

Palladium-catalyzed [3C + 2C + 2C] cycloaddition of enynylidenecyclopropanes: efficient construction of fused 5-7-5 tricyclic systems†‡

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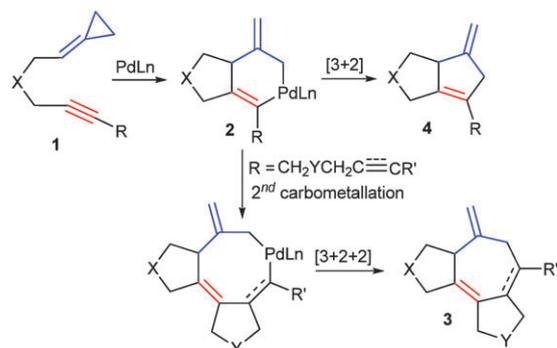
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We report a Pd-catalyzed intramolecular [3C + 2C + 2C] cycloaddition between alkylidenecyclopropanes, alkynes and alkenes. The method provides synthetically relevant 5-7-5 tricyclic structures, with good chemoselectivity and complete diastereoselectivity.

Modern organic synthesis is eagerly demanding methods that allow the preparation of target-relevant products from simple and readily available precursors in a rapid and economical fashion.¹ A particularly relevant strategy to achieve this goal consists of the development of metal-catalyzed multicomponent cycloadditions [$m + n + o + \dots$].² During the last decades, progress in this area has mainly relied on Rh-, Ir-, Ni-, Co-, or Ru-catalyzed processes,³ whereas related Pd-catalyzed methodologies have lagged behind.⁴ Additionally, while most metal-catalyzed multicomponent cycloadditions provide mono- or bi-cyclic structures, processes leading to fused tricyclic or higher polycyclic systems are very scarce.⁵

We have recently developed a Pd-catalyzed [3C + 2C] intramolecular cycloaddition of alkylidenecyclopropanes to alkynes, reaction that provides an entry to a variety of bicyclo[3.3.0]octanes.⁶ Considering that the cycloaddition may involve the generation of a palladacyclohexane intermediate like **2** (Scheme 1),⁷ we decided to investigate whether the presence of an extra 2C- π -system could provide for the construction of tricycles featuring a seven-membered carbocycle, through a carbometallation and reductive elimination sequence.⁸ Herein we demonstrate the viability of the approach by reporting several examples of Pd-catalyzed intramolecular [3 + 2 + 2] cycloadditions leading to synthetically relevant 5-7-5 tricyclic structures.

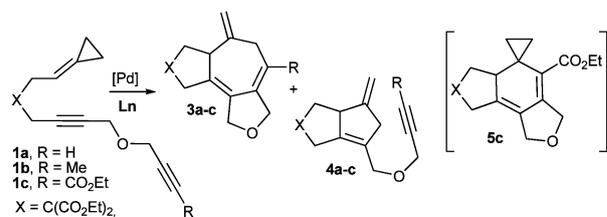
The study began by investigating the performance of substrate **1a**,⁹ which exhibits a tethered terminal alkyne unit



Scheme 1 Rationale for the [3 + 2 + 2] cycloaddition.

as an additional 2C- π -system. Several ligands previously found effective in Pd-catalyzed [3 + n] cycloadditions were tested in combination with different Pd(0) sources (Table 1).⁹ The best outcome was obtained in the presence of the catalyst generated from a mixture of Pd₂(dba)₃ and the bulky phosphite **L1**, which produced the tricyclic cycloadduct **3a** in 52% yield, after heating in toluene at 90 °C for 30 min. Phosphoramidite ligands **L2** or **L3**, previously used for inducing

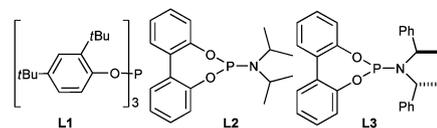
Table 1 Preliminary Pd-catalyzed cycloadditions of **1a–1c**^a



Entry	1	Ln	3:4 ratio ^b	Conv (%) ^c
1	1a	L1	1:0	100 (52)
2	1a	L2	1:1	83 (6)
3	1a	L3	—	0
4	1b	L1	0:1	27
5	1c	L1	0:0	100 (53% of 5c) ^d

^a Conditions: 10 mol% Pd₂(dba)₃, **Ln** 26 mol%, dioxane, 90 °C, 1–2 h.

^b Determined by ¹H-NMR on crude reaction mixtures. ^c Isolated yield under parenthesis. ^d Yield refers to **5c**.



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‡ Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data of previously unknown reaction products. CCDC 748242. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b919258a

Table 2 Pd-catalyzed [3C + 2C + 2C] cycloadditions of **1d–l^a**

Entry	Substrate 1	3 : 4 ratio ^b	Cycloadduct 3	3 (% Yield) ^c
1		2.3:1		68
2		1:0		84
3		1:0		58
4		2:1		51
5		1.5:1		49 ^d
6		1:1.9		16 ^e
7		1.4:1		48 ^f
8		9:1		75
9		1:0		60

^a Conditions: 10 mol% Pd₂(dba)₃, **L1** 26 mol%, dioxane, 90 °C, 1–2 h.

^b **3**:**4** ratios determined by NMR on crude mixtures. ^c Isolated yield of pure **3**. ^d [**3** + **2**] cycloadduct **4h** was isolated in 23% yield.

^e [**3** + **2**] cycloadduct **4i** was isolated in 44% yield. ^f [**3** + **2**] cycloadduct **4j** was isolated in 36% yield. E = CO₂Et.

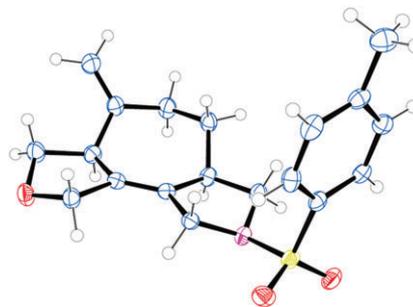
[3C + 4C] cycloadditions of alkyldenecyclopropanes,^{6e} were ineffective (entries 2 and 3). Once the feasibility of the cycloaddition was demonstrated, the impact of the alkyne substitution was studied. Unfortunately, use of a disubstituted alkyne such as in **1b**, hampered the required second carbometallation, and the [**3** + **2**] adduct **4b** was the only product that could be isolated, yet in low yield (entry 4). On the other

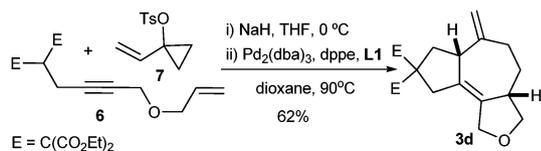
hand, substitution with an electron withdrawing group (**1c**, R = CO₂Et) triggered an alternative [2C + 2C + 2C] cycloaddition (entry 5), which occurs with preservation of the cyclopropane ring. Thus, the exclusive formation of **5c** from **1c** suggests that the Pd complex preferentially coordinates the diyne prior to the oxidative addition at the cyclopropanic unit.^{4c}

In order to avoid the competing [2 + 2 + 2] cycloaddition, and to further explore the possibilities of the process, we studied the performance of related precursors incorporating an alkene instead of an alkyne as second 2C- π -component. Gratifyingly, the cycloaddition of **1d** proceeded smoothly, providing the desired 5-7-5 tricyclic system **3d**, along with the corresponding [3C + 2C] cycloadduct **4d** in a 2.3:1 ratio. The major cycloadduct **3d** could be easily separated from the mixture and was isolated in a reasonable 68% yield (entry 1). Importantly, the reaction was completely diastereoselective, exclusively providing the isomer with the fused-hydrogens in a *cis* configuration.¹⁰ The influence of the structural characteristics of the tethers was next investigated. As shown in the table, the cycloaddition proceeded efficiently with precursors **1e–1h** providing different ratios of the [3 + 2 + 2] and [3 + 2] adducts. Complete chemoselectivities were achieved with substrates **1e** and **1f** which feature ether and amine units in the connecting tethers (entries 2 and 3). Confirmation of the structure and stereochemical assignment was unambiguously obtained by X-ray crystallographic analysis on the [3 + 2 + 2] cycloadduct **3f** (Fig. 1).⁸

Other related systems, such as **1g** or **1h** provided lower chemoselectivities (entries 4 and 5), albeit the desired [3 + 2 + 2] cycloadducts **3g** and **3h** could be still isolated in respectable yields after a simple flash chromatography (51 and 49% yield, respectively). Furthermore, it is worth to remark that, regardless of the tether moiety employed, the formation of the [3 + 2 + 2] adducts was completely diastereoselective. The use of a saturated hydrocarbon linkage between the alkene and the alkyne units (**1i**) was prejudicial for the cycloaddition, as **3i** was now obtained as a minor component and in only 16% yield (entry 6). The access to a fully carbon-based 5-7-5 tricyclic structure could however be achieved with substrate **1j**, which includes two malonate linking units (entry 7).

We next reasoned that the introduction of an electron withdrawing group at the alkene unit might increase its metal coordination ability and favour the second carbometallation step, thereby improving the [3 + 2 + 2]/[3 + 2] ratio.

**Fig. 1** X-Ray crystal structure of **3f**.



Scheme 2 Tandem Pd-catalyzed allylic alkylation and [3 + 2 + 2] cycloaddition reaction.

Gratifyingly, the cycloaddition of **1k**, which features an ester group at the alkene terminus, took place with significantly higher chemoselectivity than that obtained from the parent precursor **1j**, providing the desired [3 + 2 + 2] cycloadduct **3k** in a good 75% yield (entry 8). Importantly, the reaction was completely diastereoselective, thus allowing the direct construction of a functionalized and stereochemically rich 5-7-5 tricyclic system.¹¹ Similarly, the cycloaddition result of **1l** was clearly superior to that of the alkene-unsubstituted homologue **1g**, providing **3l** with complete selectivity, in a 60% isolated yield (entry 9).

Finally, we also analyzed the possibility of carrying out the assembly of the precursors and the [3 + 2 + 2] cycloaddition reaction in a tandem, one-step protocol, since both reactions are Pd-catalyzed processes. Gratifyingly, heating of 1-vinylcyclopropyl tosylate **7** with one equivalent of the sodium salt of **6** in the presence of the suitable proportion of dppe,¹² **L1** and Pd₂(dba)₃, provided the expected cycloadduct **3d** in 62% isolated yield (Scheme 2).

In conclusion, we have developed a new Pd-catalyzed multi-component intramolecular cycloaddition reaction between alkylidenecyclopropanes (3C), alkynes (2C) and alkenes (or a terminal alkyne, 2C). The transformation takes place with moderate to excellent chemoselectivities and complete diastereoselectivities, providing straightforward access to a variety of synthetically relevant 5-7-5 tricyclic systems.

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- See Electronic Supplementary Information for synthetic details.
- DFT calculations to confirm the mechanistic hypothesis and explain the stereochemical results are ongoing.
- In contrast to the cycloaddition of dyne **1c** (Table 1), in the cycloaddition of **1k** we did not observe the formation of [2 + 2 + 2] cycloadducts of type **5**.
- The presence of dppe ensures a small proportion of a bidentate Pd complex which facilitates the coupling reaction.