Palladium-Catalyzed Intramolecular [3C+2C] Cycloaddition of Alkylidenecyclopropanes to Allenes

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Abstract: Allenes are useful and versatile two-carbon partners in palladium catalyzed [3C+2C] intramolecular cycloadditions with alkylidenecyclopropanes enabling the preparation of dienyl bicyclo[3.3.0]octane adducts with good yields and high diastereoseletivity.

Keywords: alkylidenecyclopropanes; allenes; bicyclo[3.3.0]octanes; cycloaddition; palladium

$$(1)$$

while the cycloaddition seems still to be the major reaction pathway, there are competitive processes that result in an important decrease in the efficiency of the transformation.

We envisaged that using allenes instead of alkenes might provide a good solution to the above problem and perhaps lead to more efficient [3+2] cycloaddition processes owing to the presumably higher reactivity of the allene unit. Allenes are being increasingly used in metal-catalyzed annulation reactions due to their unique reactivity and the special manipulation possibilities that they offer to the resulting products owing to their retaining one double bond of the allene.[5] Despite these potential advantages, we are not aware of studies on the behaviour of this type of π-system in transition metal-catalyzed [3C+2C] cycloadditions with methylene- or alkylidenecyclopropanes.[6] Herein, we describe the first examples of palladium-catalyzed intramolecular cycloadditions between allenes and alkylidenecyclopropanes, examples that confirm the special utility of allenes as two-carbon partners in this type of annulation.

Allene **4a**, which can be easily assembled from 1-vinylcyclopropyltosylate and diethyl malonate in two steps,[7] was used as model substrate to investigate the reaction conditions (Table 1). Heating a solution of **4a** with 8 mol% of Pd$_2$dba$_3$ and 32 mol% of P(O-i-Pr)$_3$ in refluxing dioxane gave the expected [3+2] cycloadducts but in a fairly poor yield and as an equimolecular mixture of *cis*- and *trans*-fused isomers (entry 1). Interestingly, use of the bulky ligand tris(2,4-di-*tert*-
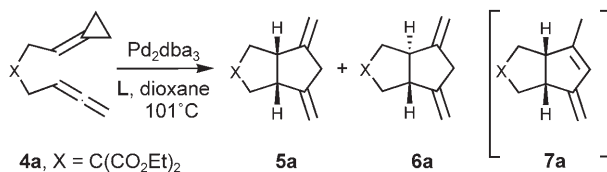
Alkylidenecyclopropanes are strained but readily accessible structures which can participate as three-carbon components in metal-catalyzed cycloadditions to afford different types of π-systems.[1] Our group has recently shown that alk-5-ynylidenecyclopropanes undergo a mild [3C+2C] intramolecular cycloaddition upon treatment with appropriate palladium or ruthenium catalysts to provide a variety of fused bicyclo[3.3.0]octenes.[2] More recently we have also demonstrated that it is possible to use alkenes in place of alkynes as two-carbon components in the cycloaddition. Although attaining good efficiencies in these cycloadditions requires a relatively high catalyst loading (6% of Pd$_2$dba$_3$, and 20% of the ligand), the reactions provide a rapid and direct entry to bicyclopentanoid rings equipped with up to three stereogenic centers.[3] The cycloadditions can be performed with either activated (electron-deficient) or non-activated alkenes, but it is less efficient when the terminal position of the alkene is substituted by an alkyl group due to competing β-hydride elimination processes on putative palladacyclic intermediates. Thus, treatment of the cyclopropylideneethylamine **1** with Pd$_2$dba$_3$ (6 mol%) and ligand **L1** (20 mol%) in refluxing dioxane provided the cycloadduct **2** in only 57% yield because of concomitant formation of the dienyl cycloisomerization side product **3** [25% yield, Eq.(1)].[4] Thereby,

Table 1. Palladium-catalyzed cycloaddition of allenyl derivative **4a**.

Entry	mol % Pd$_2$dba$_3$	L (mol %)	5a:6a[a]	Time [h]	Yield [%]
1	8	P(O-*i*.Pr)$_3$ (32)	1:1.1	6	29
2	3	**L1** (8)	3:1	1.3	87
3	8	**L2** (32)	1:1	6	24
4	8	**L3** (32)	1.1:1	6	20
5	6	**L4** (24)	1:1.1	2	92
6[b]	3	**L1** (8)	3:1	0.5	99[d]
7[b,c]	1	**L1** (2.6)	3:1	2	99[d]
8[b]	0.1	**L1** (0.26)	3:1	2	99[d]

[a] Determined by ^{1}H NMR of the crude reaction mixture.
[b] Experiment carried out after a thorough deoxygenation of the reaction mixture.
[c] Reaction carried out at 80 °C.
[d] Conversion by GC.

butylphenyl) phosphite (**L1**) in place of P(O-*i*-Pr)$_3$ brought about an important improvement in the chemical yield as well as in the stereoselectivity of the cycloaddition. Thus, the reaction of **4a** with 3 mol% Pd$_2$dba$_3$ and 8 mol% of **L1** afforded, after refluxing in dioxane for 80 min, a 3:1 mixture of **5a** and **6a** in 87% overall yield (entry 2). Together with these two cycloadducts we also detected traces of the isomeric derivative **7a** (aprox. 5%), especially when the reaction was allowed to proceed for longer times. This conjugated diene **7a** must result from an *in situ* isomerization of the *cis* addut **5a** since treatment of a mixture of **5a** and **6a** under the cycloaddition conditions promoted the conversion of **5a** into **7a**, while the *trans*-fused isomer **6a** remained unaltered.[8]

Other phosphorus-based monodentate ligands such as **L2**, **L3** or **L4** (Figure 1), some of which have been recently shown to be effective in the cycloaddition of

alk-5-ynylidenecyclopropanes,[2c] also catalyzed the process, but led to lower yields and/or selectivities (Table 1, entries 3–5). Worth of note is the efficiency of the reaction in the presence of the chiral phosphoramidite ligand **L4** (entry 5),[9] a result which warrants the study of enantioselective versions of the cycloaddition using this type of ligand.

Interestingly, a careful analysis by ^{31}P and ^{1}H NMR of the crude reaction mixture resulting from the process described in entry 2 allowed us to detect the presence of a considerable amount of tris(2,4-di-*tert*-butylphenyl) phosphate (**8**, Figure 1), a side product that must arise from oxidation of ligand **L1**. Further studies (^{31}P NMR) confirmed that such an oxidation was occurring prior to and during the cycloaddition reaction, therefore decreasing the amount of the active catalytic species. Consequently, we tested whether a careful deoxygenation of the reaction mixture could improve the cycloaddition outcome. Indeed, ensuring the removal of oxygen from the reaction mixture prevented the formation of phosphate **8** and led to a remarkable acceleration of the cycloaddition process (entry 6). Under these conditions the reaction could be accomplished at lower temperatures (80 °C) reaching full conversion after 2 h (entry 7). More importantly we could decrease the substrate-to-catalyst ratio so that the reaction can be efficiently performed in refluxing dioxane (2 h) even with catalyst loadings as low as 0.1 mol% of Pd$_2$dba$_3$ (0.26 mol% **L1**) (entry 8), which represents the highest turnover so far described in a metal-catalyzed [3+2] cycloaddition process.

A preliminary investigation on the scope of the reaction showed that it can be carried out with substrates like **4b** which contains an amine instead of a
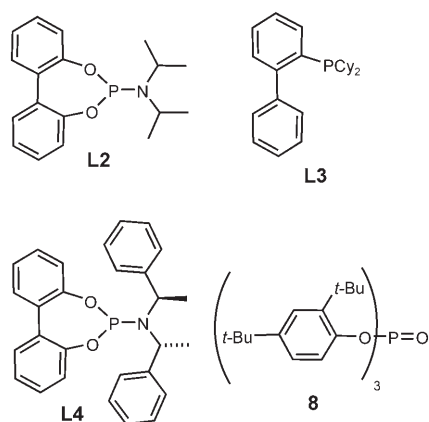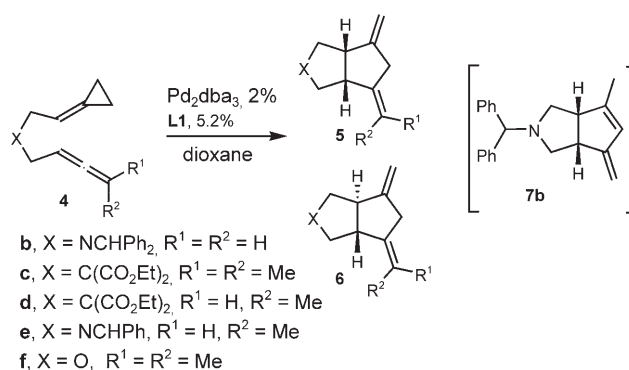

Figure 1.

malonate unit in the connecting tether.[10] Interestingly, in this case the reaction is almost completely diastereoselective and yields the *cis*-fused product in 68% isolated yield. We also observed the formation of a small proportion of **7b**, a product which can be readily obtained from **5b** by refluxing under the cycloaddition conditions for 2 h.[7] The [3+2] cycloaddition reaction turned out to be tolerant to the introduction of substituents in the non-reactive double bond of the allene. Indeed the dimethylated substrate **4c** underwent an efficient cycloaddition to give products with better *cis/trans* selectivity than in the case of the unsubstituted allene (Table 2, entry 2). On the other hand, the monomethylated derivative **4d** was also efficiently converted into the cycloadduct **5d** with excellent diastereoselectivity (Table 2, entry 3). These results indicate that the diastereoselectivity of the process can be improved by adjusting the substitution of the non-reactive double bond of the allene. In the case of amine **4e** the reaction gave the cycloadduct **5e** as a single diasteroisomer (Table 2, entry 4). The high diastereoselectivity attained from **4d** and **4e** together with the clear possibility for obtaining this type of allenyl precursors in an enantioselective manner,[11] augurs well for the application of this methodology in the synthesis of enantiomerically enriched bicyclo-[3.3.0]octanes. The cycloaddition is also viable with the ether derivative **4f**, to give the *cis*-fused cycloadduct **5f** with high distereoselectivity (Table 2, entry 5). This result demonstrates that the presence of a substituted amine or a geminal diester in the tether is not required for success.

Finally it is worth noting that the cycloaddition reaction can be coupled to the assembly of the precursors so that both Pd-catalyzed processes can be carried out in a tandem, one-step process. Thus, treatment of 1-vinylcyclopropyl tosylate with 1 equivalent of the sodium carbanion of diethyl 2-(4-methylpenta-2,3-dienyl)malonate (**9**) in the presence of the suitable proportion of dppe, **L1** and Pd_2dba_2 provides, after heating, the expected cycloadducts in a 62% isolated yield (unoptimized) [Eq. (2)].

$$\text{(2)}$$

5c/6c = 6:1
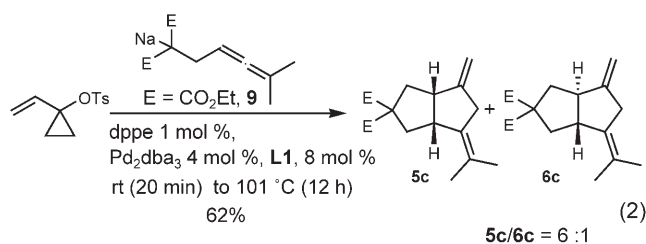
In summary, we have reported the first examples on the use of allenes in palladium-catalyzed [3C+2C] intramolecular cycloaddditions with alkylidenecyclopropanes. The cycloaddition proceeds with high efficiency using low catalyst loadings, and its diastereoselectivity can be improved by using allenes with appropriate substituents at the non-reactive double bond. Further work on the scope and limitations of the process as well as on the development of enantioselective versions is underway.

Table 2. Cycloaddition of allenyl derivatives **4b–4d**.

b, X = NCHPh₂, R¹ = R² = H
c, X = C(CO₂Et)₂, R¹ = R² = Me
d, X = C(CO₂Et)₂, R¹ = H, R² = Me
e, X = NCHPh, R¹ = H, R² = Me
f, X = O, R¹ = R² = Me

Entry	**4**	T [°C]	Products	**5:6**	Time [min]	Yield [%]
1	**4b**	90°C	**5b**	>20:1[a]	60	68
2	**4c**	101°C	**5c/6c**	6:1[a]	15	80
3[c]	**4d**	101°C	**5d/6d**	>14:1[b]	25	90
4	**4e**	90°C	**5e/6e**	>20:1[a]	60	77
5	**4f**	90°C	**5f/6f**	>9:1[b]	90	70

[a] Determined by ¹H NMR of the crude reaction mixture.
[b] Determined by GC of the crude reaction mixture.
[c] Carried out with Pd_2dba_3 (3 mol%) and **L1** (7.8 mol%).

Experimental Section

General Remarks

Commercially available compounds, including ligands **L1** and **L3** were used as supplied. **L2** and **L4** were prepared according to published procedures.[2c] Solvents for chromatography were technical grade and distilled prior to use. All reactions were conducted in dry solvents under an argon atmosphere unless otherwise stated. The reactions were followed by silica gel TLC and by GC-MS using the Agilent Technologies 6890N, Network GC System, equipped with the Agilent 190915–433 column and the Agilent 5973 Inert Mass Selective Detector in electron impact or chemical ionization mode (with methane). ^{1}H and ^{13}C NMR spectra were recorded in CDCl$_3$, on Bruker 250 MHz, Varian 300 and Bruker 500 MHz spectrometers. ^{31}P NMR spectra were recorded in CDCl$_3$ at 121 MHz using an internal phosphoric acid standard. Data of known compounds were in agreement with literature data, while the new compounds were characterized.

General Procedure for the Cycloaddition

To a Schlenk tube containing deoxygenated dioxane (3.6 mL) – obtained by three short vacuum-argon cycles – Pd$_2$dba$_3$ (3.3 mg, 3.6 μmol), **L1** (6.0 mg, 9.4 μmol) and the substrate **4a** (100 mg, 0.36 mmol) were added, deoxygenating the mixture after the addition of every component. The reaction mixture was heated under reflux, cooled to room temperature and filtered through a short pad of silica gel, eluting with EtOAc/hexanes (10%). The filtrate was concentrated and purified by flash chromatography (1% EtOAc/hexanes) to afford **5a** (yield: 65 mg, 65%) and **6a** (yield: 22 mg, 22%).[7]

Acknowledgements

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[4] When the reaction is carried out with a substrate containing an (EtO$_2$C)$_2$C unit in the tether, instead of the NBn group, we obtained a complex mixture containing cycloadducts and cycloisomerization products, which could not be separated by chromatography.

[5] For selected recent examples of metal-catalyzed reactions with allenes, see: a) B. Alcaide, P. Almendros, *Eur. J. Org. Chem.* **2004**, 3377–3383; b) K. M. Brummond, H. Chen, B. Mitasev, A. D. Casarez, *Org. Lett.* **2004**, *6*, 2161–2163; c) T. Shibata, S. Kadowaki, K. Takagi, *Organometallics* **2004**, *23*, 4116–4120; d) K. M. Brummond, B. Mitasev, *Org. Lett.* **2004**, *6*, 2245–2248; e) P. A. Wender, M. Fuji, C. O. Husfeld, J. A. Love, *Org. Lett.* **1999**, *1*, 137–139; f) H. A. Wegner, A. de Meijere, P. A. Wender, *J. Am. Chem. Soc.* **2005**, *127*, 6530–6531; g) J. Barluenga, R. Vicente, P. Barrio, L. A. López, M. Tomás, *J. Am. Chem. Soc.* **2004**, *126*, 5974–5975.

[6] On page 132 of the review in ref.[1a] there is a comment suggesting that the intermolecular reaction between methylenecyclopropane and allene gives the [3+2] cycloadduct, but in very poor yields. In any case we are not aware of the publication of these results.

[7] See Supporting Information for details.

[8] Compound **7a** could not be obtained from **5a** or **6a** by simple heating or by treatment with acids (i.e., *p*-TsOH, toluene, reflux).

[9] B. L. Feringa, *Acc. Chem. Res.* **2000**, *33*, 346–353.

[10] Reactions were carried out with 2 mol% Pd$_2$dba$_3$ for practical reasons and to induce faster cycloaddition process so that the isomerization of the products to **7b** can be minimized.

[11] There are numerous and powerful catalytic methods to obtain enantiomerically rich allenyl precursors. For an excellent recent example, see: B. M. Trost, D. R. Fandrick, D. C. Dinh, *J. Am. Chem. Soc.* **2005**, *127*, 14186–14187.