Palladium Catalysis

DOI: 10.1002/ange.201106619

Palladium-Catalyzed Divergent Reactions of α-Diazocarbonyl Compounds with Allylic Esters: Construction of Quaternary Carbon Centers**

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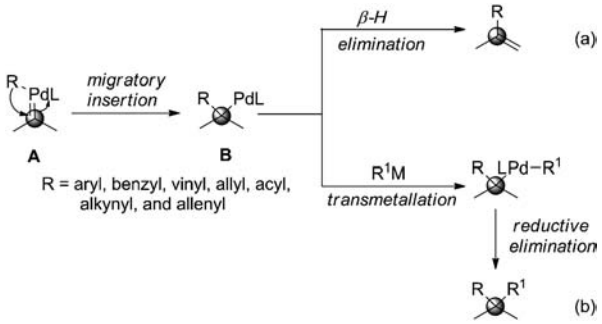
The efficient construction of quaternary carbon centers remains an important challenge for organic chemists.[1] Quaternary carbon centers are prevalent throughout most classes of naturally occurring, biologically active compounds and pharmaceutical agents.[2] Synthetic studies on these special units have been extensively carried out in recent years.[1] Although many methods are available for the synthesis of quaternary carbon centers,[1] it is highly desirable to develop alternative methods that could be advantageous in terms of functional-group tolerance, operational simplicity, and the use of readily available and stable starting materials.

Palladium is a versatile transition metal with intriguing reactivity with various functional groups.[3] In particular, palladium-catalyzed cross-couplings are nowadays recognized as one of the most powerful and reliable methods for the formation of C–C bonds.[4] Recently, palladium-catalyzed cross-coupling with diazo compounds as nucleophilic coupling partners has been introduced as a new method for the formation of C–C bonds.[5] The characteristic steps of the mechanism that differentiate it from traditional cross-couplings are shown in Scheme 1. Generation of a palladium carbene species (**A**), followed by the migratory insertion of an aryl,[6] benzyl,[7] vinyl,[8] allyl,[9] acyl,[10] alkynyl,[11] or allenyl[12] group, gives rise to the alkyl-palladium complex (**B**). In most cases, this complex undergoes β-hydride elimination to afford an olefin[5] (Scheme 1, pathway a). Alternatively, intermediate **B** can undergo transmetalation followed by reductive elimination to form two different C–C bonds at the same carbon atom in a single reaction[6g,13](Scheme 1, pathway b). However, this transmetalation step either involves the use of reagents that are toxic (tributylphenyltin)[13] and/or reagents that necessarily produce stoichiometric quantities of unwanted byproducts.[6g,13] Thus, the development of effective new methods for the cross-coupling of diazo compounds with organopalladium species generated from other precursors will facilitate the synthesis of more valuable compounds.



Scheme 1. Palladium-catalyzed cross-coupling reactions of diazo compounds.

Palladium-catalyzed decarboxylative coupling is a new strategy for the generation of organopalladium intermediates that utilizes readily available carboxylic acids[14,15] or esters[16] and produces CO_2 as its only byproduct. On the basis of our study of palladium-catalyzed migratory insertion reactions,[12] decarboxylative couplings,[12,17,18] and others,[19] it occurred to us that the transmetalation step could be circumvented by decarboxylative metalation of carboxylic acid derivatives (Scheme 2), where the palladium carbene species (**E**)[9] might be obtained through a palladium allyl acetylide (**D**).[19] Herein, we present the ready decarboxylation of propiolic acid derivative **1a** in the presence of catalytic palladium, and the coupling of palladium allyl acetylide (**D**) with methylphenyldiazoacetate (**2a**), in which an all-carbon quaternary center is generated to afford 1,5-enyne **3a** (Scheme 2). Five-membered ring frameworks, which widely occur in natural products and biologically active molecules, can be efficiently constructed by the transition-metal-catalyzed cycloisomerization of these products.[20]

To put the above hypothesis to the test, allylic alkynoate **1a** was treated with α-diazocarbonyl compound **2a** in the presence of $[Pd(PPh_3)_4]$. The desired product, 1,5-enyne **3a** was obtained in 43% yield (Table 1, entry 1). Encouraged by this initial result, we proceeded to optimize the reaction conditions (for details, see the Supporting Information). Changing the substrate ratio of **1a**/**2a** from 1.0:1.2 to 1.0:2.0 resulted in a lower yield (entry 2). Under these conditions, we detected the formation of a 1,4-enyne byproduct, which was attributed to the palladium-catalyzed, decarboxylative coupling of allylic alkynoate **1a**.[19] So, the yield of the expected

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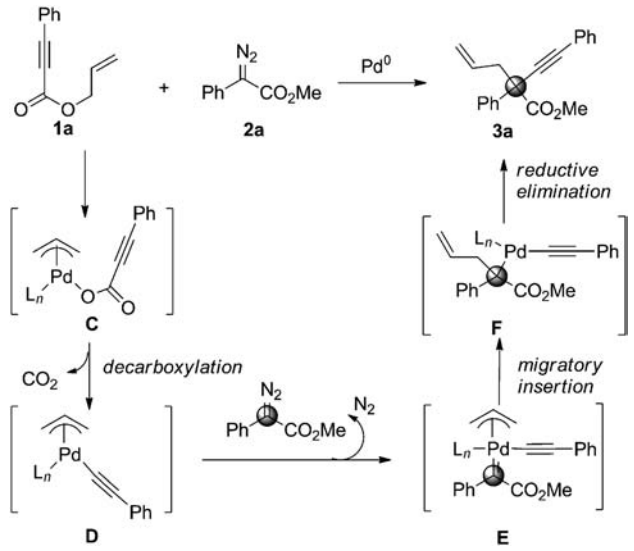
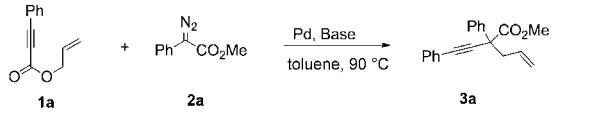
[**] We thank the National Science Foundation (NSF 21072080), the National Basic Research Program of China (973 Program) 2010CB833203, and the "111" program of the Ministry of Education for financial support. Xin-Hua Duan thanks the Fundamental Research Funds for the Central Universities for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201106619.



Scheme 2. Construction of quaternary carbon centers by decarboxylation and migratory insertion.

Table 1: Screening conditions for the palladium-catalyzed reaction of **1a** and **2a**.[a]

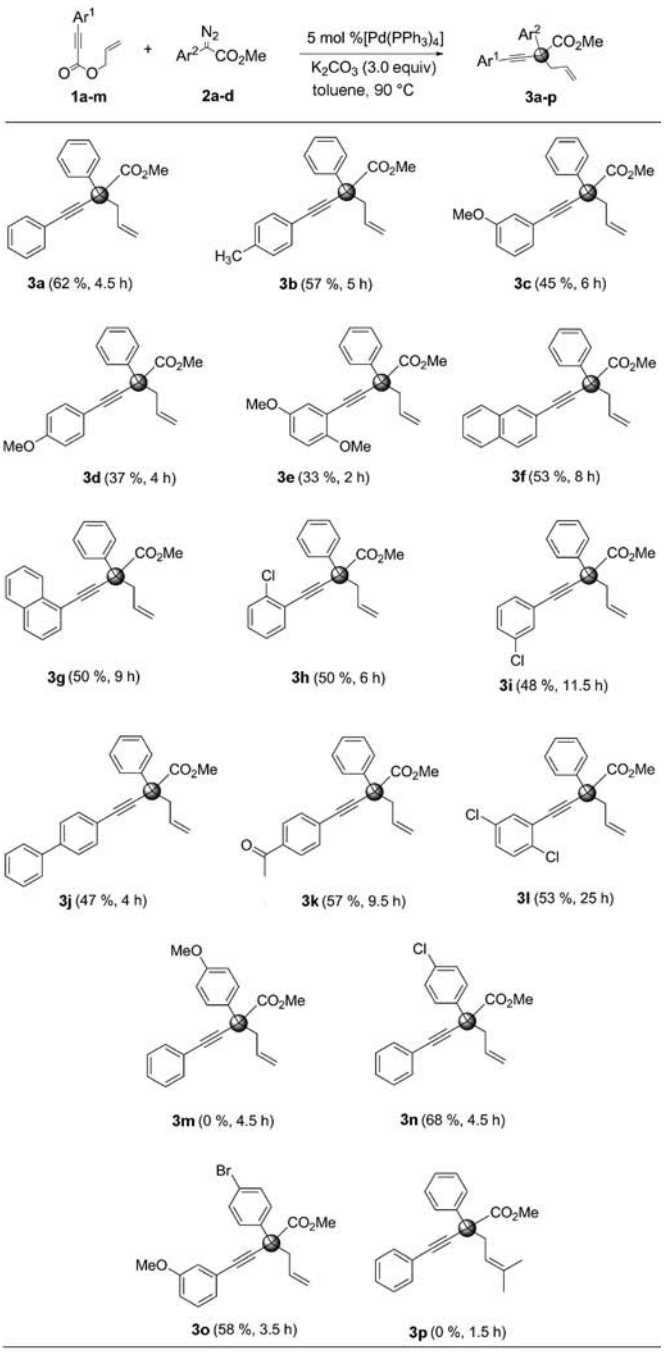


Entry	Pd catalysis [b]	Base [b]	*t* [h]	Yield [%][c]
1	$[Pd(PPh_3)_4]$ (5)	–	4.5	43
2[d]	$[Pd(PPh_3)_4]$ (5)	–	3.0	41
3[e]	$[Pd(PPh_3)_4]$ (5)	–	4.5	55
4[f]	$[Pd(PPh_3)_4]$ (5)	–	5.5	52
5[e]	**$[Pd(PPh_3)_4]$ (5)**	**K_2CO_3 (300)**	**4.5**	**62**

[a] Reaction conditions: **1a** (0.1 M, 1.0 equiv), **2a** (0.12 M, 1.2 equiv) in toluene, at 90 °C. [b] Number given in parenthesis is mol% used. [c] Yield of isolated product. [d] **1a**/**2a** = 1.0:2.0. [e] **1a**/**2a** = 2.0:1.0. [f] **1a**/**2a** = 3.0:1.0.

product was improved by simply changing the substrate ratio of **1a**/**2a** from 1.0:1.2 to 2.0:1.0 (entry 3). Finally, the yield could be further improved by adding K_2CO_3 (entry 5), which may suppress the formation of the protonation byproduct.[16]

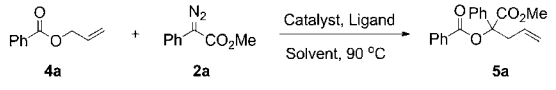
After having optimized the conditions, the scope and generality of the reaction was studied. Examples of the reactions between allylic alkynoates and α-diazocarbonyl compounds are shown in Scheme 3. Reaction of allylic alkynoates **1** and α-diazocarbonyl compounds **2** in the presence of a palladium catalyst affords the corresponding products **3** in moderate yields. The reaction was not significantly affected by the substituents on the aromatic ring of the allylic alkynoates. Both electron-donating and electron-withdrawing groups were tolerated under the reaction conditions (**3b–l**, Scheme 3), although the reaction rate decreased in the case of electron-withdrawing groups. The reaction was also not noticeably affected by the position of the substituents on the aromatic ring of the allylic alkynoates. However, substituents on the aromatic ring of the α-diazocarbonyl compounds did significantly affect the reaction. Electron-withdrawing groups were tolerated under the same reaction conditions (**3n** and **3o**, Scheme 3), but the expected product (**3m**) could not be obtained from α-diazocarbonyl compound **2b**, which bears an electron-donating group (Scheme 3). The reaction also did not give the corresponding product (**3p**) from 1,1-disubstituted allylic alkynoate **1m** (Scheme 3). This result indicates that steric hindrance significantly inhibits the reaction.



Scheme 3. Palladium-catalyzed reaction of allylic alkynoates **1** and α-diazocarbonyl compounds **2**. Reaction conditions: **1** (0.2 M, 2.0 equiv), **2** (0.1 M, 1.0 equiv), K_2CO_3 (0.3 M, 3.0 equiv), and $[Pd(PPh_3)_4]$ (5 mol%) in toluene at 90 °C. All yields refer to product isolated after chromatography on silica gel.

Inspired by these results, we wished to further investigate the scope of the reaction by using aromatic and benzylic acid derivatives, which could be synthesized from commercially available aromatic and benzylic acids through esterfication. However, the corresponding product 2,2-diphenylpent-4-enoic acid methyl ester could not be obtained by decarboxylation under the above optimized conditions (Table 2, entry 1). Surprisingly, a product with an O-substituted quaternary carbon center was obtained in 17% yield, a result that we attribute to direct reductive elimination instead of decarboxylation. Encouraged by this result, we further optimized these reaction conditions (for details, see the Supporting Information). To our delight, it was found that using $[Pd_2(dba)_3]$/P(2-furyl)$_3$ (dba = dibenzylideneacetone) could significantly improve the yield (entry 2); so, we proceeded to screen other reaction parameters with this complex. The reaction was found to be more efficient in CH_3CN (entry 3). When the ratio of substrates was examined, it was found that a **4a**/**2a** ratio of 1.0:1.4 afforded a higher yield of **5a** (entry 4). Finally, the yield could be further improved by increasing the loading of P(2-furyl)$_3$ to 20% (entry 6).

Table 2: Screening conditions for the palladium-catalyzed reaction of **4a** with **2a.**[a]

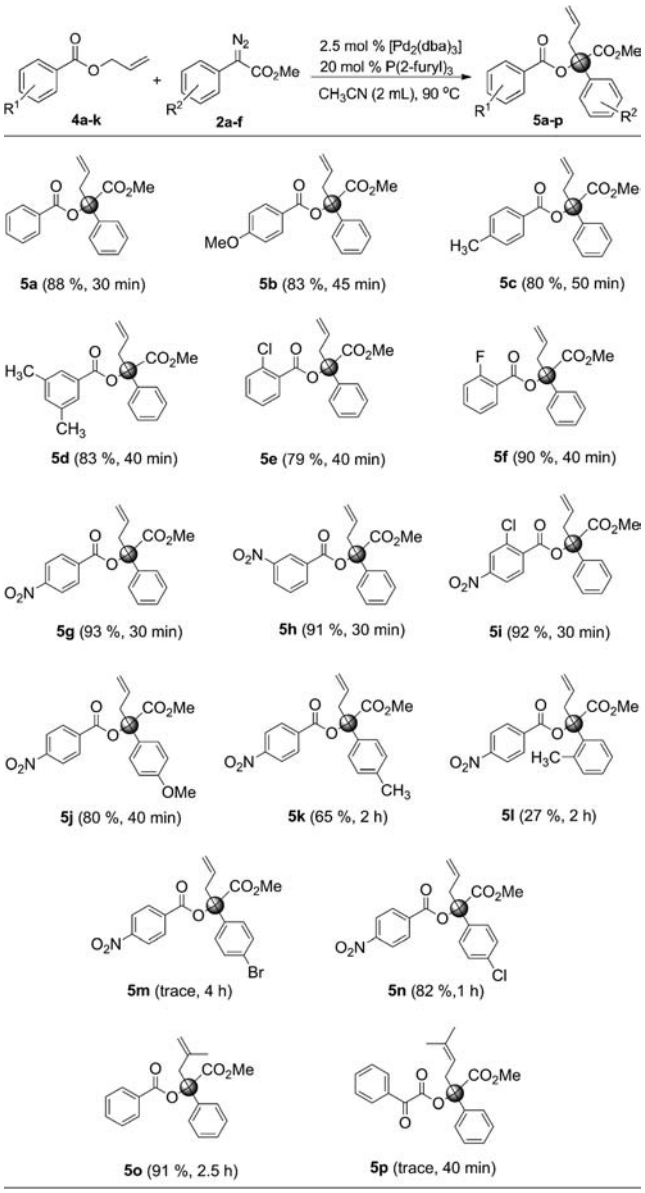


4a **2a** **5a**

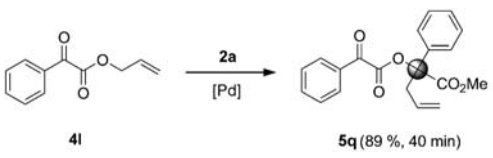
Entry	Catalyst [b]	Ligand [b]	Solvent	*t* [h]	Yield [%][c]
1	$[Pd(PPh_3)_4]$ (5)/K_2CO_3 (300)	–	toluene	4.0	17
2	$[Pd_2(dba)_3]$ (2.5)	P(2-furyl)$_3$ (10)	toluene	2.0	53
3	$[Pd_2(dba)_3]$ (2.5)	P(2-furyl)$_3$ (10)	CH_3CN	0.5	66
4[d]	$[Pd_2(dba)_3]$ (2.5)	P(2-furyl)$_3$ (10)	CH_3CN	0.5	70
5[e]	$[Pd_2(dba)_3]$ (2.5)	P(2-furyl)$_3$ (10)	CH_3CN	0.5	40
6[d]	**$[Pd_2(dba)_3]$ (2.5)**	**P(2-furyl)$_3$ (20)**	**CH_3CN**	**0.5**	**88**

[a] Reaction conditions: **4a** (0.1 M, 1.0 equiv), **2a** (0.12 M, 1.2 equiv), Pd (5 mol%), and the ligand (10 mol%) in solvent, at 90°C. [b] Number given in parenthesis is mol % used. [c] Yield of isolated product. [d] **4a**/**2a** = 1.0:1.4. [e] **1a**/**2a** = 1.0:1.8. dba = dibenzylideneacetone.

To demonstrate the generality of this reaction, a series of aromatic and benzylic acid derivatives **4** were reacted with α-diazocarbonyl compounds **2** under the optimized reaction conditions. As presented in Scheme 4, this reaction afforded the corresponding products in moderate to excellent yields. Both electron-rich and electron-poor aromatic acid derivatives can be used. The functional group tolerance of the process is remarkable: chloro, fluoro, and nitro groups on the aromatic ring of aromatic acid derivatives had no effect on the reaction (**5e**–**g**, Scheme 4). However, a bromo group on the aromatic ring of α-diazocarbonyl compounds was not tolerated (**5m**; Scheme 4). We were delighted to find that allyl cinnamate **4m** and allyl 2-phenylacetate **4n** were also suitable substrates for the reaction ($[Pd_2(dba)_3]$ (2.5%), P(2-furyl)$_3$ (20%), CH_3CN (2 mL), 90 °C), affording **5r** and **5s** in 86% and 57% yields, respectively [Eqs (2) and (3)]. However, decarboxylation did not occur when using allyl 2-oxo-2-phenylacetate **4l** [Eq (1)].[21] Finally, the molecular structure



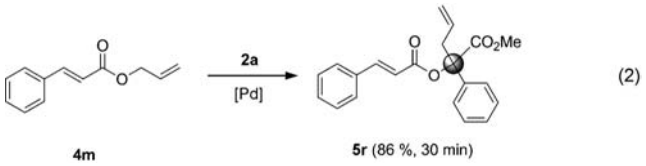
Scheme 4. Palladium-catalyzed reaction of aromatic acid derivatives **4** with α-diazocarbonyl compounds **2**. Reaction conditions: **4** (0.1 M, 1.0 equiv), **2** (0.14 M, 1.4 equiv), P(2-furyl)$_3$ (20 mol%), and $[Pd_2(dba)_3]$ (2.5 mol%) in CH_3CN at 90°C. All yields refer to isolated product after chromatography on silica gel. dba = dibenzylideneacetone.



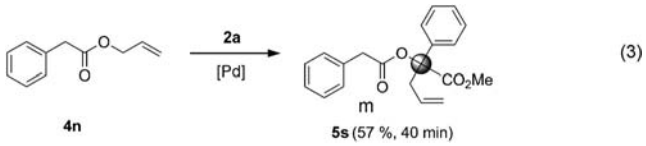
4l **5q** (89 %, 40 min) (1)

of **5n** was unambiguously confirmed through X-ray crystallography.[22]

Although the precise mechanism of our reaction remains unclear at this moment, we believe that the reaction may



(2)



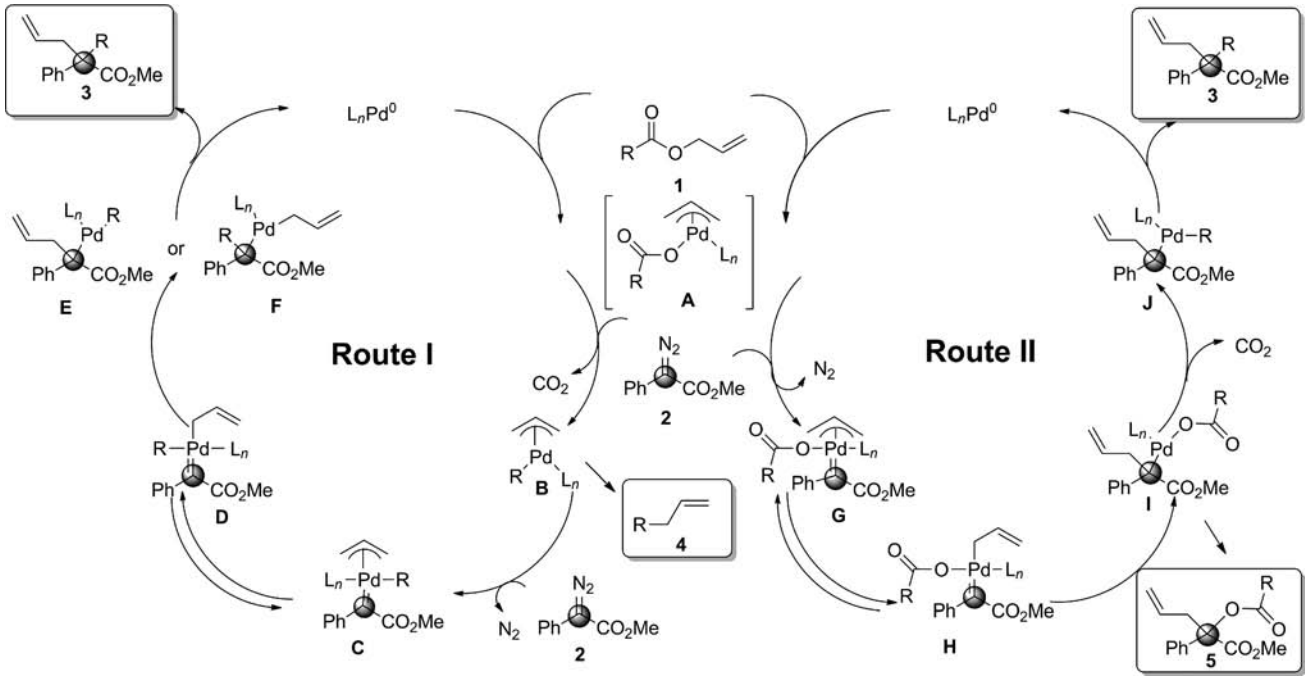
(3)

involve two different routes. As shown in Scheme 5, the palladium catalyst initially promotes the oxidative addition of allyl esters **1** to generate π-allyl palladium intermediate **A**.[23] In route I, π-allyl palladium carbene intermediate **C**, generated from the interaction of palladium intermediate **B**[19](obtained by decarboxylation of π-allyl palladium intermediate **A**) with α-diazocarbonyl compound **2**, isomerizes to σ-allyl palladium carbene intermediate **D**.[9] Then, migratory insertion of the allyl[9,24] group of **D** most likely occurs to afford the alkyl palladium intermediate **E**, although the alkyl palladium intermediate **F** may also be obtained from migratory insertion of the alkynyl[11] group of **D**. Subsequent reductive elimination of intermediate **E** or **F** then gives product **3**, with an all-carbon quaternary center, and regenerates the Pd^0 catalyst. It should be noted that palladium intermediate **B** might also be converted into product **4** through reductive elimination.[19] In route II, π-allyl palladium carbene intermediate **G** may be produced by the reaction of **A** with α-diazocarbonyl compound **2**.[9] Isomerization leads to σ-allyl palladium carbene intermediate **H**, from which migratory insertion of the allyl group occurs to afford the alkyl palladium intermediate **I**.[9] Decarboxylation of **I** gives palladium intermediate **J**,[19,25] which undergoes reductive elimination to afford product **3** and regenerate the Pd^0 catalyst. Product **5**, with an O-substituted quaternary carbon center, could also be obtained from **I** if it directly undergoes reductive elimination.

In conclusion, we have developed a new method for the formation of two different C–C bonds on the same carbon atom in a single reaction involving a palladium-catalyzed decarboxylation and migratory insertion process. This reaction provides a novel method for the generation of all-carbon quaternary centers. Furthermore, the palladium-catalyzed coupling of aromatic and benzylic acid derivatives with α-diazocarbonyl compounds to prepare aromatic and benzylic ester derivatives with an O-substituted quaternary carbon center in moderate to excellent yields was also developed. This new approach is complementary to prior methods for the construction of quaternary carbon centers. The reaction involves the use of stable, readily available starting materials and is operationally simple.

Experimental Section

General procedure for the preparation of **5**: Allyl ester **4** (0.20 mmol, 1.0 equiv), diazoester (**2a–f**) (0.28 mmol, 1.4 equiv), P(2-furyl)$_3$ (0.04 mmol, 20 mol%), and [Pd_2(dba)$_3$] (0.005 mmol, 2.5 mol%) were added to an oven-dried Schlenk tube under an argon atmosphere. Anhydrous CH_3CN (2.0 mL) was then introduced by syringe and the mixture was stirred at 90°C. When the reaction was



Scheme 5. Proposed reaction mechanism.

considered complete (determined by TLC analysis), the reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure and the corresponding product (**5**) was purified by chromatography on silica gel using a mixture of 40:1 petroleum ether/ethyl acetate as eluent.

Received: September 18, 2011
Published online: December 23, 2011

Keywords: cross-coupling · decarboxylation · homogeneous catalysis · palladium · quaternary carbon

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[22] The molecular structure of product **5n** was determined by means of X-ray crystallographic studies. CCDC 842399 (**5n**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[24] See the Supporting Information.

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