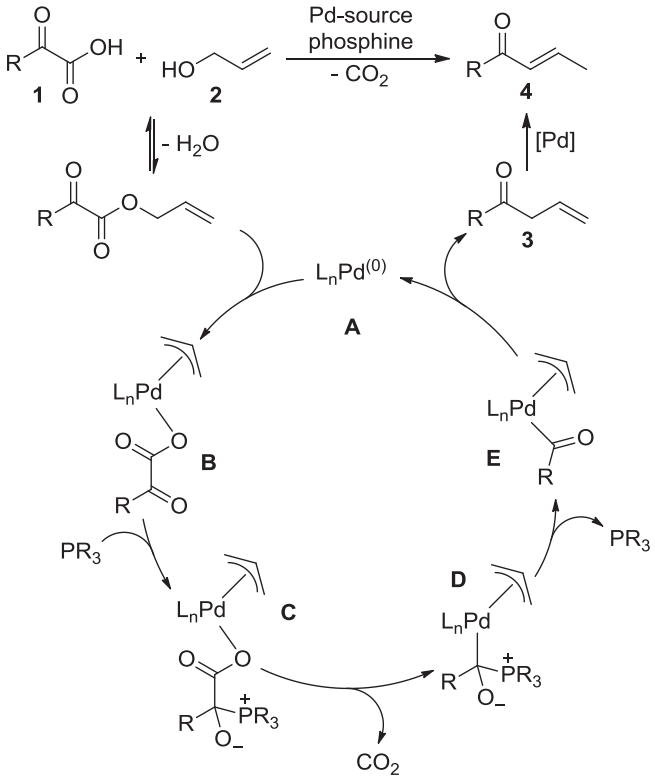


Scheme 1. Decarboxylative allylations.

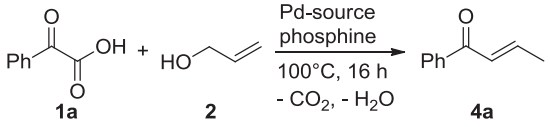
complex **B**. The phosphine should then add to the carbonyl group of the arylglyoxylate (**C**), promoting the extrusion of CO_2 with the formation of the acyl palladium complex **D**. In a reductive elimination step, the allylketone **3** would be released, regenerating the initial palladium(0) complex **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

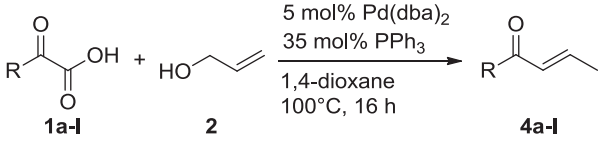
[a] Reaction conditions: phenylglyoxylic acid (**1a**) (0.50 mmol), allyl alcohol (**2**) (0.75 mmol), Pd-source (5 mol%), ligand (30 mol%), 4 mL solvent, 100 °C, 16 h.
[b] Yields were determined by GC analysis, with *n*-tetradecane as an internal standard.
[c] 35 mol% PPh_3.

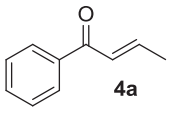
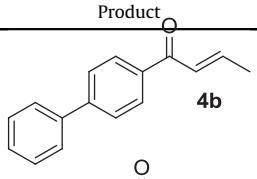
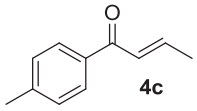
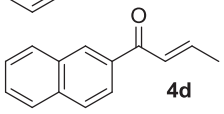
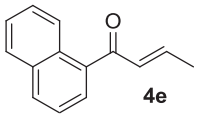
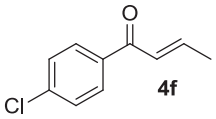
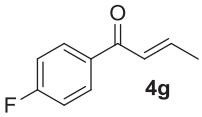
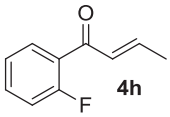
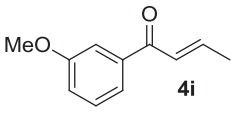
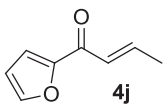
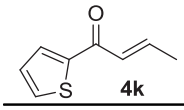
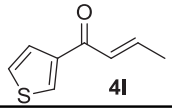
Having thus found an efficient reaction protocol, we next investigated the scope of the new transformation. As can be seen from the examples in Table 2, various aromatic and heteroaromatic glyoxylic acids were converted in good yields into the corresponding α,β-unsaturated ketones. Several functional 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

Table 2
Scope of the reaction.[a]



Product	Yield [%]	Product	Yield [%]
 4a	88	 4b	85
 4c	81	 4d	86
 4e	87	 4f	86
 4g	96	 4h	82
 4i	77	 4j	80
 4k	73	 4l	63

[a] Reaction conditions: arylglyoxylic acid (1.00 mmol), allyl alcohol (1.50 mmol), $Pd(dba)_2$ (5 mol%), PPh_3 (35 mol%), 8 mL 1,4-dioxane, 100 °C, 16 h.

formed *in situ* from easily available $Pd(dba)_2$ and PPh_3, as well as the mild reaction conditions are particular advantages of this reaction protocol. This is a first step towards a new generation of salt-free cross-coupling reactions, in which the substrates are generated in an equilibrated esterification process that releases only water as byproduct, combined with a regiospecific coupling reaction, in which only CO_2 is released. If this concept could be extended, e.g., to biaryl couplings, the sustainability of such processes could dramatically be improved (Scheme 3).

4. Experimental section

4.1. General methods

All reactions were performed in oven-dried vessels equipped with teflon-coated stirrer bars and septa using degassed solvents under a nitrogen atmosphere. 1,4-Dioxane was used without further purification. All reactions were monitored by GC using *n*-tetradecane as an internal standard. Response factors of the products with regard to *n*-tetradecane were obtained experimentally by analyzing known quantities of the substances. GC analyses were carried out using an HP-5 capillary column (phenyl methyl siloxane, 30 m|320|0.25, 100/2.3–30–300/3) and a time program beginning with 2 min at 60 °C followed by 30 °C/min ramp to 300 °C, then 3 min at this temp. Column chromatography was performed using a Combi Flash Companion-Chromatography-System (Isco-Systems) and Grace Reveleris packed flash columns (12 g). Melting points were determined with a Mettler FP61. NMR spectra were obtained on a Bruker AMX 400 system using $CDCl_3$ as solvent, with proton and carbon resonances at 400 MHz and 101 MHz, respectively. Infrared spectra were recorded on a Perkin Elmer Fourier transform spectrometer. Mass spectral data were acquired on a GC–MS Saturn 2100 T (Varian). CHN–elemental analysis was performed with a Hanau Elemental Analyzer vario Micro cube. Compounds **1b** [CAS: 5449-21-8], **1c** [CAS: 7163-50-0], **1d** [CAS: 14289-45-3], **1e** [CAS: 26153-26-4], **1f** [CAS: 7099-88-9], **1g** [CAS: 2251-76-5], **1h** [CAS: 79477-86-4], **1i** [CAS: 26767-10-2] and **1l** [CAS: 39684-36-1] were synthesized in 61–98% yield following known synthetic procedures [2a,15]. All other compounds were commercially available and used without further purification.

4.2. Standard procedure for the synthesis of α,β-unsaturated ketones from α-oxocarboxylic acids

A 20 mL crimp-cap vessel was charged with bis(dibenzylideneacetone)palladium(0) (28.8 mg, 0.05 mmol) and triphenylphosphine (91.8 mg, 0.35 mmol). A solution of the α-oxocarboxylic acid (**1a**–**l**) (1.00 mmol) in 1,4-dioxane (8 mL) and allyl alcohol (**2**) (104 μL, 1.50 mmol) were added via syringe. The reaction mixture was stirred at 100 °C for 16 h and was then cooled to room temperature. The solvent was removed in vacuo (40 °C, 100 mbar) and the remaining residue was further purified by flash chromatography (SiO_2, ethyl acetate/hexane (1:10)), yielding the corresponding ketones **4a**–**l** (63–96%).

4.2.1. Synthesis of (E)-1-phenylbut-2-en-1-one (*4a*) [CAS: 495-41-0]

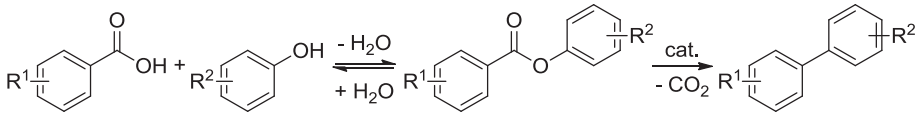
Compound **4a** was prepared following the standard procedure, starting from phenylglyoxylic acid (**1a**) (155 mg, 1.00 mmol). After purification, **4a** was isolated as colourless oil (129 mg, 88%). The spectroscopic data matched those reported in the literature.

4.2.2. Synthesis of (E)-1-([1,1′-biphenyl]-4-yl)but-2-en-1-one (*4b*) [CAS: 71823-67-1]

Compound **4b** was prepared following the standard procedure, starting from 4-biphenylglyoxylic acid (**1b**) (226 mg, 1.00 mmol). After purification, **4b** was isolated as beige solid (189 mg, 85%). The spectroscopic data matched those reported in the literature.

4.2.3. Synthesis of (E)-1-(4-tolyl)but-2-en-1-one (*4c*) [CAS: 3837-95-4]

Compound **4c** was prepared following the standard procedure, starting from 4-tolylglyoxylic acid (**1c**) (164 mg, 1.00 mmol). After purification, **4c** was isolated as colourless oil (129 mg, 81%). The spectroscopic data matched those reported in the literature.



Scheme 3. "Dream reaction" for biaryl synthesis.

*4.2.4. Synthesis of (E)-1-(naphthalen-2-yl)but-2-en-1-one (**4d**) [CAS: 128113-44-0]*

Compound **4d** was prepared following the standard procedure, starting from 2-napththylglyoxylic acid (**1d**) (200 mg, 1.00 mmol). After purification, **4d** was isolated as colourless solid (168 mg, 86%). The spectroscopic data matched those reported in the literature.

*4.2.5. Synthesis of (E)-1-(naphthalen-1-yl)but-2-en-1-one (**4e**) [CAS: 128113-46-2]*

Compound **4e** was prepared following the standard procedure, starting from 1-napththylglyoxylic acid (**1e**) (200 mg, 1.00 mmol). After purification, **4e** was isolated as yellow solid (170 mg, 87%). The spectroscopic data matched those reported in the literature.

*4.2.6. Synthesis of (E)-1-(4-chlorophenyl)but-2-en-1-one (**4f**) [CAS: 67864-02-2]*

Compound **4f** was prepared following the standard procedure, starting from 4-chlorophenylglyoxylic acid (**1f**) (185 mg, 1.00 mmol). After purification, **4f** was isolated as colourless solid (156 mg, 86%). The spectroscopic data matched those reported in the literature.

*4.2.7. Synthesis of (E)-1-(4-fluorophenyl)but-2-en-1-one (**4g**) [CAS: 28122-15-8]*

Compound **4g** was prepared following the standard procedure, starting from 4-flourophenylglyoxylic acid (**1g**) (168 mg, 1.00 mmol). After purification, **4g** was isolated as colourless oil (158 mg, 96%). The spectroscopic data matched those reported in the literature.

*4.2.8. Synthesis of (E)-1-(2-fluorophenyl)but-2-en-1-one (**4h**) [CAS: 79477-86-4]*

Compound **4h** was prepared following the standard procedure, starting from 2-fluorophenylglyoxylic acid (**1h**) (168 mg, 1.00 mmol). After purification, **4h** was isolated as colourless oil (135 mg, 82%). The spectroscopic data matched those reported in the literature.

*4.2.9. Synthesis of (E)-1-(3-methoxyphenyl)but-2-en-1-one (**4i**) [CAS: 1087399-25-4]*

Compound **4i** was prepared following the standard procedure, starting from 3-methoxyphenylglyoxylic acid (**1i**) (180 mg, 1.00 mmol). After purification, **4i** was isolated as yellow oil (135 mg, 77%). The spectroscopic data matched those reported in the literature.

*4.2.10. Synthesis of (E)-1-(furan-2-yl)but-2-en-1-one (**4j**) [CAS: 131323-45-0]*

Compound **4j** was prepared following the standard procedure, starting from furanyl-2-glyoxylic acid (**1j**) (140 mg, 1.00 mmol). After purification, **4j** was isolated as yellow solid (109 mg, 80%). The spectroscopic data (NMR, IR) matched those reported in the literature.

*4.2.11. Synthesis of (E)-1-(thiophen-2-yl)but-2-en-1-one (**4k**) [CAS: 13196-29-7]*

Compound **4k** was prepared following the standard procedure, starting from thiophenyl-2-glyoxylic acid (**1k**) (156 mg, 1.00 mmol). After purification, **4k** was isolated as yellow oil (111 mg, 73%). The spectroscopic data (NMR, IR) matched those reported in the literature.

*4.2.12. Synthesis of (E)-1-(thiophen-3-yl)but-2-en-1-one (**4l**) [CAS: 1308249-57-1]*

Compound **4l** was prepared following the standard procedure, starting from thiophenyl-3-glyoxylic acid (**1l**) (156 mg, 1.00 mmol). After purification, **4l** was isolated as colourless solid (95.5 mg, 63%). M.p. = 42.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.05 (dd, J = 2.8, 1.2 Hz, 1H), 7.58 (dd, J = 5.1, 1.3 Hz, 1H), 7.31 (dd, J = 5.1, 2.8 Hz, 1H), 7.08 (dq, J = 15.1, 6.8 Hz, 1H), 6.79 (dq, J = 15.3, 1.4 Hz, 1H), 1.97 ppm (dd, J = 6.8, 1.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 183.9, 144.0, 142.6, 131.8, 127.9, 127.3, 126.2, 18.3 ppm (2C; CH_3); IR ν = 3105 (s), 2909 (m), 1667 (vs), 1619 (vs), 1511 (m), 1443 (m), 1411 (m), 1291 (m), 1231 (m), 1179 cm^{-1} (m); MS (Ion trap, EI): m/z (%) = 152 (20), 151 (100), 136 (27), 91 (11), 69 (25), 45 (20), 41 (20); elemental analysis calcd (%) for C_8H_8OS: C 63.13, H 5.30, S 21.07; found: C 63.43, H 5.50, S 20.90.

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