

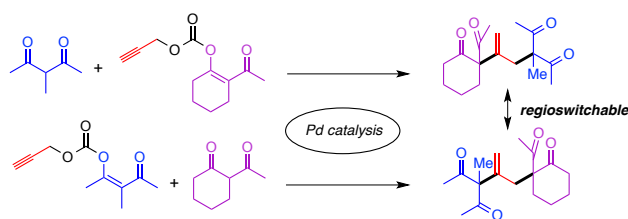
Regioswitchable Palladium-Catalyzed Decarboxylative Coupling of 1,3-Dicarbonyl Compounds

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Supporting Information Placeholder

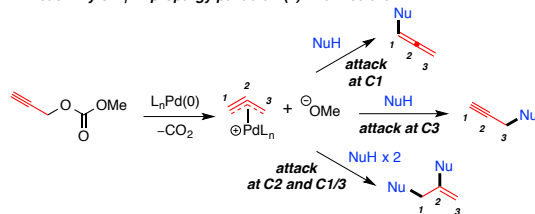


ABSTRACT: A palladium-catalyzed chemo- and regioselective coupling of 1,3-dicarbonyl compounds via an allylic linker has been developed. This reaction, which displays broad substrate scope, forms two C–C bonds and installs two all-carbon quaternary centers. The regioselectivity of the reaction can be predictably controlled by utilizing an enol carbonate of one of the coupling partners.

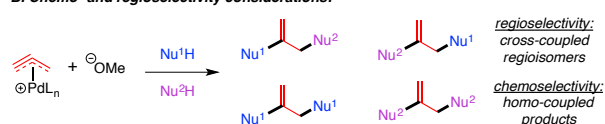
The palladium(0)-catalyzed alkylation reaction of carbon nucleophiles with allylic electrophiles has over the years matured into a powerful C–C bond-forming tool,¹ which enables the stereoselective introduction of congested all-carbon quaternary centers.² These processes typically make use of allylic acetates, carbonates or halides, which undergo oxidative addition to give η^3 - π -allylpalladium(II) intermediates. The analogous reaction of palladium(0) with propargylic electrophiles proceeds via η^3 - π -propargylpalladium(II) intermediates (A, Scheme 1),³ which exhibit three distinct modes of reactivity.⁴ Nucleophilic addition to one of the terminal carbon atoms results in either allenylation or propargylation processes.⁵ In addition, with stabilized anions as nucleophiles, η^3 - π -propargylpalladium(II) intermediates can undergo sequential double addition:⁶ first at the central carbon atom and subsequently at either one of the terminal carbon atoms.⁷ The synthetic utility of the latter reactivity mode becomes apparent if two *different* nucleophiles are coupled, rapidly generating complexity in a single operation (B, Scheme 1). The challenges associated with this process are the control of both chemoselectivity, whereby the formation of homocoupling products is avoided, and regioselectivity, whereby the order of addition of the nucleophiles is controlled. The associated selectivity issues are typically overcome by designing the transformation such that one of the nucleophilic addition steps is intramolecular.⁸ In contrast, the regioselective coupling of two different nucleophiles in an intermolecular sense is much more challenging.⁹

Scheme 1. Reactivity modes of propargylic compounds with nucleophiles

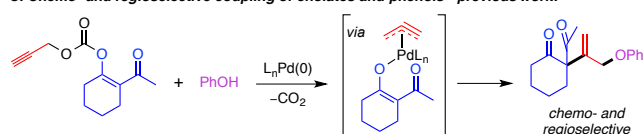
A. Reactivity of η^3 - π -propargylpalladium(II) intermediate:



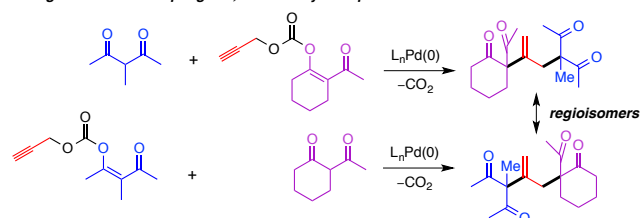
B. Chemo- and regioselectivity considerations:



C. Chemo- and regioselective coupling of enolates and phenols - previous work:



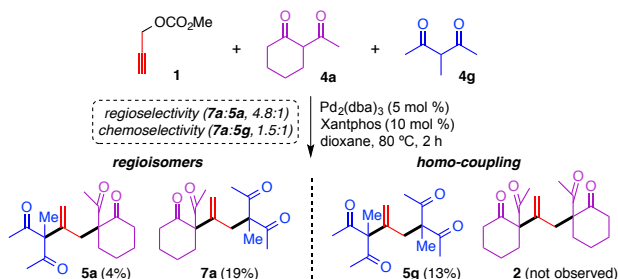
D. Regioswitchable coupling of 1,3-dicarbonyl compounds - this work:



Inspired by palladium-catalyzed decarboxylative allylic alkylation processes,¹⁰ which enable the regioselective formation of enolates under mild and neutral reaction conditions,¹¹ we have recently disclosed the first palladium-catalyzed chemo- and regioselective coupling of enolates

and phenols via an η^3 - π -propargylpalladium(II) intermediate (C, Scheme 1).¹² In this approach, the regioselectivity is governed by the tight association of the η^3 - π -propargylpalladium(II) intermediate with the enolate. Given the recent drive by the pharmaceutical industry for new methodologies which facilitate the synthesis of sp^3 -rich molecules,¹³ we envisaged that a similar strategy could facilitate the chemo- and regioselective coupling of two 1,3-dicarbonyl compounds, resulting in the formation of two C–C bonds and two quaternary all-carbon centers in a single operation (D, Scheme 1). In particular, we postulated that both regioisomers of the product could be predictably accessed by judiciously subjecting one of the coupling partners to the reaction as the enol carbonate. Herein, we report a regioswitchable palladium-catalyzed decarboxylative coupling reaction of 1,3-dicarbonyl compounds via an allylic linker, thus resulting in the formation of two new C–C bonds and the installation of two quaternary all-carbon centers.

Scheme 2. Selectivity issues in intermolecular coupling of carbon nucleophiles



At the outset, the intermolecular coupling reaction of two 1,3-diketone nucleophiles **4a** and **4g** in the presence of propargylic carbonate **1** in equimolar amounts was investigated (Scheme 2). Of the four possible products, three were obtained with moderate regioselectivity, low chemoselectivity and poor yield. Specifically, regioisomers **7a** and **5a** were obtained in a 4.8:1 ratio in 19% and 4% yield, respectively, in addition to significant quantities of undesired homocoupling product **5g**, which was formed in 13% yield. These results show that the direct coupling of two similar partners leads to significant homocoupling, whereas the sense of regioselectivity of heterocoupling is difficult to predict. In addition, this process does not allow for efficient access to both regioisomers. Therefore, we reasoned that the use of one of the coupling partners as the enol carbonate could bestow predictable regiocontrol and increased efficiency on the transformation.

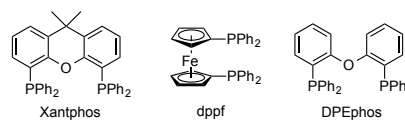
Pleasingly, the coupling of propargyl enol carbonate **3** with 1,3-diketone **4a** with Xantphos as the ligand for palladium in 1,4-dioxane as the solvent proceeded with complete regioselectivity and moderate chemoselectivity (Table 1, entry 1), predictably affording **5a** as the major product in good yield. A similar result was obtained with palladium tetrakis(triphenylphosphine) as the catalyst (entry 2). Finally, the best yield of product was obtained when using large bite-angle ligands, dppf and DPEphos (entries 3 and 4), with DPEphos providing product **5a** with complete regioselectivity, good chemoselectivity and excellent yield.

It is worthy of note that the reaction in other solvents, such as toluene, dichloromethane, DMF and acetonitrile, resulted in significant erosion in both selectivity and yield of **5a** (see Supporting Information).

Table 1. Ligand screen

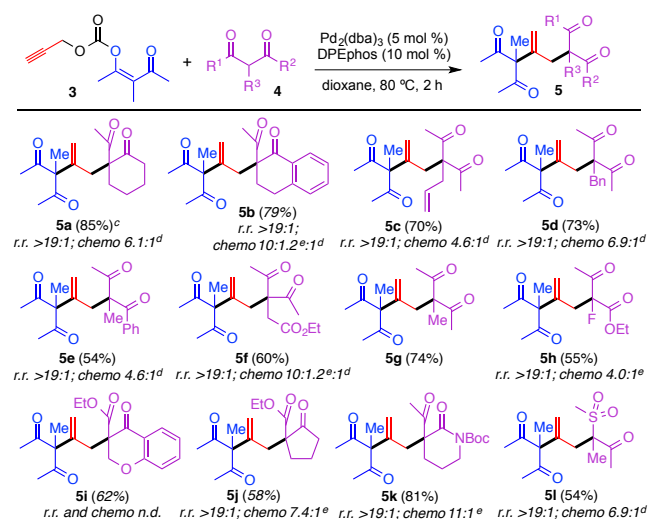
entry	ligand	selectivity ^a		yield (5a) (%) ^b
		regio (5a : 7a)	chemo (5a : 5g)	
1	Xantphos	>19:1	5.8:1	56
2	PPh ₃ ^c	>19:1	5.9:1	59
3	dppf	>19:1	6.4:1	73
4	DPEphos	>19:1	6.1:1	85

^aRatio determined by ¹H NMR analysis of the crude product mixture. ^bYield of isolated **5a**. ^c[Pd(PPh₃)₄] used in place of [Pd₂(dba)₃].



Having identified the optimal ligand for palladium, the reaction scope was investigated by testing the coupling of linear propargyl enol carbonate **3** with a range of 1,3-dicarbonyl compounds **4** (Scheme 3).

Scheme 3. 1,3-Dicarbonyl scope^{a,b,c}



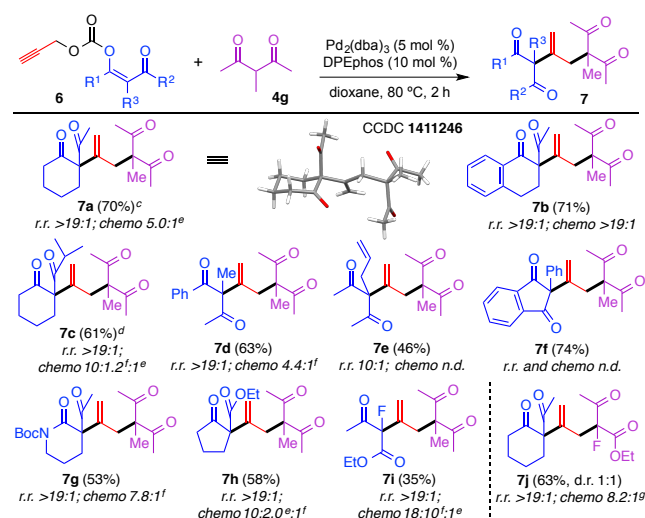
^aReaction stoichiometry: 0.24 mmol of **3** and **4**; concn 0.16 M. ^bRegioselectivity and chemoselectivity ratios determined by ¹H NMR analysis of the crude product mixture. ^cYield of isolated **5**. ^dRefers to homocoupling of **3**. ^eRefers to homocou-

pling of **4**. r.r. = regioselectivity; chemo = chemoselectivity; n.d. = not determined due to overlapping signals.

Specifically, all products were obtained with complete regioselectivity. Cyclohexanone-based 1,3-diketones as external coupling partners provided products **5a** and **5b** in high yields. Acyclic diketones also took part in regioselective coupling, giving rise to **5c-f** in good yields. Unsurprisingly, the use of 3-methyl-2,4-pentanedione (**4g**) as the nucleophile afforded homocoupled **5g**. β -Ketoesters as nucleophiles, both acyclic and cyclic, gave products **5h-j** in good yields. Finally, the incorporation of a β -ketolactam and β -ketosulfone was also successful, providing the respective coupled products **5k** and **5l**.

Because the enolate generated in situ following decarboxylation is regioselectively alkenylated and the externally added partner is allylated, we next investigated the scope of reversing the regioselectivity by reacting the propargyl enol carbonates of a range of 1,3-dicarbonyl compounds in the presence of 3-methyl-2,4-pentanedione (**4g**) as the external nucleophile (Scheme 4). In this context, both cyclic and acyclic 1,3-diketones led to the predictable formation of products **7a-f**, in which the original enol carbonate substrate had been alkenylated. Although the structure of the products is readily identifiable by long-range HMBC correlations, we obtained an X-ray crystal structure of **7a** to confirm the sense of regioselectivity of the reaction.¹⁴ In the case of a β -ketolactam and a β -ketoester, both were alkenylated successfully (**7g** and **7h**). However, the use of a carbonate of a fluorinated β -ketoester gave the corresponding product **7i** in low chemoselectivity and yield. Finally, when the coupling reaction leads to the installation of two stereogenic centers, such as in **7j**, the yield of product was high, but a mixture of diastereoisomers was obtained.

Scheme 4. Carbonate scope^{a,b,c}

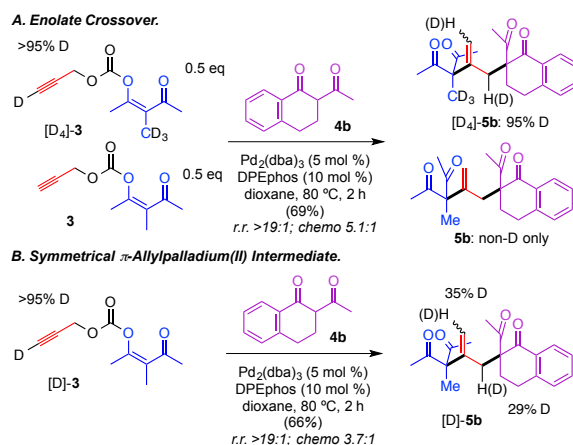


^aReaction stoichiometry: 0.24 mmol of **6** and **4g**; concn 0.16 M. ^bRegioselectivity and chemoselectivity ratios determined by ¹H NMR analysis of the crude product mixture. ^cYield of isolated **7**. ^dReaction was run for 4 h. ^eRefers to homocoupling of **4g**. ^fRefers to homocoupling of **6**. ^gRefers to homocoupling of β -ketoester **4h**. r.r. = regioselectivity; chemo =

chemoselectivity; d.r. = diastereoselectivity; n.d. = not determined due to overlapping signals.

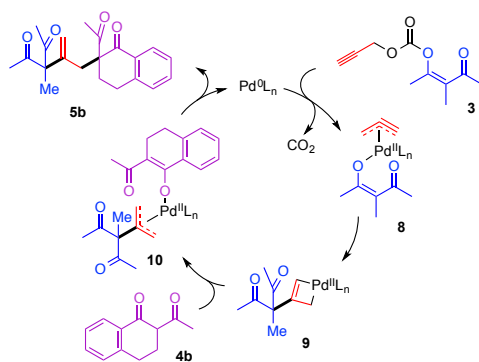
To rationalize the high regioselectivity of these reactions, an enolate cross-over experiment using equimolar amounts of $[\text{D}_4]$ -**3** and non-deuterated **3** in the presence of 1,3-diketone **4b** as the external nucleophile was performed (A, Scheme 5): the reaction afforded $[\text{D}_4]$ -**5b** and non-deuterated **5b** as the only products, as determined by mass spectrometry. The absence of enolate cross-over strongly suggests a tight association of the η^3 - π -propargylpalladium(II) complex with the enolate following decarboxylation. The intermediacy of an η^3 - π -allylpalladium(II) complex, which participates in the second nucleophilic addition, was supported by the scrambling of the deuterium label in $[\text{D}]$ -**5b**, when carbonate $[\text{D}]$ -**3** was coupled with 1,3-diketone **4b** (B, Scheme 5).

Scheme 5. Deuterium-labeling experiments



In light of the deuterium-labeling studies, we propose a reaction mechanism, in which the palladium(0) catalyst undergoes oxidative addition to carbonate **3** to give intermediate **8** following decarboxylation (Scheme 6). Because the palladium metal center is likely to be strongly associated with the enolate in **8** (see above, Scheme 5), we believe that the intramolecular inner-sphere mode of addition of the enolate to the central carbon atom of the η^3 - π -propargylpalladium(II) species in the next step determines the high regioselectivity of the reaction. However, this observation is at variance with the outer-sphere mechanism proposed for the addition of stabilized nucleophiles to η^3 - π -allylpalladium(II) intermediates.¹⁵ Although the involvement of a palladacyclobutene intermediate **9** following nucleophilic addition has been previously suggested,^{8b,8m,16} the lack of experimental evidence for its existence intimates that nucleophilic addition of the enolate in **8** is followed by immediate protonation by the external nucleophile **4b** in a synchronous manner to give **10**.¹⁷ In the final step, the resulting η^3 - π -allylpalladium(II) complex in **10** undergoes nucleophilic addition by the second enolate coupling partner, affording product **5b** with complete regiocontrol and regenerating the palladium(0) catalyst.

Scheme 6. Proposed catalytic cycle



In summary, a regio- and chemoselective decarboxylative palladium-catalyzed coupling of two carbon nucleophiles is disclosed, a transformation that generates two C–C bonds and two all-carbon quaternary centers in a single operation. The reaction is predictably regioswitchable, providing access to either of the two regioisomers of product depending on the choice of the propargyl enol carbonate substrate. We are now exploring avenues of accessing these products in an enantioselective manner.

ASSOCIATED CONTENT

Supporting Information

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

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