ORGANIC LETTERS

2013
Vol. 15, No. 14
3778–3781

Catalytic Decarboxylative Alkenylation of Enolates

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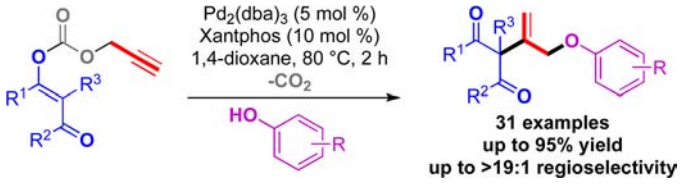
Received June 20, 2013

ABSTRACT



A palladium-catalyzed decarboxylative alkenylation of stabilized enolates has been developed, which gives rise to alkenylated dicarbonyl products from enol carbonates regioselectively with concomitant installation of a quaternary all-carbon center. The broad scope of the reaction has been demonstrated by successfully utilizing a range of enolates and external phenol nucleophiles.

Over the past decade, the transition-metal-catalyzed decarboxylative coupling of organic molecules has grown into a versatile synthetic tool, offering atom-economical and waste-minimized alternatives to conventional cross-coupling.[1] One practical approach to generating sterically congested sp^3 centers is the palladium-catalyzed intramolecular decarboxylative allylation of enolates (Scheme 1),[2] which proceeds via π-allylpalladium(II) enolate **2** under very mild and neutral conditions without the need for external base.[3] This pioneering work has resulted in the development of a number of elegant enantioselective approaches for the decarboxylative allylation of enolates,[4] generating an all-carbon quaternary stereogenic center. In contrast, the structurally similar *propargylic* counterparts **4** are known to provide η^3-π-allenylpalladium(II) intermediates **5** with palladium catalysis.[5] In particular, if the η^3-π-allenylpalladium(II) unit is unsymmetrical, enolate addition at either C-1 or C-3 in **5** can in principle take place, resulting in the formation of either propargylated or allenylated products **6** or **7**, respectively.[6]

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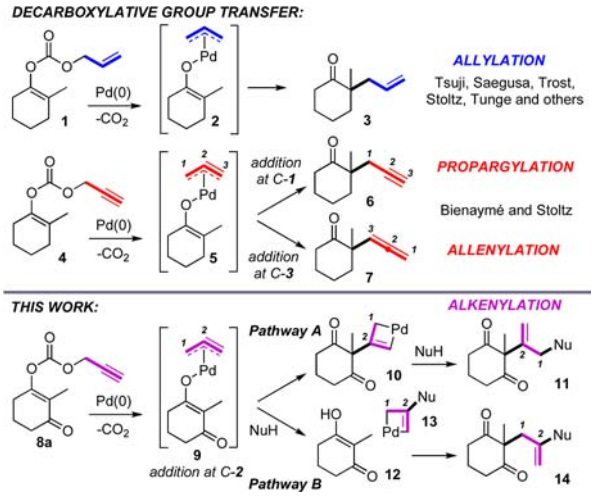
10.1021/ol401729m
Published on Web 07/08/2013

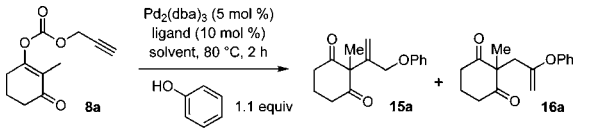
We postulated that, by utilizing diketone-derived enol carbonate **8a** and, therefore, making the enolate following decarboxylation softer (**9**), addition at the central C-2 position of the π-allenylpalladium(II) intermediate **9** by the enolate could take place[7,8] and furnish palladacyclobutene **10** in the first instance (pathway A). In the absence of acidic hydrogen atoms, reaction with an external nucleophile would then afford alkenylated diketone **11**. The proposed reaction was likely to pose selectivity challenges, whereby the order of addition of the enolate and the external nucleophile had been reversed, affording regioisomer **14** via palladacyclobutene **13** (pathway B). Herein, we report the first regioselective palladium-catalyzed decarboxylative alkenylation of stabilized enolates, which enables the concomitant installation of a quaternary all-carbon center in a single pot without the need for pre-functionalized coupling partners and/or a strong base for enolate generation.

Scheme 1. Decarboxylative Coupling Processes



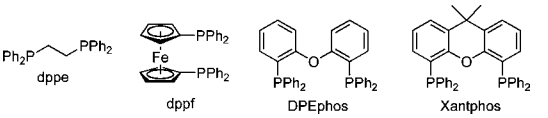
From the outset of this work, enol carbonate **8a** was used as the test substrate in combination with phenol as the external nucleophile (1.1 equiv) in our optimization studies (Table 1). It was found that the reaction with $Pd(PPh_3)_4$ as the catalyst in THF at 80 °C for 2 h did indeed result in decarboxylation and formation of a new C−C bond (entry 1), although the ratio of isomers **15a** and **16a** was in favor of the undesired isomer and the overall yield was moderate (no propargylated or allenylated products resulting from attack at either C-1 or C-3 were observed). With the exception of electron-poor phosphine ligands for palladium (entry 2), which halted the reaction altogether, the use of other standard phosphines, such as dppe, dppf, and DPEphos (entries 3−5), led to improved results (see the Supporting Information for full details). Finally, Xantphos as the ligand offered the best balance between ratio and yield (entry 6), and following a solvent screen (entries 7−10), 1,4-dioxane was settled upon as optimal, providing easily separable **15a** and **16a** in 77% yield and 3.6:1 ratio in favor of the desired alkenylated diketone **15a**.

Table 1. Optimization of Reaction Conditions[a]



entry	ligand	solvent	ratio (**15a**:**16a**)[b]	yield[c] (%)
1	$Pd(PPh_3)_4$[d]	THF	1:1.5	41
2	$P(C_6F_5)_3$[e]	THF		no reaction
3	dppe	THF	2.5:1	51
4	dppf	THF	1.1:1	79
5	DPEphos	THF	1.3:1	79
6	Xantphos	THF	1.6:1	72
7	Xantphos	CH_2Cl_2	1.7:1	87
8	Xantphos	CH_3CN	2.1:1	62
9	Xantphos	DMF	3.1:1	49
10	**Xantphos**	**1,4-dioxane**	**3.6:1**	**77**

[a] Substrate concentration of all reactions was 0.16 M wrt **8a**. [b] Ratio determined by ^{1}H NMR analysis of the crude product mixture. [c] Isolated and combined yield of **15a** and **16a** following column chromatography. [d] Used instead of $Pd_2(dba)_3$. [e] Reaction time was 16 h.

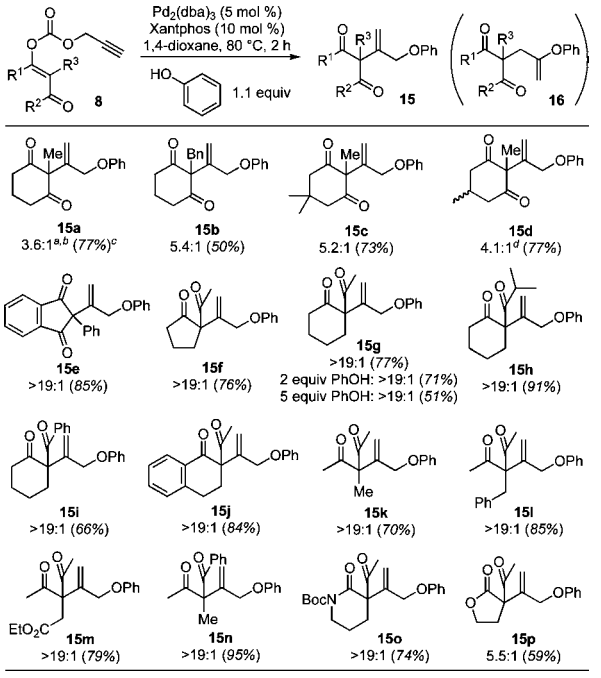


The scope of dicarbonyl-derived stabilized enolates in regioselective alkenylation was studied next (Scheme 2). It was found that six-membered diketones **15a**−**d**, bearing alkyl groups in the R^3 position, as well as ring substitution, were all formed in generally good yields and selectivity. It was then surprising to discover that the five-membered indandione **15e** was formed as a *single* isomer in excellent yield despite comparable acidity ($pK_a \sim 5$) to six-membered diketone examples **15a**−**d**. Remarkably, complete control of regioselectivity was also observed in the alkenylation of the more basic exocyclic diketone **15f**. This result is indeed worthy of attention given its close similarity in pK_a to phenol (both ∼9−10 in water). Concerning exocyclic six-membered diketones, cyclohexanone **15g** was formed as a single regioisomer, even in the presence of excess phenol. Similarly excellent yields and selectivity were obtained with cyclohexanones **15h**−**j**. Alongside the successful alkenylation of linear diketones **15k**−**n**, the reaction scope was also extended to heterocyclic systems, including lactam and lactone examples **15o** and **15p**, respectively, affording products in good yields and selectivity.

The generality of this method with a variety of phenols as the external nucleophile was probed next (Scheme 3). In this context, 2,5-dimethyl-substituted phenol, sterically demanding 2,6-diphenylphenol, as well as naphthol all afforded the desired products **17a**−**c** with > 19:1 selectivity and high efficiency.[9] Electron-rich methoxyphenols were

(9) X-ray data for **17a** has been deposited with the Cambridge Crystallographic Data Centre (CCDC 932185), which can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.

Scheme 2. Enolate Scope[a]

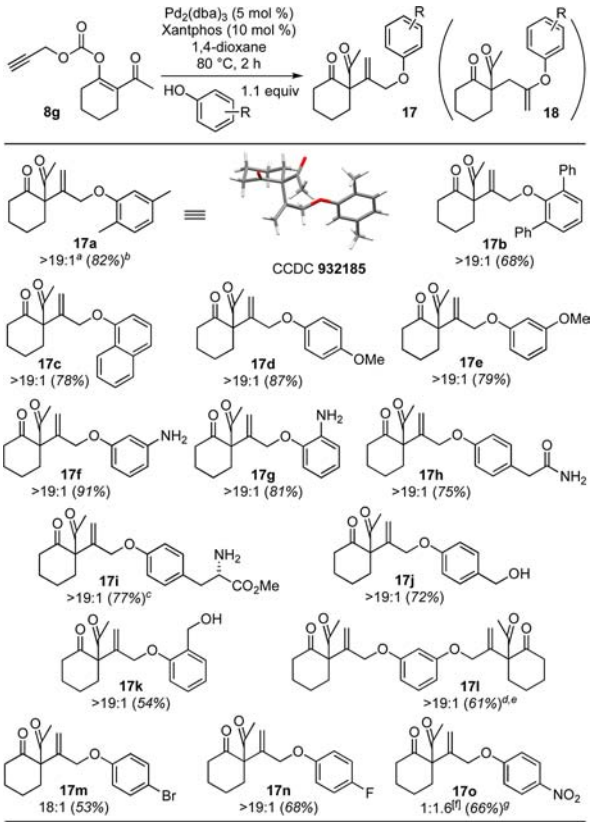


[a] Ratio of **15**:**16** was determined by ^{1}H NMR analysis of the crude product mixture. [b] Major isomer **15** shown. [c] Isolated and combined yield of **15** and **16** following column chromatography. [d] 1:1 dr.

also shown to afford the desired products **17d** and **17e** with equally good results. We had found that, unlike phenol, several other *N*- and *O*-based nucleophiles led to complex product mixtures or decomposition under the reaction conditions. We were thus intrigued to test whether other unprotected nucleophilic functionalities, appended to the phenol structure, would interfere with the desired mode of reactivity. In this context, anilines, amides, amines, and alcohols did not appear to impact the reaction, and the expected products **17f**–**k** were formed both chemo- and regioselectively without detriment to yield. Presumably, the low pK_a of phenol compared to the above functional groups is essential in facilitating the protonation of the palladacyclobutene intermediate of type **10**. Indeed, a second phenol hydroxy group in resorcinol was found to be reactive, resulting in the formation of dimer **17l** when two equivalents of the starting carbonate **8g** were used. We were also pleased to discover that 4-halophenols afforded products **17m** and **17n** as single isomers; however, use of the significantly more acidic 4-nitrophenol substrate resulted in product **17o** being formed with diminished selectivity.

In order to gain deeper insight into the mechanism of the reaction, deuterium-labeling studies were performed (Scheme 4). Subjection of [D]-**8g** to the reaction conditions resulted in deuterium incorporation at both the vinylic and allylic positions in [D]-**15g** in nearly equal amounts (A), lending support for the involvement of a symmetrical π-allylpalladium(II) intermediate. In the next experiment (B), reaction of equimolar amounts of carbonate **8g** and

Scheme 3. Phenol Scope[a]



[a] Ratio of **17**:**18** was determined by ^{1}H NMR analysis of the crude product mixture. [b] Isolated yield. [c] 1:1 dr. [d] 2 equiv of carbonate **8g** was used. [e] Single diastereoisomer. [f] Alkenylated isomer **17o** shown. [g] Isolated and combined yield of **17o** and **18o**.

deuterated diketone [D_3]-**19** afforded nondeuterated product **15g**. The lack of crossover indicates that the intermediate enolate is likely to be tightly associated with the palladium complex. This result was further corroborated by mixing carbonate [D]-**8g** and the nondeuterated isopropyl equivalent **8h** (C): only [D]-**15g** and nondeuterated **15h** were formed. This observation is in stark contrast to full enolate crossover detected in the decarboxylative allylation of simple ketone enolates.[4a] Finally, substrates [D]-**8g** and **8h** in the presence of 4-nitrophenol as the nucleophile (D), afforded the alkenylated methylketone product [D]-**17o** and nondeuterated isopropyl-containing product **17p**. In contrast, crossover had taken place in the formation of regioisomeric products **18o** and **18p**, which was each isolated as mixtures of labeled and nonlabeled material, suggesting dissociation of the enolate from the palladium.

Mechanistically (Scheme 5), starting with carbonate **8g**, oxidative addition and decarboxylation provide η^3-π-allenylpalladium(II) enolate **21**.[10] In light of the absence of enolate crossover in the formation of alkenylated

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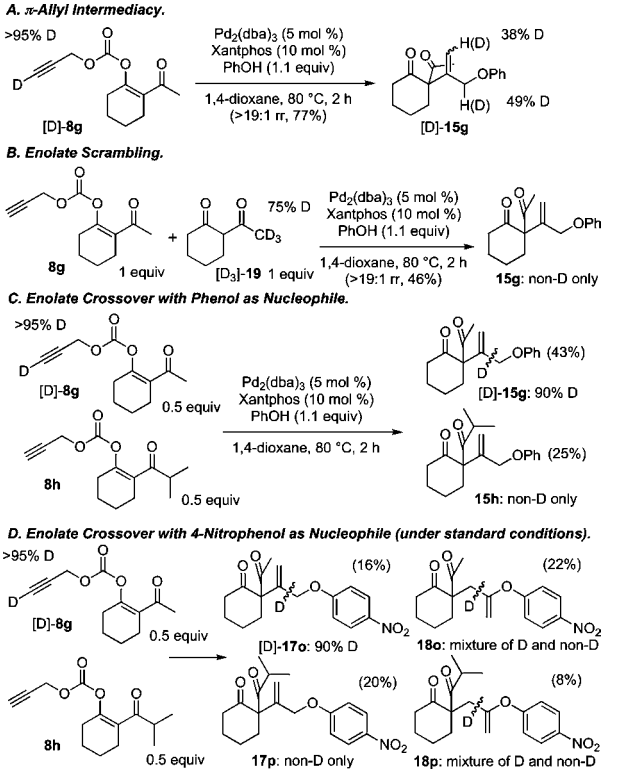
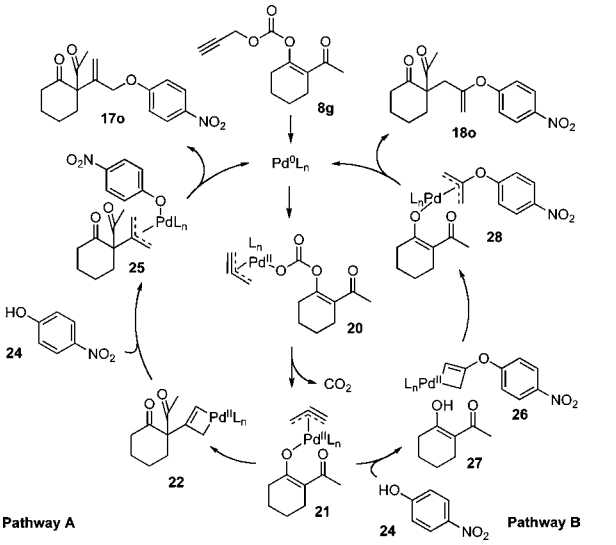
Scheme 4. Deuterium Labeling Studies



products (pathway A), addition of the enolate to the central carbon atom of the allenyl system in **21** is likely to proceed intramolecularly via inner-sphere attack. This observation is supported by DFT studies in the asymmetric allylation of ketone enolates[11] but contradicts the accepted external outer-sphere mode of addition of soft stabilized nucleophiles to η^3-π-allylpalladium(II) intermediates.[12] Following nucleophilic addition, transient palladacyclobutene complex **22** ensues,[13] and rapid protonation by 4-nitrophenol (**24**) affords the symmetrical π-allylpalladium(II) complex **25**. Finally, addition of the phenolate anion provides the alkenylated diketone **17o**. Although the examples we have studied favor pathway A, the reaction with 4-nitrophenol (**24**) also affords regioisomer **18o** (pathway B). It is plausible that the initial nucleophilic attack of η^3-π-allenylpalladium(II) intermediate **21** by phenol **24** furnishes palladacyclobutene **26** and enol **27**. However, in contrast to pathway A, significant crossover at this stage takes place, suggesting that palladacycle **26** and enol **27** and are no longer tightly associated. Finally, isomer **18o** is formed by protonation of **26** and subsequent addition of the enolate to the π-allylpalladium(II) motif in **28**.

Scheme 5. Mechanistic Rationale



In summary, a palladium-catalyzed decarboxylative alkenylation of stabilized enolates is reported which gives rise to alkenylated products from enol carbonates with generally excellent regiocontrol and concomitant installation of a quaternary all-carbon center. A broad range of enolates and external phenol nucleophiles can be readily used in the reaction and appropriate deuterium labeling studies have shed light on the mechanistic aspects of the reaction. The development of enantioselective variants of this process is underway.

Acknowledgment. We gratefully acknowledge the University of York (N.J.T. and V.F.), the EU (Erasmus Exchange Programme to S.P.S.), as well as the Nuffield Foundation and the Royal Society of Chemistry (Undergraduate Research Bursary to P.J.) for financial support. We are very grateful to Prof. R. J. K. Taylor (University of York) for the generous donation of chemicals and consumables as well as useful discussions. We also thank Dr. A. Whitwood (University of York) for X-ray crystallographic analysis and Mr. K. Heaton (University of York) for mass spectrometry analysis.

Supporting Information Available. Full experimental procedures, characterization data, HRMS, as well as ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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