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Palladium-Catalyzed Bisdiene Carbocyclizations: A Facile [3 + 2] Cycloaddition Reaction Mode

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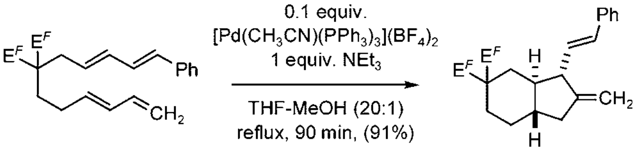
ABSTRACT

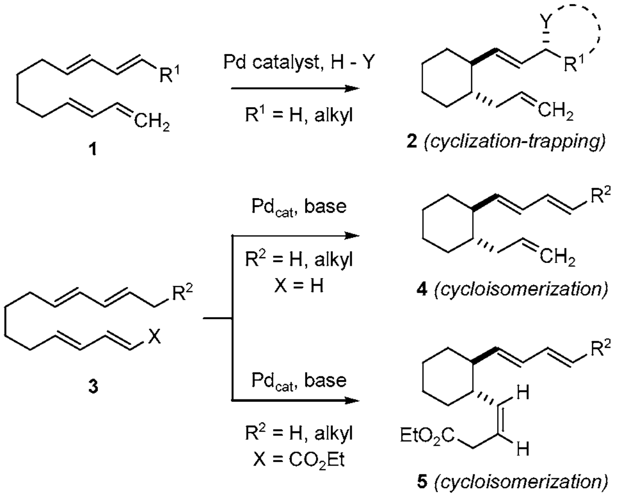


In contrast to alkyl-substituted bisdienes, aryl-substituted substrates undergo surprisingly facile palladium-catalyzed carbocyclization via a novel [3 + 2] cycloaddition mode.

A variety of polyunsaturated substrates undergo efficient transition metal-catalyzed carbon−carbon bond formation via the direct metal-mediated coupling between π-systems (e.g., coupling between combinations of carbonyl, alkene, alkyne, and diene functionalities). Such carbocyclizations typically enable the rapid increase in structural complexity from relatively simple precursors and define bond constructions and synthetic transformations that are difficult to effect via classical chemistry.[1−3] Palladium complexes are among the important catalysts in this regard.[4,5] A key challenge to developing such reactions is controlling the reaction mode.

We are interested in the palladium-catalyzed reactions of 1,3-dienes[6] and, in particular, the carbocyclization reactions of substrates containing two 1,3-diene subunits (i.e., bisdiene substrates). Wender has elegantly exploited the [4 + 4] cycloaddition mode of bisdienes via their nickel-catalyzed reaction.[7] Under palladium-catalysis, we find that several alternative reaction modes are possible. In the presence of a pronucleophile (H−Y), bisdienes represented by general structure **1** typically undergo cyclization−trapping to generate functionalized five- and six-membered ring systems as illustrated by **2** (Scheme 1).[8] The trapping reagent can be

Scheme 1. Palladium-Catalyzed Reaction Modes of Bisdienes



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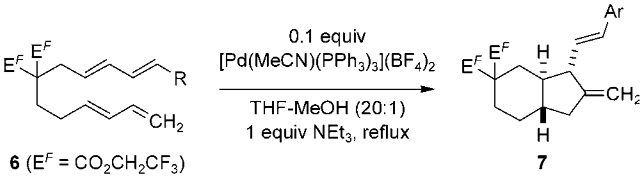
part of the bisdiene, too, thereby generating bicyclic ring systems via cascade cyclization.[9] In the absence of a pronucleophile, bisdienes represented by **3** (X = H) undergo palladium-catalyzed cycloisomerization to yield cyclized enedienes such as **4**.[10] Substituents can strongly influence the reaction mode. For example, bisdienes wherein one of the diene subunits bears an electron-withdrawing group (e.g., **3** (X = CO_2Et)) undergo palladium-catalyzed cycloisomerization via a different mode to afford products bearing a *(Z)*-β,γ-unsaturated ester side chain (i.e., **5**).[11]

Herein we report another striking substituent effect, one that defines a new reaction mode for palladium-catalyzed carbocyclizations of bisdienes, a formal [3 + 2] cycloaddition mode. Bisdienes **6a**–**d** contain an aryl substituent on one of the 1,3-diene subunits. We had expected these to undergo palladium-catalyzed cyclization–trapping; instead, the bicyclic product **7** is isolated in good to excellent yield (Table 1). For example, using $[Pd(CH_3CN)(PPh_3)_3](BF_4)_2$[12] as the catalyst precursor, the phenyl-substituted bisdiene **6a** affords cycloadduct **7a** in 91% yield. In contrast, the alkyl-substituted bisdiene **6e** affords the enediene cycloisomerization product related to **4** (80%) under these conditions.[10]

Table 1. [3 + 2] Cycloadditions of Aryl-Substituted Bisdienes



6 ($E^F = CO_2CH_2CF_3$)

7

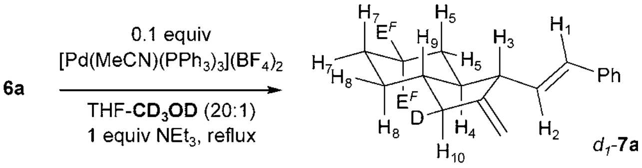
entry	6	R	time (h)	**7** (%)
1	**a**	$-C_6H_5$	1.5	91
2	**b**	$-C_6H_4CO_2CH_3$	1	71
3	**c**	$-C_6H_4OCH_3$	2.25	83
4	**d**	2-furanyl	4	52
5	**e**	$-CH_2CH_3$	6	0[a]

[a] Enediene cycloisomerization product isolated in 80% yield; see structure **4** in Scheme 1.

Cyclization substrates **6a**–**e** are readily prepared via the alkylation chemistry of bis(trifluoroethyl) malonates.[13,14] The aryl-substituted bisdienes are consumed relatively rapidly compared to other bisdiene substrates. Furthermore, a comparison of the reaction times required for complete consumption of bisdienes **6a**–**c** suggests that the presence of an electron-withdrawing substituent increases the reaction rate somewhat, while an electron-donating substituent decreases it. The results of a direct competition experiment support that conclusion. Monitoring the reaction of an equimolar mixture of **6b** and **6c** confirms that **6b** is consumed 2–3 times faster than **6c**. The electron-rich furanyl-substituted substrate **6d** is consumed even more slowly.

Several attempts to grow X-ray quality crystals of the cycloaddition products and several derivatives were unsuccessful. Consequently, NMR data was used to assign the structure (Table 2). The cyclization of **6a** was carried out using 5% CD_3OD in THF to afford the monodeuterated product *d*$_1$-**7a** (98%). The newly introduced deuterium is incorporated with high diastereoselectivity as expected from prior studies.[15] Its incorporation simplifies the ^1H NMR spectrum and the interpretation of NMR decoupling and NOE experiments carried out at 600 MHz. The key vicinal coupling constants and NOEs that led to assigning the structure shown are summarized in Table 2.

Table 2. Detected NOEs and Key Coupling Constants Relevant to Assigning the Stereochemistry of Deuterated Cycloadduct *d*$_1$-**7a**[a]



	H_2	H_3	H_4	H_{5ax}	H_{7ax}	H_9	H_{10}
H_1	*15.7*						
H_2			1.3%				
H_3			*11.2*	2.7%		3.2%	
H_4	2.1%	*11.2*				*11.5*	2.7%
H_{5ax}		1.9%					
H_9		1.8%	*11.5*	1.3%	1.6%		*11.5*
H_{10}			1.2%			*11.5*	

[a] Irradiated hydrogens are listed in the first column. Percent NOE values are given in normal typeface. Coupling constants are italicized.

A variety of transition metal-catalyzed cycloaddition reactions are known;[16] the [3 + 2] mode has been most extensively developed in metal-catalyzed reactions of trimethylene methane equivalents and methylene cyclopropane derivatives.[17] The formation of 2-methylenevinylcyclopentane (**9**) from butadiene is known in nickel-catalyzed reactions; its formation is often reported in mixtures with [4 + 2] and [4 + 4] cycloadducts and linear dimers.[18–20] Bergamini found that **9** could also be obtained via a palladium-catalyzed reaction of butadiene, but rather high

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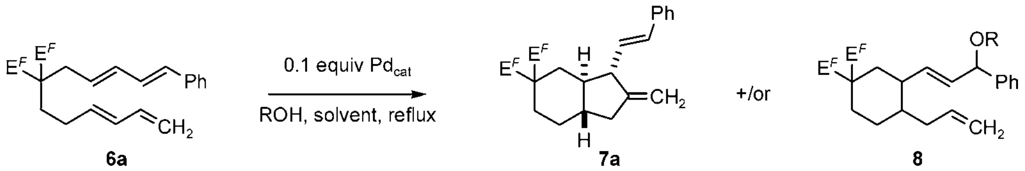
Table 3. Optimizing Reaction Conditions to Favor the [3 + 2] Cycloaddition Mode

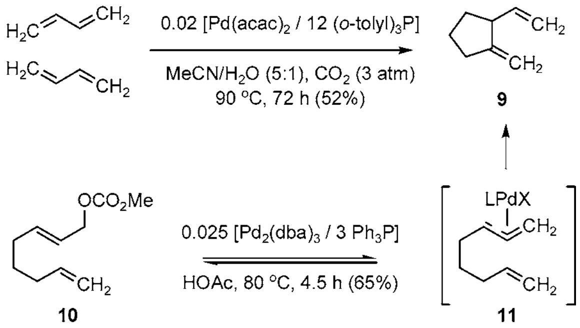


entry	solvent^a	catalyst^b	equiv of Et_3N	T (°C)	time (h)	yield (%)	**7a**:**8**^{c}
1	THF	$Pd(OAc)_2 + 2\ PPh_3$		65	1	82	3:1^d
2	CH_3CN	$Pd(OAc)_2 + 2\ PPh_3$		80	3	39	5:1^d
3	*i*-PrOH	$Pd(OAc)_2 + 2\ PPh_3$		65	2.5	74	1:1
4	F_3CCH_2OH	$Pd(OAc)_2 + 2\ PPh_3$		65	8	20	0:100^d
5	MeOH	$Pd(OAc)_2 + 2\ PPh_3$		65	1.5	79	4:1
6	MeOH	$Pd(OTFA)_2 + 2\ PPh_3$	1	65	3	90	4:1^e
7	MeOH	$[Pd(PPh_3)_3(MeCN)](BF_4)_2$	1	65	3	90	4:1^e
8	MeOH	$Pd_2(dba)_3 + 2\ PPh_3$		65	3	95	1:6^e
9	5% MeOH/THF	$Pd(OAc)_2 + 2\ PPh_3$		65	3	93	2:1^e
10	5% MeOH/THF	$Pd(OTFA)_2 + PPh_3$	1	65	3	90	3:1^e
11	5% MeOH/THF	$[Pd(PPh_3)_3(MeCN)](BF_4)_2$	1	65	1.5	98	13:1

[a] Substrate concentrations were 0.2 M in all reactions. [b] Performed with 0.1 mol equiv of catalyst. [c] Determined from isolated yields unless otherwise noted. [d] Trapping by the acetate anion (**8** (R = Ac)). [e] Determined by ^1H NMR integration of the mixture of **7a** and **8**.

temperatures and long reaction times were required (Scheme 2).[21,22] 2,7-Octadienol can be obtained from the palladium-catalyzed linear dimerization of butadiene with trapping by water. Its carbonate derivative **10** undergoes palladium-catalyzed cyclization in acetic acid to also give **9** (65%),[23] thus defining a three-step route from butadiene to **9** using palladium-catalysis to form each carbon−carbon bond.

Scheme 2. Related Routes to 2-Methylenevinylcyclopentane (**9**)



We previously found a [3 + 2] cycloadduct in a product mixture obtained from reaction of an ester-substituted bisdiene,[6] and our initial experiments with the phenyl-substituted bisdiene **6a** afforded a mixture of the [3 + 2] cycloadduct **7a** and the cyclized-trapped product **8** (R = Me) (Table 3). Using $Pd(OAc)_2$ as the catalyst precursor, we screened several reaction solvents (entries 1−5). MeOH gave the most promising result and was used to screen three additional catalyst precursors (entries 6−8). Surprisingly, $Pd_2(dba)_3$ gives predominantly the cyclized and methanol-trapped product **8** (R = Me). $Pd(OTFA)_2$ and $[Pd(PPh_3)_3(MeCN)](BF_4)_2$ give slightly better yields than $Pd(OAc)_2$; however, triethylamine had been added as a promoter in these cases. Its postulated role is to facilitate the reduction of the Pd(II) catalyst precursor to an active Pd(0) catalyst. Adding THF as a cosolvent further reduces the percentage of methanol trapped product **8** (R = Me) (entries 9−11). $[Pd(PPh_3)_3(MeCN)](BF_4)_2$ proved to be the best, strongly favoring the [3 + 2] cycloaddition mode over the trapping mode (13:1, entry 11). **7a** is isolated from the mixture in 91% yield.

Scheme 3 outlines a working model to account for the [3 + 2] cycloaddition reaction mode. The first steps are based upon the mechanism proposed by Jolly to explain the palladium-catalyzed linear dimerization of butadiene.[24] Complexation of palladium(0) to the bisdiene substrate followed by oxidative cyclization gives a palladacyclic intermediate (e.g., **12**). Its S_E2' protonation gives a chelated η^3-allylpalladium intermediate such as **13**, the intermediate presumably being cationic in the absence of coordinating anions. At this stage we suggest steps that parallel those proposed

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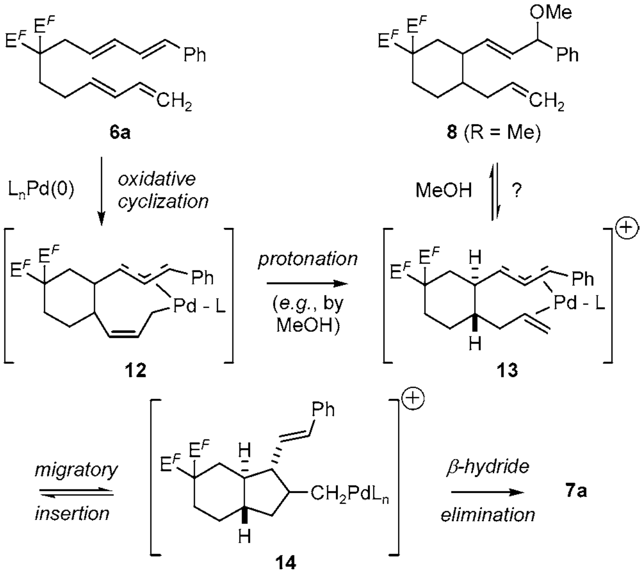
Scheme 3. Possible Mechanism for the [3 + 2] Cycloaddition

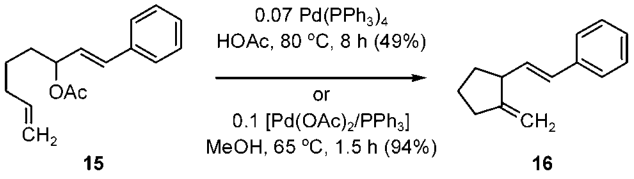


for the Oppolzer palladium-ene cyclization.[25] Ligand insertion (migratory insertion) followed by β-hydride elimination accounts for the observed [3 + 2] cycloaddition product.[26,27]

The proposed η^3-allylpalladium intermediate **13** is presumably also electrophilic and can be trapped by nucleophiles (e.g., methanol). The trapping by methanol is apparently reversible under the optimized reaction conditions. **8** (R = Me) was isolated in 42% yield by running the cyclization of **6a** under the conditions described in Table 3, entry 8.[28] When treated under the optimized cycloaddition conditions, **8** is converted to the [3 + 2] product quantitatively. However, it is not clear at this point whether methanol trapping is required or merely an allowed side reaction en route to the cycloadduct.

While the palladium-ene mechanism appears to be relevant to the bisdiene [3 + 2] cycloaddition, it was troubling that the conditions employed here are much different than those typically used for palladium-ene cyclizations. In his initial report on the latter, Oppolzer found that for a common substrate, catalyst, and reaction temperature (80 °C), the reaction time and yield varied widely as a function of the reaction solvent (i.e., THF (20%, 40 h), MeOH (65%, 8 h), HOAc (77%, 1.5 h)). Acetic acid was designated as the solvent of choice for palladium-ene reactions.[29] The palladium-catalyzed cyclization of **15** was subsequently reported and, under the prescribed conditions (0.07 $Pd(PPh_3)_4$, HOAc, 80 °C, 8 h), gave **16** in 49% yield.[30] We find that **15** cyclizes with surprising ease; acetic acid is not the required reaction medium. For example, treatment with $[Pd(OAc)_2/PPh_3]$ in methanol (65 °C, 1.5 h) gives **16** in 94% yield.

Scheme 4. Unusually Facile Palladium-Ene Reaction of **15**



In summary, aryl-substituted bisdienes undergo palladium-mediated carbocyclization via a novel [3 + 2] cycloaddition mode. The presence of the aryl ring makes trapping of the η^3-allylpalladium intermediate reversible and its subsequent palladium-ene reaction more facile. Further studies are planned.

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Supporting Information Available: Procedures and spectral data for **7a**–**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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