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Palladium-Catalyzed Synthesis of Conjugated Allenynes via Decarboxylative Coupling

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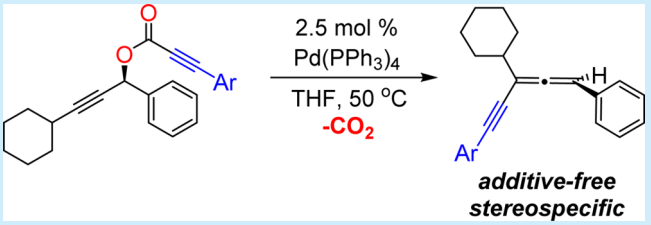
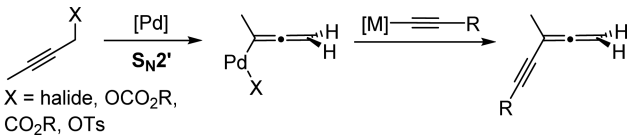
Supporting Information

ABSTRACT: A new strategy to access conjugated allenynes via a decarboxylative coupling of propargyl esters of propiolates has been developed. In this process, allenyl-palladium intermediates are coupled with acetylides that are generated *in situ* to form the conjugated allenynes. Finally, the coupling is demonstrated to be highly stereospecific, providing a route to enantioenriched allenes.



Allenes, when appropriately functionalized, are important synthetic targets due to their presence in both natural products and biologically active compounds,[1] as well as their utility as uniquely reactive intermediates.[2] While there are a myriad of ways to synthesize allenes,[1,3] cross-coupling of propargyl or allenyl substrates with organometallics remains a common method to make conjugated allenynes (Scheme 1).[4]

Scheme 1. Palladium-Catalyzed Allenyne Synthesis



The palladium-catalyzed cross-coupling protocols, while powerful, have inherent issues related to the required use of preformed organometallics and/or stoichiometric amounts of base and metal salts.

An early example of palladium-catalyzed cross-coupling of a propargyl bromide with a stoichiometric amount of zinc acetylide to form a conjugated allenyne was reported by Vermeer.[5] Later, Linstrumelle and Jeffery-Luong synthesized allenynes via cross-coupling of allenyl bromides and copper acetylides under Sonogashira conditions.[4a] While this method utilized catalytic amounts of copper to achieve transmetalation, the reaction still required the use of basic diethylamine as the solvent. Tsuji further developed the Sonogashira cross-coupling by employing propargyl carbonates as the electrophilic partner; however, superstoichiometric salt additives as well as diethylamine cosolvent were required for a clean, high yielding reaction.[4b,c] Guegnot and Linstrumelle also demonstrated the need for salt additives (3 equiv of $ZnCl_2$) when propargyl acetates were utilized in the coupling.[4d] We envisioned that the use of palladium-catalyzed decarboxylative coupling of propargyl esters would allow the synthesis of conjugated allenynes under base-free conditions without the need for stoichiometric organometallics or metal salt additives. The use of decarboxylation to generate acetylide intermediates should, in principle, allow this sp–sp^2 coupling, producing only CO_2 as a byproduct.[6]

Decarboxylative coupling has gained significant attention as a method for the formation of carbon–carbon bonds.[7] Since the development of decarboxylative allylation by Tsuji[8] and Saegusa,[9] palladium-catalyzed decarboxylative coupling has been broadly applied to both allylic and benzylic electrophiles.[6b,d,10] Comparatively, propargyl electrophiles have received far less attention.[11−13] This may be due to the higher degree of difficulty in achieving chemo- and regioselectivity.[11b] Previous efforts to develop palladium-catalyzed decarboxylative coupling of propargyl electrophiles by Bienyamé[12] and later Stoltz[13] employed enolates as the nucleophiles; however, both are extremely limited in scope and exhibit different regioselectivities (Scheme 2). The method described herein aims to use acetylide nucleophiles which would significantly expand the scope of these decarboxylative reactions.

Our initial studies focused on the palladium(0)-catalyzed decarboxylative coupling of butynyl phenylpropiolate **1a** to form allenyne **2a**. A brief screening of solvents revealed to our delight that the reaction proceeds cleanly when catalyzed by $Pd(PPh_3)_4$ in a variety of solvents (Table 1, entries 1–3, 5), though the reaction time is decreased in more polar solvents. Furthermore, it was determined that the amount of palladium could be reduced to 5 mol % without any detriment to the yield (Table 1, entry 4).

Though palladium tetrakis(triphenylphosphine) was shown to be a competent catalyst for the coupling, a ligand screening was performed in order to probe the regioselectivity of the reaction; it has previously been shown that ligand choice can influence the regioselectivity of couplings with propargyl electrophiles.[14] In all cases the coupling proved to be

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Scheme 2. Decarboxylative Coupling with Propargyl Electrophiles

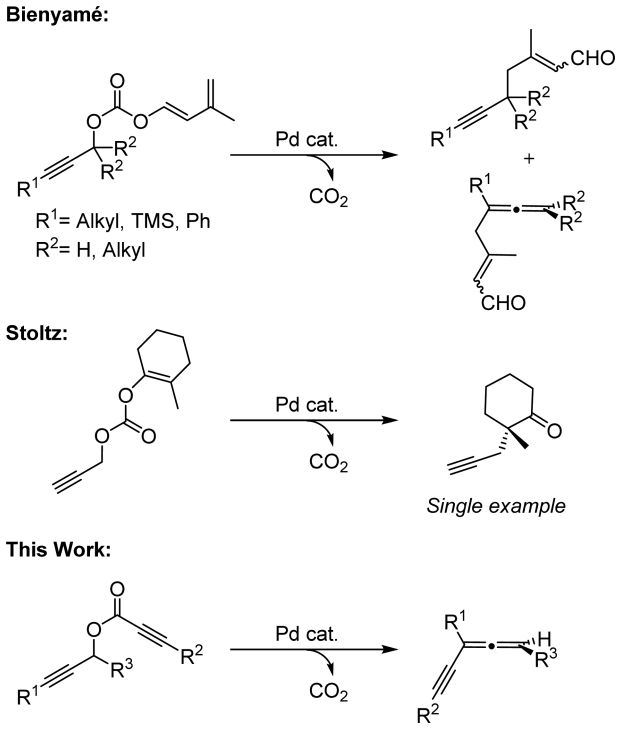
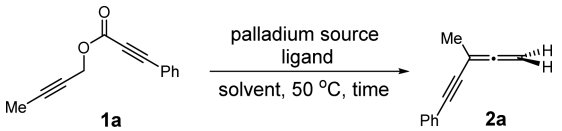


Table 1. Optimization of Reaction Conditions



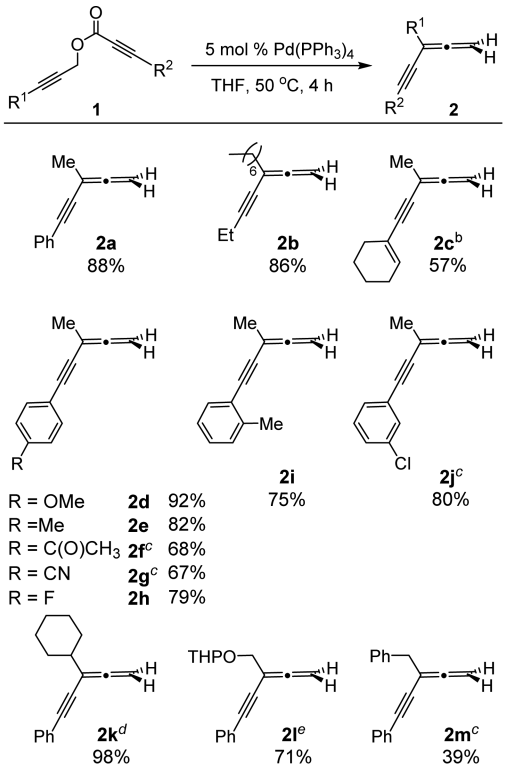
entry	Pd source	ligand	solvent	time (h)	conv (%)[a]	yield (%)[a]
1	$Pd(PPh_3)_4$ 10 mol %	none	DMSO-d_6	2	100	17
2	$Pd(PPh_3)_4$ 10 mol %	none	toluene-d_8	4	100	80
3	$Pd(PPh_3)_4$ 10 mol %	none	CD_3CN	2	100	78
4	$Pd(PPh_3)_4$ 5 mol %	none	CD_3CN	3	100	77
5	**$Pd(PPh_3)_4$ 5 mol %**	**none**	**THF**	**4**	**100**	**88[b]**
6	$Pd_2(dba)_3$ 5 mol %	none	CD_3CN	4	0	0
7	$Pd_2(dba)_3$ 5 mol %	PPh_3 20 mol %	CD_3CN	4.5	100	76
8	$Pd_2(dba)_3$ 5 mol %	Xphos 20 mol %	CD_3CN	2	100	62
9	$Pd_2(dba)_3$ 5 mol %	P^nBu_3 10 mol %	CD_3CN	22	0	0
10	$Pd_2(dba)_3$ 5 mol %	rac-binap 10 mol %	CD_3CN	15	16	7
11	$Pd_2(dba)_3$ 5 mol %	dppb 10 mol %	CD_3CN	6	12	11
12	$Pd_2(dba)_3$ 5 mol %	dppf 10 mol %	CD_3CN	23	100	13

[a]Conversion of starting material **1a** and yield of **2a** as determined by ^1H NMR spectroscopy with 1,4 dioxane as internal standard. [b]Isolated yield.

completely selective for the allenyne regioisomer, as no change in regioselectivity was observed. However, it was found that the reaction was more successful with monodentate aryl phosphine ligands (Table 1, entries 7–8) than with trialkyl phosphine (Table 1 entry 9) or bidentate ligands (Table 1, entries 10–12). Overall, $Pd(PPh_3)_4$ was determined to be the most ideal catalyst system.

With the optimized conditions in hand, the substrate scope of the reaction was explored. A variety of propargyl esters were synthesized via the coupling of readily available propargyl alcohols and propiolic acids. Treatment of primary propargyl esters under the standard conditions lead to the formation of disubstituted allenynes in moderate to good yields (Scheme 3).

Scheme 3. Disubstituted Allene Synthesis[a]



[a]Yield of isolated product. All products were stored under argon at ca. −15 °C upon isolation. [b]4.5 h. [c]18 h. [d]5 h [e]60 °C for 5 min then cooled to 50 °C for 18 h.

The coupling tolerated aromatic, alkyl, and vinyl propiolates (**2a–c**). Electron-rich substituents at the *para* position of the phenylpropiolate (**2d,e**) provided the allene in high yield, whereas electron-poor substituents (**2f,g**) lead to decreased yields and longer reaction times. Additionally, the reaction was tolerant of halogen substituents at various positions on the phenyl ring, (**2h,j**) as well as an *o*-methyl substituent (**2i**). Further, the terminal position of the propargyl ester tolerated methyl, long-chain, and cyclic alkyl groups (**2a**, **2b**, **2k**) as well as protected propargyl alcohols (**2l**). Unfortunately benzyl substitution at the propargyl terminus was not as well tolerated (**2m**), giving the allene in only 39% yield.

To further expand the scope of the reaction we then explored the coupling utilizing secondary propargyl esters to synthesize trisubstituted allenynes (Scheme 4). Unfortunately, initial efforts into the synthesis of trisubstituted allenynes proved to be unsuccessful, as when the coupling of hexynyl phenylpropiolate (**3a**) was attempted, only 27% of the desired

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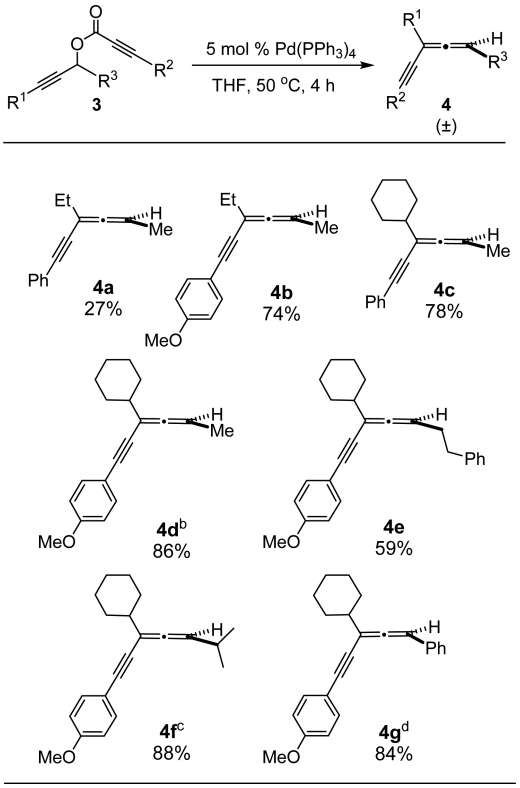
Scheme 4. Trisubstituted Allene Synthesis[a]

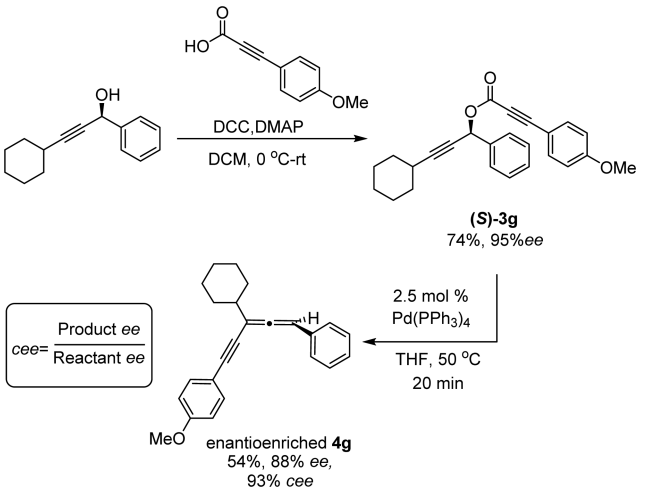


[a]Yield of isolated product. All products were stored under argon at ca. −15 °C upon isolation. [b]6 h. [c]18 h [d]0.5 h

allenyne (**4a**) was isolated. Reasoning that the low yield of product may be the result of volatility of the allene, we chose to make modification to the starting ester. To our delight, when the *p*-OMe phenylpropiolate was employed as the nucleophile, the coupling proceeded with a satisfactory 74% yield. Additionally, increasing the size at the propargyl terminus of the ester with a cyclohexyl group (**3c**) allowed for the isolation of the desired allenyne (**4c**) in high yield. Combining the two previous modifications of the diyne starting material (**3d**) lead to a further increase in the yield (**4d**). Additionally, other alkyl groups were tolerated at the secondary position (**4e,f**), as well as an aromatic group (**4g**); however, the bulky isopropyl group required a longer reaction time (18 h), while the aryl group accelerated the reaction.

Finally, it has been observed that palladium addition to propargyl electrophiles occurs in an *anti*-S_N2' fashion.[15] With this knowledge, we hypothesized that the reported decarboxylative coupling could occur stereospecifically.[4e] To test this, we first synthesized the enantioenriched propargyl ester (*S*)-**3g** in 95% *ee*, from the corresponding propargyl alcohol.[16] Disappointingly, attempting the stereospecific coupling under the previously optimized conditions led to the isolation of the nearly racemic **4g**. The palladium-catalyzed racemization of allenes has previously been observed.[17] With that in mind, we decreased the catalyst loading by half, as well as limited the reaction time to 20 min. Indeed, these conditions allowed for the stereospecific coupling to occur, yielding the enantioenriched allenyne in 88% *ee* with 93% conservation of enantiomeric excess (cee) (Scheme 5). While the absolute stereochemistry for the product was not determined, analogy to known processes suggest that the process will occur with inversion of stereochemistry.[4e,h]

Scheme 5. Stereospecific Decarboxylative Coupling



In conclusion, we have developed a decarboxylative coupling that forms conjugated allenynes. To our knowledge, this is the first example of a stereospecific palladium-catalyzed decarboxylative coupling involving propargyl electrophiles. The coupling is a more waste-free alternative to previous methods used to synthesize similar conjugated allenes, as CO_2 is the only stoichiometric byproduct.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01751.

Experimental procedures, ^1H, ^{13}C, NMR spectra, HPLC, and characterization data of all novel products (PDF)

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Notes

The authors declare no competing financial interest.

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