Allylation

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Migratory Decarboxylative Coupling of Coumarins: Synthetic and Mechanistic Aspects**

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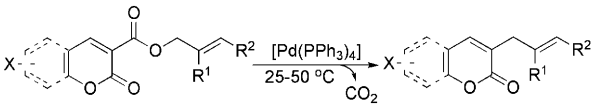
Construction of new C–C bonds by decarboxylative coupling is a powerful synthetic method since it avoids highly basic reaction conditions and preformed organometallic reagents that produce stoichiometric metal waste.[1] In addition, the byproduct (CO_2) is nontoxic and requires no special separation procedures. Thus several research groups have demonstrated that decarboxylative couplings are practical alternatives to standard cross-coupling reactions.[1–6] For example, Gooßen and co-workers have reported a Pd^{II}-catalyzed coupling of benzoic acids with haloaromatics to generate biaryl products.[3] Furthermore, Myers et al. have shown a Pd^{II}-catalyzed decarboxylative variant of the Heck reaction.[4] Our research has focused on the development of decarboxylative allylation and benzylation reactions.[5] In this arena we have reported the decarboxylative allylation (DcA) of heteroaromatic coumarin substrates under mild conditions [Eq. (1)].[6]



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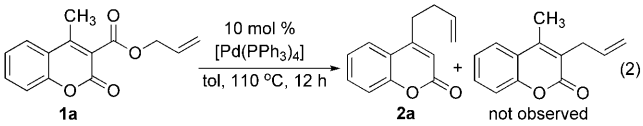
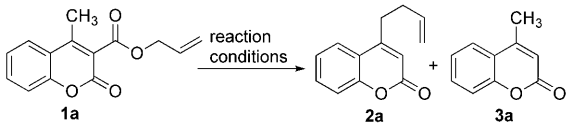
Coumarins are not only "privileged" scaffolds of biological and pharmaceutical interest,[7,8] but they are also widely used in dyes because of their photophysical properties.[9] In our continuing investigations of the DcA of coumarins, we turned our attention to the investigation of decarboxylative couplings of 4-substituted coumarins. Thus, 4-methyl-3-allylcoumarate **1a** was synthesized and subjected to our previous conditions for Pd^0-catalyzed decarboxylative coupling at 50 °C.[6] Disappointingly, the starting material remained intact even after prolonged heating. However, upon heating the substrate at 110 °C in toluene for 6 h, we observed decarboxylation and C–C bond formation (**2a**) as well as protiodecarboxylation [Eq. (2)]. Closer analysis of the products by ^{1}H NMR spectroscopy revealed that allylation occurs at the methyl terminus providing 4-homoallylcoumarin in lieu of the expected allylation of the 3-position of the coumarin.[6] In every other case of decarboxylative coupling that we have investigated, allylation occurs regiospecifically at the site that bears the carboxylate.[10] Thus, the observation of remote decarboxylative allylation warranted further investigation. Herein, we report that many other substituted coumarins exhibit similar regiochemistry in their allylation and we present a mechanism that explains this unusual regiochemical outcome.



(2)

Encouraged by the unexpected regiochemistry of allylation, we optimized the reaction conditions with the goal of suppressing the undesired protonation product (**3a**). After rigorous catalyst and solvent screening (Table 1) it was found

Table 1: Optimization of reaction conditions.[a]



Entry	Catalyst[b]	Solvent[b]	Yield [%][c]	**2a**:**3a**[c]
1	5 mol% $[Pd(PPh_3)_4]$	$[D_8]$tol	99	77:23
2	5 mol% $[Pd(PPh_3)_4]$	CD_3CN	65	63:37
3	5 mol% $[Pd(PPh_3)_4]$	$[D_7]$DMF	95	80:20
4	5 mol% $[Pd(PPh_3)_4]$	$[D_8]$THF	87	83:17
5	3 mol% $[Pd_2(dba)_3]$, 6 mol% dppe	$[D_8]$tol	75	70:30
6	3 mol% $[Pd_2(dba)_3]$, 6 mol% dppb	$[D_8]$tol	67	77:23
7	3 mol% $[Pd_2(dba)_3]$, 6 mol% *rac*-BINAP	$[D_8]$tol	77	70:30
8	**3 mol% $[Pd_2(dba)_3]$, 6 mol% Xantphos**	**$[D_8]$tol**	**99**	**94:6**
9	3 mol% $[Pd_2(dba)_3]$, 6 mol% Xantphos	$[D_7]$DMF	80	80:20
10	3 mol% $[Pd_2(dba)_3]$, 6 mol% dppf	$[D_8]$tol	75	72:28

[a] All reactions were carried out at 70 °C for 12 h, 0.1 mmol scale, 0.2 M. [b] dba = dibenzylideneacetone; dppe = 1,2-bis(diphenylphosphino)-ethane; dppb = 1,4-bis(diphenylphosphino)butane; BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; dppf = 1,1′-bis(diphenylphosphino)-ferrocene; tol = toluene. [c] Yields and product distributions were determined by ^{1}H NMR spectroscopy.

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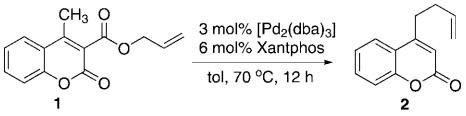
that 3 mol% $[Pd_2(dba)_3]$ in combination with 6 mol% Xantphos provided excellent yields of 4-butenylcoumarin (**2a**) when allowed to react with substrate **1a** in toluene at 70 °C.

Under the optimized reaction conditions, we explored the substrate scope for this decarboxylative allylation reaction (Table 2). A wide variety of 4-methyl-3-allylcoumarates with substitution on arene were synthesized and examined. Gratifyingly, it was found that a variety of aryl substitutions

Table 2: Migratory decarboxylative allylation.



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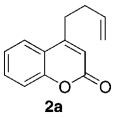
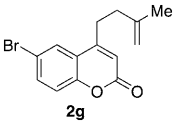
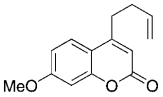
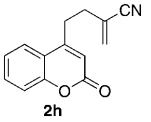
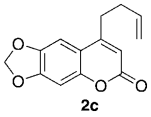
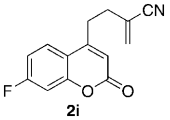
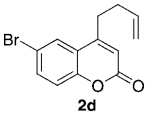
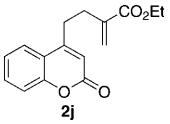
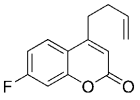
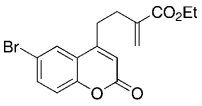
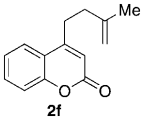
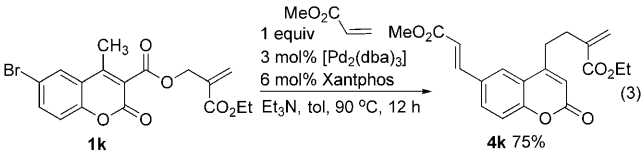
Product	Yield [%][a]	Product	Yield [%][a]
 **2a**	90	 **2g**	93
 **2b**	88	 **2h**	90
 **2c**	90	 **2i**	92
 **2d**	87	 **2j**	93
 **2e**	92	 **2k**	90
 **2f**	92		

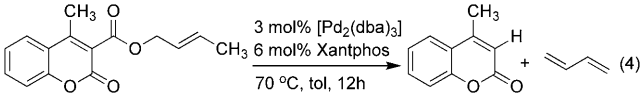
[a] Yields of isolated products for reactions performed at 0.2 M on a 0.5 mmol scale.

allow formation of coupling products in excellent yields, irrespective of the electronics. Even halogen substituents, such as Br, are compatible with our coupling conditions (**2d**, **2g**, **2k**, Table 2). Thus, one-pot decarboxylative allylation/cross-coupling reactions are feasible [Eq. (3)]. In addition to the couplings of unsubstituted allyl esters, a variety of substituted and functionalized allyl esters undergo coupling to provide products in excellent yields. However, one limitation of the reaction is that allyl esters that possess β-hydrogens preferentially form elimination products [Eq. (4)].

Since the successful substrates for the remote allylation were 4-methyl substituted, we became curious whether larger 4-alkyl groups would participate in migratory allylation as



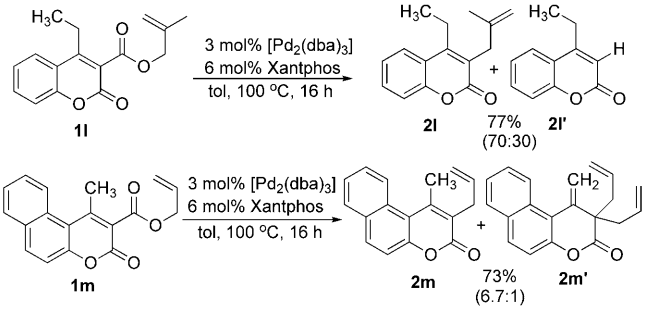
(3)



(4)

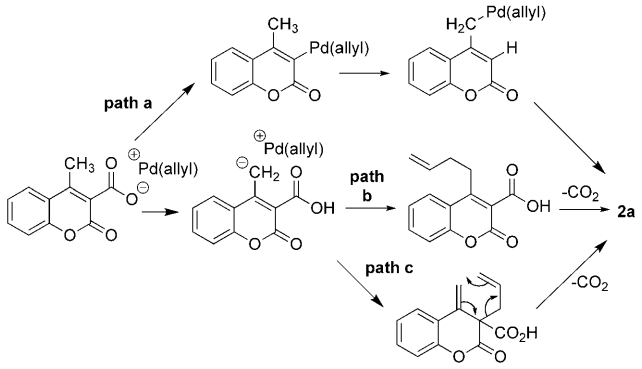
well. Toward this end, the 4-ethyl-substituted substrate **1l** was prepared and allowed to react under our standard reaction conditions. Interestingly, the substrate underwent typical site-specific allylation as previously reported.[6] Thus, it appears that sterics disfavor the mechanism by which the 4-alkyl group is allylated. Similarly, substrate **1m** did not undergo remote allylation of the methyl group, rather it underwent α-allylation to give (**2m**) along with the diallylation to give **2m′**.

At the outset, several mechanisms seemed reasonable for the formation of the remotely allylated coumarins such as **2a**. First, decarboxylative metalation could produce an aryl palladium species that is capable of undergoing a 1,3-migration (path a; Scheme 2).[11] Alternatively, the intermediate carboxylate may deprotonate the methyl group to generate a stabilized malonic acid dienolate. Such a proposal is reasonable given that the pK_a values of carboxylates (ca. 12 in DMSO) and malonates (ca. 14 in DMSO) are comparable.[12] Allylation and decarboxylation would then produce **2a**. Lastly, the observation of the diallylated product (**2m′**, Scheme 1) suggested that the allylation of the methyl group might be proceeding through an α-allylation/Cope rearrangement mechanism (path c, Scheme 2).[13]



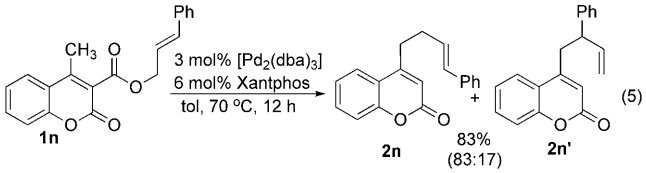
Scheme 1. Sterics inhibit migration.

The mechanism illustrated by path c (Scheme 2) is easily probed, since such a mechanism predicts that a substituted allyl ester will react to form the branched allylated product rather than the linear product.[5e,14] To test this, the coumaryl cinnamyl ester **1n** was treated with Pd catalyst [Eq. (5)]. The resulting product forms in high yield with a 83:17 linear/branched (*l*:*b*) ratio. The regioselective formation of the linear allylated product, **2n**, suggests that the methyl group is directly allylated and that α-allylation/Cope rearrangement is not the dominant mechanism for product formation. How-

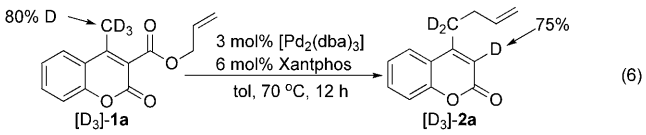


Scheme 2. α-Allylation versus γ-allylation.

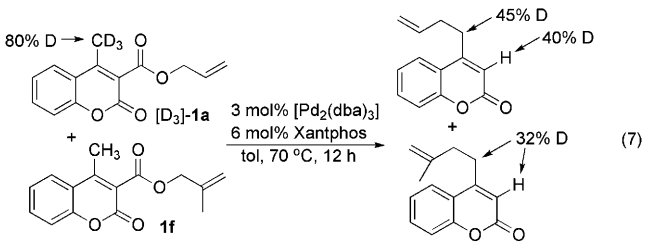
ever, most decarboxylative cinnamylations provide product with *l*:*b* ratios of >95:5,[2a,g,5f,h,6,15] so the relatively low selectivity in this case may indicate a minor contribution of the allylation/Cope rearrangement mechanism.



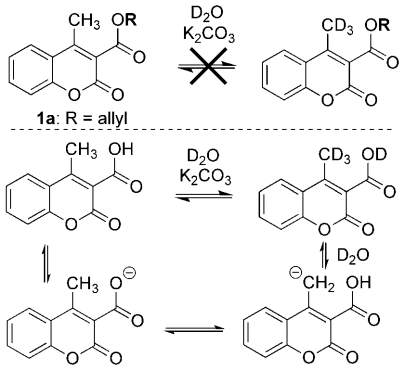
With the above information in hand, further mechanistic studies were necessary to refine our mechanistic hypothesis. To begin, a deuterium-labeling study was performed to determine the origin of proton that comes at the α-carbon after decarboxylation. Toward this end, [D_3]-**1a** was prepared and allowed to undergo decarboxylative coupling. The α-carbon of the resulting product was 75% deuterated at the α-position. Thus, deuterium is clearly transferred from the methyl group to the α-carbon.



Next, a crossover experiment showed extensive crossover between the deuterated reactant [D_3]-**1a** and a protiocoumarin [Eq. (7)].

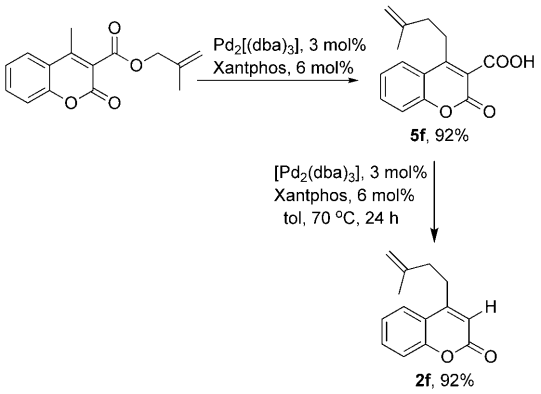


In addition to the observation of crossover, some mechanistic insight was obtained from the preparation of the requisite deuterated coumarin ([D_3]-**1a**). Specifically, it was observed that treatment of the allyl ester **1a** with K_2CO_3 and D_2O did not lead to any appreciable deuterium incorporation (Scheme 3). However, treatment of the carboxylic acid under the same conditions led to extensive deuterium incorporation. Thus, the carboxylate group is necessary to facilitate deprotonation of the 4-methyl coumarin.



Scheme 3. Carboxylate-assisted deuteration.

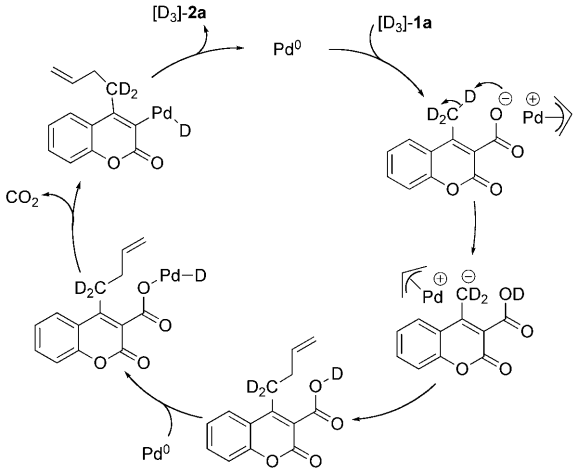
While the observations of extensive crossover and carboxylate-assisted deprotonation seemed to implicate a mechanism that follows path b, path a could not be ruled out based on these experiments alone. The mechanistic ambiguity was further clarified by a simple but crucial experiment. When a typical reaction was arrested after 2 h, the γ-allylated, α-coumaric acid **5f** was isolated in good yield. When the coumaric acid **5f** was resubjected to the reaction conditions, the decarboxylated γ-allylation product **2f** was obtained (Scheme 4).



Scheme 4. Isolation of an intermediate.

It is noteworthy that a Pd^{II} source, $Pd(OAc)_2$, failed to catalyze decarboxylation of **5f** under the reaction conditions.[2b,d,14] However, Pd^0 sources such as [$Pd(PPh_3)_4$] and [$Pd_2(dba)_3$]/Xantphos were effective catalysts for decarboxylation of **5f**. Thus, it appears that decarboxylation is catalyzed by Pd^0.

Combination of all of the mechanistic studies suggests the following mechanism for this unusual decarboxylative γ-allylation. First palladium undergoes oxidative addition to form a π-allyl palladium complex and the coumarin carboxylate counterion. Then 1,5-proton transfer occurs to generate a stabilized carbanion at the methyl terminus. Next, nucleophilic substitution of the π-allyl palladium complex forms the C–C bond. The C–C bond could form by nucleophilic attack on the allyl ligand from the stabilized carbanion (Scheme 5)



Scheme 5. Mechanistic pathway of γ-allylation.

or by reductive elimination from a bisallyl-like Pd complex.[16] We favor the former mechanism because enolate nucleophiles that are related to our coumarin nucleophiles are known to react by backside attack on Pd(π-allyl) cations.[17,18] Lastly, protonation of palladium results in a palladium carboxylate that can undergo decarboxylation followed by C–H bond forming reductive elimination (Scheme 5).[19]

In conclusion, we have observed remote decarboxylative allylation for the first time and developed a simple method for the γ-allylation of coumarins based on this finding. Mechanistic studies suggest that the remote allylation is made possible by a carboxylate-assisted deprotonation to generate the nucleophile prior to decarboxylation. After allylation, decarboxylation of the carboxylic acid is catalyzed by Pd^0, contrary to more commonly observed Pd^{II}-catalyzed decarboxylations.[2,5,13]

Experimental Section

General procedure for the palladium-catalyzed decarboxylative γ-allylation of 3-allylcoumarates: In an oven-dried Schlenk flask, **1a** (0.50 mmol) was dissolved in toluene (2.5 mL) under argon followed by the addition of $[Pd_2(dba)_3]$ (0.015 mmol, 3 mol%) and Xantphos (0.03 mmol, 6 mol%). The resulting reaction mixture was heated at 70°C for 12 h. The solution was then concentrated on a rotary evaporator and the residue was purified directly by flash chromatography on silica gel (EtOAc/hexane 20:80).

See the Supporting Information for full experimental procedures and ^1H NMR, ^{13}C NMR, and GC–MS data.

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