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Palladium-Catalyzed Decarboxylative Coupling of Allylic Alkynoates with Arynes

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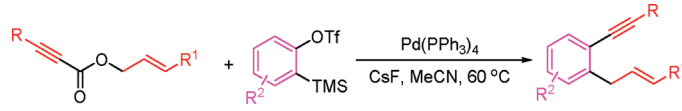
ABSTRACT



A novel and selective protocol for the synthesis of 1-allyl-2-ethynylbenzenes has been developed by palladium-catalyzed decarboxylative coupling of allylic alkynoates with arynes. This new route allows for both sp−sp^2 and sp^2−sp^3 couplings of allylic alkynoates with arynes in one pot involving a decarboxylation process.

The transition-metal-catalyzed decarboxylative coupling, such as the decarboxylative Heck coupling,[1] aldol additions,[2] decarboxylative enolate alkylation,[3] and decarboxylative cross-coupling reactions,[4,5] is a useful route for constructing the carbon−carbon bonds. Among the numerous transformations, palladium-catalyzed intramolecular decarboxylative couplings are particularly interesting because they often include the challenging sp^3 coupling partner via Pd−π-allyl intermediates.[5] Tunge and Rayabarapu, for instance, have reported a palladium-catalyzed intramolecular decarboxylative sp−sp^3 coupling of allylic alkynoates to synthesize 1,4-enynes.[5a] The protocol was conducted via two Pd−π-allyl intermediates **A** and **B**, followed by reductive elimina-

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(4) For selected papers on Pd-catalyzed intermolecular decarboxylative cross-coupling reactions, see: (a) Gooβen, L. J.; Gooβen, K.; Rodríguez, N.; Blanchot, M.; Linder, C.; Zimmermann, B. *Pure Appl. Chem.* **2008**, *80*, 1725. (b) Gooβen, L. J.; Rodríguez, N.; Gooβen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100. (c) Tatamidani, H.; Yokota, K.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.* **2004**, *69*, 5615. (d) Gooβen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662. (e) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350. (f) Maehara, A.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1259. (g) Nakano, M.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1851. (h) Wang, C.; Tunge, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 8118. (i) Becht, J.-M.; Drian, C. L. *Org. Lett.* **2008**, *10*, 3161. (k) Shintani, R.; Park, S.; Shirozu, F.; Murakami, M.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 16174. (l) Shang, R.; Fu, Y.; Li, J.-B.; Zhang, S.-L.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 5738−5739.

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10.1021/ol900643r CCC: $40.75
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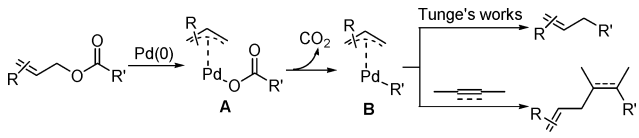
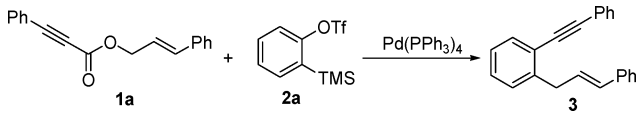
tion that affords the 1,4-enyne product (Scheme 1). Strategies in trapping the two active reaction partners from a decarboxylative process, π-allyl and R′ groups, by an unsaturated carbon−carbon bond are attractive[7,8] because the products are valuable synthetic intermediates.[6] It is well-known that an aryne having powerful electrophiles reacts with a nucleophile to afford an aryl carbanion that can be trapped with an electrophile.[7,8] This prompted us to attempt the decarboxylative coupling of allylic alkynoates with arynes using Pd catalysts.[8] Herein, we report a novel protocol for palladium-catalyzed decarboxylative couplings of allylic alkynoates with arynes to synthesize 1-allyl-2-ethynylbenzenes.

Scheme 1



The reaction of cinnamyl 3-phenylpropiolate (**1a**) with 2-(trimethylsilyl)phenyl triflate (**2a**), a benzyne precursor, was first investigated to optimize the reaction conditions (Table 1). After a series of trials, we found that the reaction could be conducted efficiently with $Pd(PPh_3)_4$ and CsF in MeCN at 60 °C to afford the best yield of the target product **3** (entry 4). Among the fluorides and solvents examined, CsF combined with MeCN was the most effective (entries 1−3 and 5). While 45% yield of **3** was obtained at room temperature in the presence of CsF and MeCN (entry 1), KF provided only 18% yield in THF (entry 2). A mixture of products was observed using TBAF (entry 3). We were pleased to find that the yield was enhanced to 72% at 60 °C (entry 4). Although the substrate **1a** could be consumed completely in 1 h at 100 °C, the yield was reduced to 66% (entry 6). Finally, the effect of Pd catalysts was investigated (entries 4 and 7−9). The results demonstrated that both $Pd(OAc)_2$ and $Pd(OAc)_2/PPh_3$ were inferior to $Pd(PPh_3)_4$, and the reaction could not proceed without Pd catalysts.

Table 1. Screening Optimal Conditions[a]



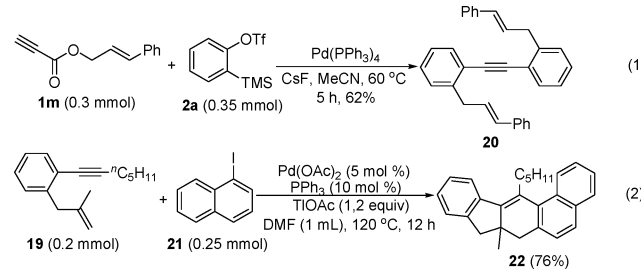
entry	[Pd]	fluoride	solvent	temp (°C)	t (h)	yield (%)[b]
1	$Pd(PPh_3)_4$	CsF	MeCN	25	5	45
2[c]	$Pd(PPh_3)_4$	KF	THF	25	6	18
3	$Pd(PPh_3)_4$	n-Bu_4NF	MeCN	25	6	mixture
4	$Pd(PPh_3)_4$	CsF	MeCN	60	5	72
5	$Pd(PPh_3)_4$	CsF	toluene	60	5	38
6	$Pd(PPh_3)_4$	CsF	MeCN	100	1	66
7	$Pd(OAc)_2$	CsF	MeCN	60	5	45
8[d]	$Pd(OAc)_2$	CsF	MeCN	60	5	63
9	—	CsF	MeCN	60	5	0

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.25 mmol), $Pd(PPh_3)_4$ (5 mol %), base (2 equiv), and solvent (2 mL). [b] Isolated yield. Both the substrates **1a** and **2a** were consumed completely in the indicated time. [c] 18-Crown-6 (2 equiv) was added. [d] PPh_3 (10 mol %) was added.

The scope was investigated under the standard conditions, and the results are summarized in Table 2.[9] A set of arynes **2b**−**2e** reacted with propiolate **1a**, $Pd(PPh_3)_4$ and CsF were first examined (entries 1−4). Arynes **2b** and **2c**, bearing alkyl groups on the aryl moiety, provided the target products in moderate yields (entries 1 and 2), but benzyne **2d** with two fluoro groups reduced the yield (entry 3). A moderate yield was still achieved from the reaction of 2-(trimethylsilyl)naphthalen-1-yl trifluoromethanesulfonate (**2e**) with alkynoate **1a** (entry 4). The standard conditions are also compatible with both terminal and alkyl-substituted olefins (entries 5−9). Terminal olefin **1b**, for instance, afforded the product **8** in 51% yield (entry 5), and internal olefin **1f** gave an 82% yield (entry 9). Substituents at the terminal alkynoate moiety, including aryl, H, and alkyl, were perfectly tolerated except for the p-FC_6H_4 group. Both electron-rich aryl propiolate **1g** and heteroaryl propiolate **1i** were treated with benzynes **2a** or **2b** in good yields (entries 10, 12, and 13), whereas electron-deficient aryl propiolate **1h** gave only 38% yield (entry 11). The reactions between alkyl alkynoates **1j**−**1l** and benzyne **2a**, respectively, were also successful in moderate yields (entries 14−16).

Interestingly, cinnamyl propiolate **1m**, a terminal alkyne, underwent the dual decarboxylative couplings to offer the product **20** in 62% yield (eq 1 in Scheme 2). We also tested the product **19** as a synthetic intermediate in the synthesis of a polyaryl compound (eq 2). In the presence of $Pd(OAc)_2$, PPh_3, and TlOAc, **19** was treated with iodide **21** smoothly to afford the product **22** in 76% yield.[6c,8a]

Scheme 2

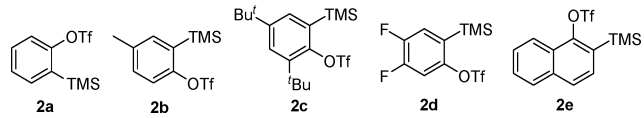


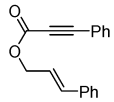
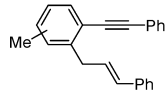
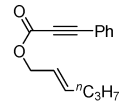
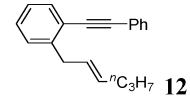
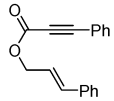
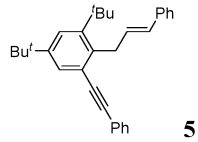
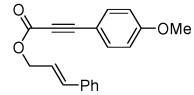
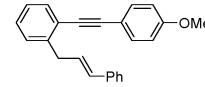
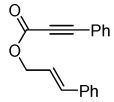
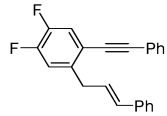
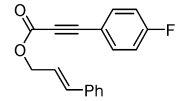
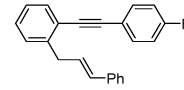
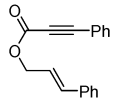
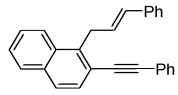
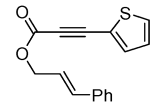
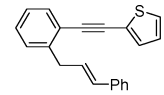
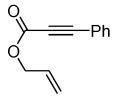
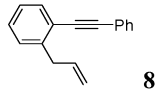
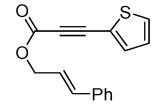
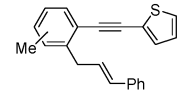
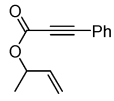
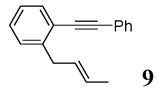
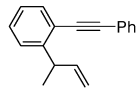
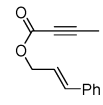
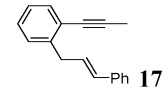
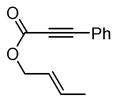
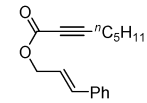
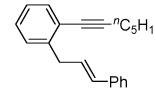
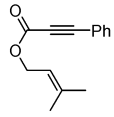
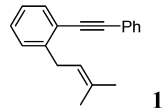
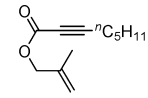
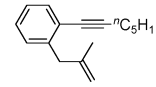
Possible mechanisms were proposed as outlined in Scheme 3.[4,5,7,8] Reaction of Pd(0) with allylic alkynoate **1** affords intermediate **C**, followed by (i) decarboxylation that gives

(6) For selected papers, see: (a) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (b) Fairamb, I. J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1048. (c) Brown, S.; Clarkson, S.; Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 157.

(7) For selected reviews, see: (a) Kessar, S. V. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, p 483. (b) Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579. (c) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701.

Table 2. Palladium-Catalyzed Decarboxylative Couplings of Allylic Alkynoates (**1**) with Arynes (**2**)[a]



entry	substrate **1**	**2**	product	yield (%)[b]	entry	substrate **1**	**2**	product	yield (%)[b]
1[c]	 **1a**	**2b**	 **4**	60% (6 h)	9[h]	 **1f**	**2a**	 **12**	82 (5 h)
2[d]	 **1a**	**2c**	 **5**	62% (6 h)	10	 **1g**	**2a**	 **13**	92% (6 h)
3	 **1a**	**2d**	 **6**	22 (7 h)	11	 **1h**	**2a**	 **14**	38% (6 h)
4[e]	 **1a**	**2e**	 **7**	46 (3 h)	12	 **1i**	**2a**	 **15**	88% (5 h)
5	 **1b**	**2a**	 **8**	51 (6 h)	13[i]	 **1i**	**2b**	 **16**	59% (6 h)
6[f]	 **1c**	**2a**	 **9** and  **10**	78 (5 h)	14	 **1j**	**2a**	 **17**	55% (7 h)
7[g]	 **1d**	**2a**	**9** and **10**	66 (5 h)	15	 **1k**	**2a**	 **18**	51% (6 h)
8	 **1e**	**2a**	 **11**	53 (5 h)	16	 **1l**	**2a**	 **19**	65% (5 h)

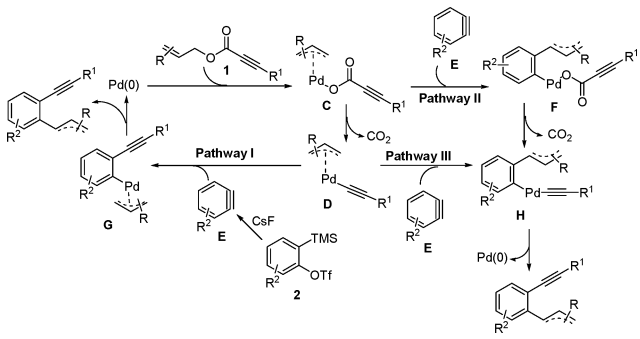
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.25 mmol), $Pd(PPh_3)_4$ (5 mol %), CsF (2 equiv), and MeCN (2 mL) at 60 °C. [b] Isolated yield. The reaction time is given in the parentheses, and ratios of the products were determined by ^{1}H NMR and HMPC spectra. [c] 1-((*E*)-3-(5-Methyl-2-(2-phenylethynyl)-phenyl)prop-1-enyl)benzene/1-cinnamyl-4-methyl-2-(2-phenylethynyl)benzene = 1:1. [d] 1,5-Di-*tert*-butyl-2-cinnamyl-3-(2-phenylethynyl)benzene/1,5-di-*tert*-butyl-3-cinnamyl-2-(2-phenylethynyl)benzene = 1.8:1. [e] 1-Cinnamyl-2-(2-phenylethynyl)naphthalene/2-cinnamyl-1-(2-phenylethynyl)naphthalene = 3:1. [f] **9**/**10** = 3.2:1. [g] **9**/**10** = 2:1. [h] 1-((*E*)-Hex-2-enyl)-2-(2-phenylethynyl)benzene/1-(hex-1-en-3-yl)-2-(2-phenylethynyl)benzene = 2.7:1. [i] 2-(2-(2-Cinnamyl-4-methyl-phenyl)ethynyl)thiophene/2-(2-(2-cinnamyl-5-methylphenyl)ethynyl)thiophene = 1:1.

intermediate **D**[5] or (ii) interception by aryne **E**, which from the reaction of **2** with CsF in situ forms an aryl−Pd−carboxylate **F**.[4l] Intermediate **D** undergoes the addition with aryne **E** to yield intermediate **G** or intermediate **H**. Another route to intermediate **H** is decarboxylation of intermediate **F**. Reductive elimination of intermediates **G** or **H** affords the product and regenerates the active Pd(0) species. The Pd−π-allyl intermediate **G** in Pathway I is supported by the observed regiochemistry of the products (entries 6, 7, and 9 in Table 2). However, we can not rule out the Pathways II and III. The steric hindrance of substituents on the allyl

(8) For papers on capturing the Pd−π-allyl intermediates, which is generated from the reaction of Pd, allyls, and alkynes, to synthesize 1-allyl-2-ethynylbenzenes by a three-component coupling process including arynes, see: (a) Jeganmohn, M.; Chen, C.-H. *Org. Lett.* **2004**, *6*, 2821. (b) Xie, C.; Liu, L.; Zhang, Y.; Xu, P. *Org. Lett.* **2008**, *10*, 2393. (c) Bhuvaneswari, S.; Jeganmohan, M.; Yang, M. C.; Cheng, C. H. *Chem. Commun.* **2008**, 2158. (d) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2009**, *48*, 391.

(9) The selectivities were determined according to ^{1}H NMR and C−H COSY (HSQC and HMBC) spectra of the product **5** (see Supporting Information).

Scheme 3. Working Mechanisms



moiety favors the selectivity of sp^3-sp^2 coupling toward the 1-position of the π-allyl moiety in intermediate **G**.

The reason for the product **20** may be that a homocoupling of the terminal alkyne process has taken place under the present conditions. Study of the true mechanism is in progress.

In summary, we have disclosed arynes as compatible electrophiles for intercepting Pd(0)-catalyzed decarboxylative allylations. This work is the first to demonstrate that a nonenolate *C*-centered anionic nucleophile, specifically an alkyne anion, can be generated and intercepted by an alternative electrophile (aryne) prior to allylation via the transient Pd(II)−allyl intermediate. Most importantly, this new route allows for both $sp-sp^2$ and sp^2-sp^3 couplings of allylic alkynoates with arynes in one pot involving a decarboxylation process. Work to extend the reaction and study the detailed mechanism is currently underway.

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Supporting Information Available: Analytical data and spectra (^1H and ^{13}C NMR) for all the products; typical procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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