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Rhodium-catalyzed Intramolecular (3 + 2 + 2) Cycloadditions between Alkylidenecyclopropanes, Alkynes and Alkenes

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Polycyclic structures containing seven-membered carbocycles are important synthetic targets because they constitute the key structural core of many classes of bioactive natural products.[1] Among the different strategies for their assembly, those involving the transition metal-catalyzed cycloaddition of readily available acyclic substrates is particularly attractive.[2] In this context, we have demonstrated that alkylidenecyclopropanes (ACPs) can work as 3C-atom components in several metal catalyzed cycloadditions that afford seven membered-containing polycyclic structures,[3] including an intramolecular (3 + 2 + 2) annulation promoted by Pd(0) catalysts (Scheme 1 *route a*).[3b] Despite the utility of this latter method, which generally proceeds with good yields and complete diastereoselectivity to give *syn* fused (3 + 2 + 2) cycloadducts, its synthetic potential is somewhat compromised by the competitive formation of cyclopentanic side products resulting from a formal (3 + 2) annulation.[4]

In a related work, Evans and coworkers demonstrated in 2008 that Rh catalysts derived from $[Rh(COD)Cl]_2$ and $P(OPh)_3$ promote intermolecular (3 + 2 + 2) cycloadditions between alkenylidenecyclopropanes and activated alkynes, to afford 5,7-fused bicyclic systems (Scheme 1, *route b*).[5,6] Curiously, although this method uses alkynes as external cycloaddition components, intramolecular (3 + 2) cycloadducts were not isolated. Stimulated by this observation, and as part of our program on the discovery of new transition metal-catalyzed cycloadditions,[7] we analyzed the viability of a Rh-catalyzed intramolecular (3 + 2 + 2) cycloaddition of dienyne precursors of type **1**.[3b] Herein, we report the implementation of such cycloaddition, a reaction that affords synthetically relevant 5,7,5-fused tricyclic systems of type **2** with moderate to good yields, high diastereoselectivities and total chemoselectivity (Scheme 1, bottom). Moreover, and in contrast to the Pd-catalyzed (3 + 2 + 2) annulations,[3b] the current methodology allows the use of di- or even tri-substituted alkenes. Also interestingly, an appropriate selection of the Rh catalyst allowed in particular cases a divergent access to the *syn* or *anti* cycloadducts **2** and **2'**. We also provide preliminary DFT calculations that qualitatively support the experimental results and shed light on the mechanism and on the differences between the Pd- and the Rh-catalyzed versions of these cycloaddition reactions.

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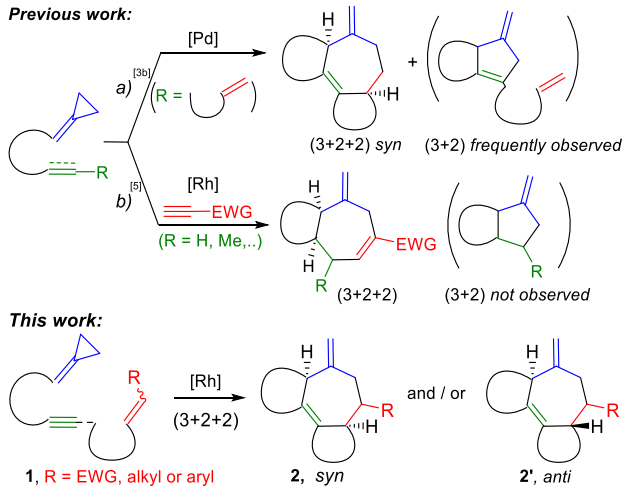
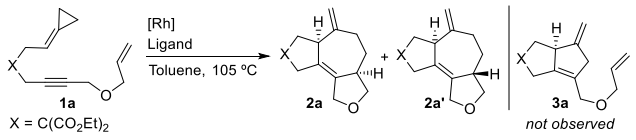


Scheme 1. Transition metal-catalyzed (3 + 2 + 2) cycloadditions of ACPs.

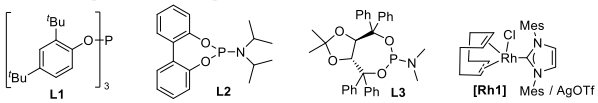
Treatment of substrate **1a**, which features an internal alkyne and a terminal alkene, with $[Rh(COD)Cl]_2$ (10%)/ $(PhO)_3P$ (25%), conditions related to those previously used by Evans,[5a] provided a 1 : 3 mixture of the *syn* cycloadduct **2a** and its epimer **2a'**, in a modest 36% overall yield (Table 1, entry 1).[8] Importantly, (3 + 2) cycloadducts (i.e. **3a**) were not detected in the ^{1}H-NMR spectra of the crude reaction mixture.[9] Therefore, we further analyzed other ligands and Rh sources in order to improve the yield and diastereoselectivity of the cycloaddition. Curiously, the use of a bulkier phosphite such as **L1**, instead of $(PhO)_3P$, allowed to invert the diastereoselectivity (**2a** : **2a'** > 20 : 1), although the yield of the process was lower (entry 2). As exemplified in entries 3-7, the combination of $[Rh(COD)Cl]_2$ with other phosphorous-based ligands was not particularly successful, as in most of the cases we observed the formation of complex reaction mixtures. The use of $[Rh(COD)_2]BF_4$ instead of $[Rh(COD)Cl]_2$, or of the complex **[Rh1]**, featuring a *NHC* ligand, did not lead to better results (entries 8-10). However, treatment of **1a** with Wilkinson catalyst at 105 ºC provided the cycloadducts **2a** and **2a'** in a 4.5 : 1 ratio and a good 61% yield (entry 11). Remarkably, a related Rh complex containing an electron-poor phosphine $[(pCF_3Ph)_3P]$,[10] led to the *syn* cycloadduct **2a** with very high diastereoselectivity and 65% yield (entry 12).

Table 1. Preliminary screening on the Rh-catalyzed (3 + 2 + 2) cycloaddition of **1a**.



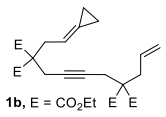
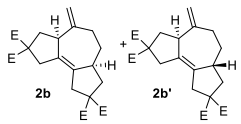
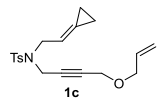
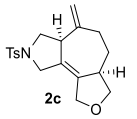
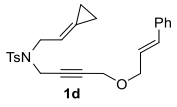
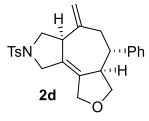
entry	[Rh] (%)	Ligand (%)	Time (h)[a]	**2a** : **2a'**[b]	**2a**+**2a'** (%)[c]
1	$[Rh(cod)Cl]_2$ (10)	$P(OPh)_3$ (25)	1.5	1 : 3	36
2	$[Rh(cod)Cl]_2$ (10)	**L1** (25)	3.6	>20 : 1	21
3	$[Rh(cod)Cl]_2$ (10)	$P(O^iPr)_3$ (25)	4	1.1 : 1	16[d]
4	$[Rh(cod)Cl]_2$ (10)	$P(OEt)_3$ (25)	12	–	0[d]
5	$[Rh(cod)Cl]_2$ (10)	Ph_3P (25)	15	–	0[d]
6	$[Rh(cod)Cl]_2$ (10)	**L2** (25)	2	–	0[d]
7	$[Rh(cod)Cl]_2$ (10)	**L3** (25)	12	3 : 1	30[d]
8	$[Rh(cod)_2]BF_4$ (10)	$P(OPh)_3$ (25)	3	3 : 1	24[d]
9	$[Rh(cod)_2]BF_4$ (10)	**L1** (25)	12	5 : 1	10[d]
10	**[Rh1]**	–	12	–	0[d]
11	$(Ph_3P)_3Rh$ Cl (10)	–	1.25	4.5 : 1	61
12	**$[(pCF_3Ph)_3P]_3RhCl$ (10)**	–	**0.6**	**> 20 : 1**	**65**

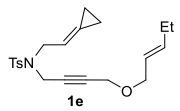
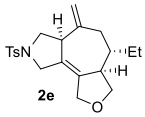
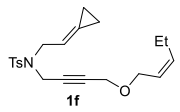
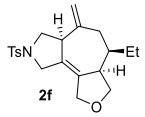
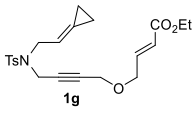
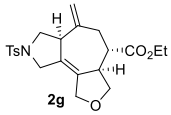
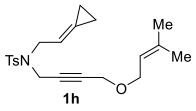
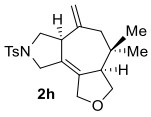
[a] Refers to the time required for the full disappearance of **1a** (^{1}H-NMR). [b] Determined by ^{1}H-NMR of the crude mixture. [c] Isolated combined yield of **2a** and **2a'**. [d] A complex mixture of products was detected (^{1}H-NMR) in the crude mixture.



The scope of the process was then analyzed using this latter catalyst. As can be seen in Table 2, the cycloaddition of **1b**, featuring a germinal diester at the carbon chain that links the ACP and the alkyne provided a 2.4 : 1 mixture of the *syn* and *anti* isomers **2b** and **2b'** in a global 69% yield (Table 2, entry 1). In this particular case, performing the reaction at 90 ºC allowed to slightly increase the diastereoselectivity and the yield (entry 2). The *N*-tosyl precursor **1c** undergoes a very clean and completely diastereoselective cycloaddition to give **2c** in an excellent 85% yield (entry 3).[11] The relative stereochemistry of this cycloadduct was unambiguously determined by X-ray analysis (Figure 1, left).[12] To further explore the synthetic potential of the process, the cycloaddition of precursors that incorporate substituents at the alkene distal position was next analyzed. As can be seen in entries 4 and 5, the reaction tolerates a phenyl or an ethyl group at the *trans* terminal position of the alkene and, gratifyingly, **2d** and **2e** were obtained with complete diastereoselectivity and moderate yields. An unequivocal confirmation of the relative stereochemistry of **2d**, which features three stereocenters, could be obtained by X-ray analysis (Figure 1, right).[13] On the other hand, the cycloaddition of **1f**, analog of **1e** but equipped with a *cis* instead of a *trans* alkene, also proceeded with complete selectivity affording the epimeric adduct **2f** in an excellent 88% yield (entry 6), a result which supports the stereospecificity of the reaction. The cycloaddition of a precursor **1g**, featuring an electron-withdrawing carboxylate at the *trans* terminal position of the alkene was also feasible, leading to the expected tryciclic system with complete stereoselectivity and 52% yield (entry 7). Finally, the cycloaddition of precursors containing trisubstituted alkenes like **1h** was also viable, although the yield of the resulting adduct, **2h**, was somewhat lower (entry 8), most probably due to the steric constrains imposed by the two methyl groups which would retard the coordination of the alkene to the Rh. In any case, the ability of this Rh-catalyst to promote the (3 + 2 + 2) cycloadditions of precursors incorporating substituted alkenes like **1d-h** (entries 4-8), sharply contrasts with the performance of the previously reported Pd-catalyst,[3b] which failed to induce the tandem annulation with these precursors.[14]

Table 2. Scope of the Rh-catalyzed (3 + 2 + 2) cycloaddition of ACPs of type **1**.[a]

entry	**1**	Products	**2** : **2'**[b]	Yield (%)[c]
1			2.4 : 1	69
2	**1b**, E = CO_2Et	**2b** **2b'**	3 : 1	80[d]
3	 **1c**	 **2c**	>20 : 1	85
4	 **1d**	 **2d**	>20 : 1	51

5			>20 : 1	54
6			>20 : 1	88
7			>20 : 1	52
8			>20 : 1	43

[a] Conditions: $[(p\text{CF}_3\text{Ph})_3\text{P}]_3\text{RhCl}$ (10%), in toluene at 105ºC for 90 min, unless otherwise noted. Full conversions were observed by ^{1}H-NMR. [b] Determined by ^{1}H-NMR of the crude reaction mixture. [c] Isolated yield. [d] Carried out at 90ºC.

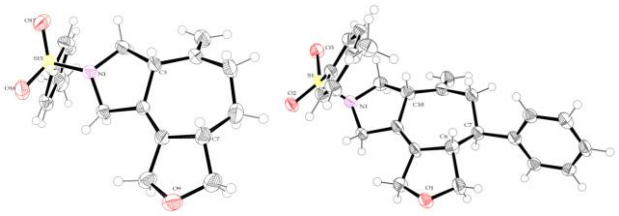
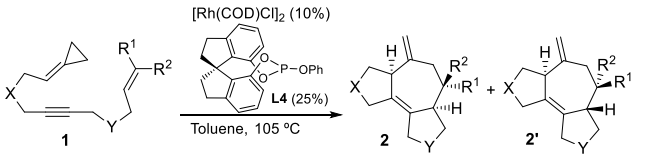


Figure 1. Solid structure of **2c** and **2d** determined by X-ray analysis.[12, 13]

The results of entries 1 and 2 in Table 1 suggest that the use of different phosphite ligands in combination with $[\text{Rh(COD)Cl}]_2$ allows a divergent access to both *syn* and *anti* diastereoisomers **2** and **2'**. A screening of several phosphites revealed that using the phosphite **L4**, instead of $(\text{PhO})_3\text{P}$, the reaction of **1a** provides a good yield of the expected cycloadducts, with the *anti* isomer **2a'** as the major product (**2a** : **2a'** ratio = 1 : 3, 80% yield, Table 3, entry 1). The related precursor **1b**, provided a similar yield and identical diastereoselectivity in favor of the *anti* isomer **2b'** (entry 2). Moreover, the cycloaddition of **1i**, featuring two oxygen atoms at the connecting tethers, was significantly more selective, providing a 1:10 mixture of **2i** and **2i'**, in 63% yield (entry 3). High diastereoselectivity favoring the *anti* isomer was also observed in the cycloaddition of **1c**, which provided a 1 : 7 ratio of **2c** and **2c'** in 65% yield.[15,16] The same Rh catalyst also promoted the (3 + 2 + 2) cycloaddition of precursors containing terminally-substituted alkenes, such as **1d**, **1f** or **1g** (entries 5-7). However, in these cases the reactions afforded the *syn* diastereoisomers (**2d**, **2f** and **2g**), the same isomers previously obtained when using $[(p\text{CF}_3\text{Ph})_3\text{P}]_3\text{RhCl}$. Therefore, the presence of additional substituents at the alkene seems to be a dominant factor governing the formation of *syn*-fused adducts, regardless of the Rh catalyst.

Table 3.Rh-catalyzed (3+2+2) cycloadditions. Inversion of the diastereoselectivity.[a]



entry	**1**	X	Y	R^1	R^2	**2** : **2'**[b]	yield, %[c]
1	**1a**	$C(CO_2Et)_2$	O	H	H	1 : 3	80
2	**1b**	$C(CO_2Et)_2$	$C(CO_2Et)_2$	H	H	1 : 3	67
3	**1i**	O	O	H	H	1 : 10	63
4	**1c**	NTs	O	H	H	1 : 7	65
5	**1d**	NTs	O	Ph	H	>20 : 1	46
6	**1f**	NTs	O	H	Et	>20 : 1	56
7	**1g**	NTs	O	CO_2Et	H	>20 : 1	51

[a] Conditions: $[\text{Rh(COD)Cl}]_2$ (10 %), **L4** (25%) in toluene at 105 ºC. Reaction times from 1 to 4 h. [b] Determined by ^{1}H-NMR of the crude reaction mixture. [c] Isolated yield of the mixture of isomers **2** and **2'** after column chromatography.

In order to obtain mechanistic information on these Rh-catalyzed cycloadditions as well as to shed light on the differences between the Rh and Pd catalyzed processes,[3b] we performed preliminary DFT calculations using precursor **1j** and $\text{RhCl(PMe}_3)_2$ or $\text{Pd[P(OH)}_3]_2$ as model catalysts, respectively (Figures 2 - 3).[17] Previous theoretical calculations, in the context of (3 + 2) and (3 + 2 + 2) cycloadditions supported the formation of metallacycles like **Int-Rh-1** (Figure 2) and **Int-Pd-1** (Figure 3) as key intermediates resulting from the initial oxidative cyclometallation of the corresponding ACP.[18,5c] From these intermediates, a reductive elimination would provide cyclopentene cycloadducts, whereas a migratory insertion of the alkene, followed by reductive elimination, would lead to the cycloheptenyl products. Thus, we initiate our computational studies by locating these key intermediates with both, the Rh and the Pd model systems. The results suggest that in **Int-Rh-1** the three carbon atoms of the former ACP unit coordinate the Rh as a π-allyl ligand (Figure 2). In the case of the square planar **Int-Pd-1**, this unit is coordinated to the Pd through a σ–bond (Figure 3).

In the case of the Rh-promoted reaction (Figure 2), the pathway leading to the cycloheptenyl adducts begins with the coordination of the tethered alkene to the Rh atom of **Int-Rh-1**. Depending on the orientation of the double bond, two different intermediates, **Int-Rh-1**$_{anti}$ and **Int-Rh-1**$_{syn}$ were located, lying respectively 7.1 and 8.2 kcal mol^{-1} over **Int-Rh-1**. Subsequent carbometallations of the alkene from both intermediates were located and, importantly, the path providing the *syn* rhodacyclooctene **Int-Rh-2**$_{syn}$, via **TS-Rh-1**$_{syn}$ is significantly favored kinetically [$\Delta\Delta G^{\ddagger}$ = 15.5 kcal·mol^{-1}]. Final reductive elimination processes generate the cycloadducts **2j** and **2j'**, via **TS-Rh-2**$_{syn}$ and **TS-Rh-2**$_{anti}$, respectively. Thus, the theoretical calculations are consistent with the strong preference for the formation of the *syn* cycloadducts under catalysis with $\text{RhCl(PR}_3)_3$ (see above). The transition states associated with the direct reductive eliminations to give the (3 + 2) cycloadduct **3j** were also explored, resulting in the identification of two possible alternatives: via **TS-Rh-3** (from **Int-Rh-1**) or through **TS-Rh-3'** (from **Int-Rh-1**$_{anti}$). As can be seen in the Figure 2, these reductive eliminations are quite costly (barriers of 31.4 and 43.3 kcal·mol^{-1}), which is in agreement with the absence of (3 + 2) adducts in the Rh-catalyzed cycloadditions of ACPs of type **1**.

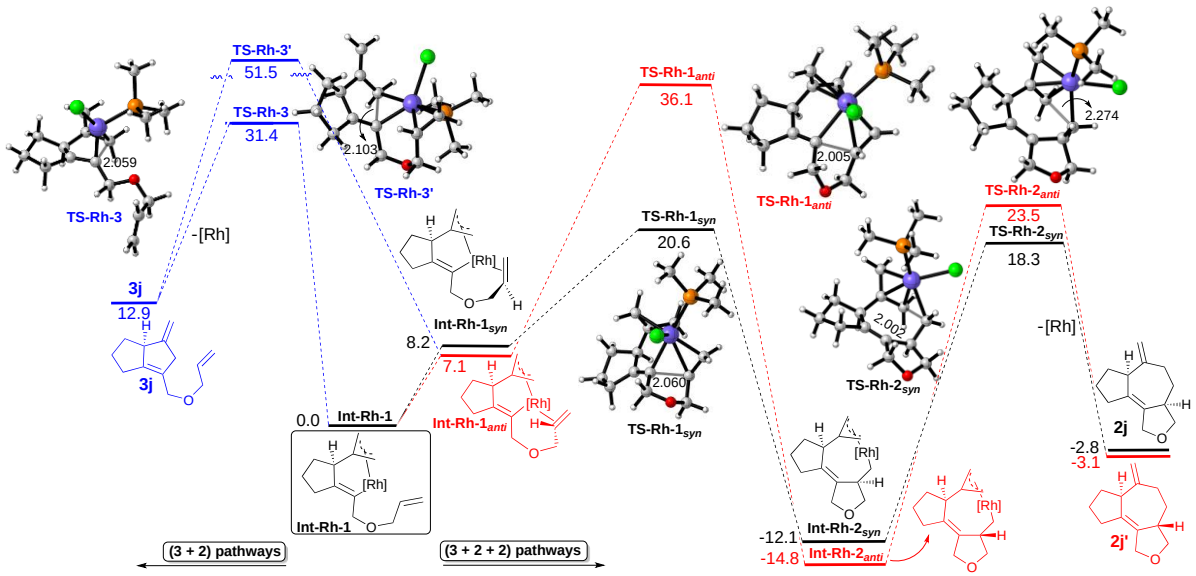


Figure 2. Computed reaction profile with a model Rh catalyst. [Rh] = Rh(PMe_3)Cl. Free energies (ΔG_{298}) and bond distances are given in kcal·mol^{-1} and angstroms, respectively. All data have been computed at the B3LYP/SVP level.

An analogous energy profile for the (3 + 2 + 2) and (3 + 2) Pd-catalyzed cycloadditions was also explored from **Int-Pd-1**. As indicated in the Figure 3, two different palladacyclohexene intermediates, **Int-Pd-1**$_{syn}$ and **Int-Pd-1**$_{anti}$, may be formed depending on the orientation of the alkene that coordinates the Pd. Analysis of the subsequent carbometallations revealed that the formation of the *syn* palladacyclooctane species **Int-Pd-2**$_{syn}$ is again significantly favored kinetically [$\Delta\Delta G^{\ddagger}$ = 19.6 kcal·mol^{-1}]. The final reductive elimination leading to the *syn* adduct **2j** is also favored by 2.0 kcal mol^{-1}. In contrast to the high activation barrier of the reductive elimination to give the formal (3+2) adduct **3j** observed in the case of the rhodium system, reductive eliminations from either **Int-Pd-1** or **Int-Pd-1**$_{anti}$ are competitive with the carbapalladation of the alkene to give **Int-Pd-2**$_{syn}$. Therefore, these data nicely match our previous experimental results with Pd catalysts, since both, the (3 + 2) and the *syn* (3 + 2 + 2) adducts were usually isolated, whereas the *anti* counterparts were never detected.[3b]

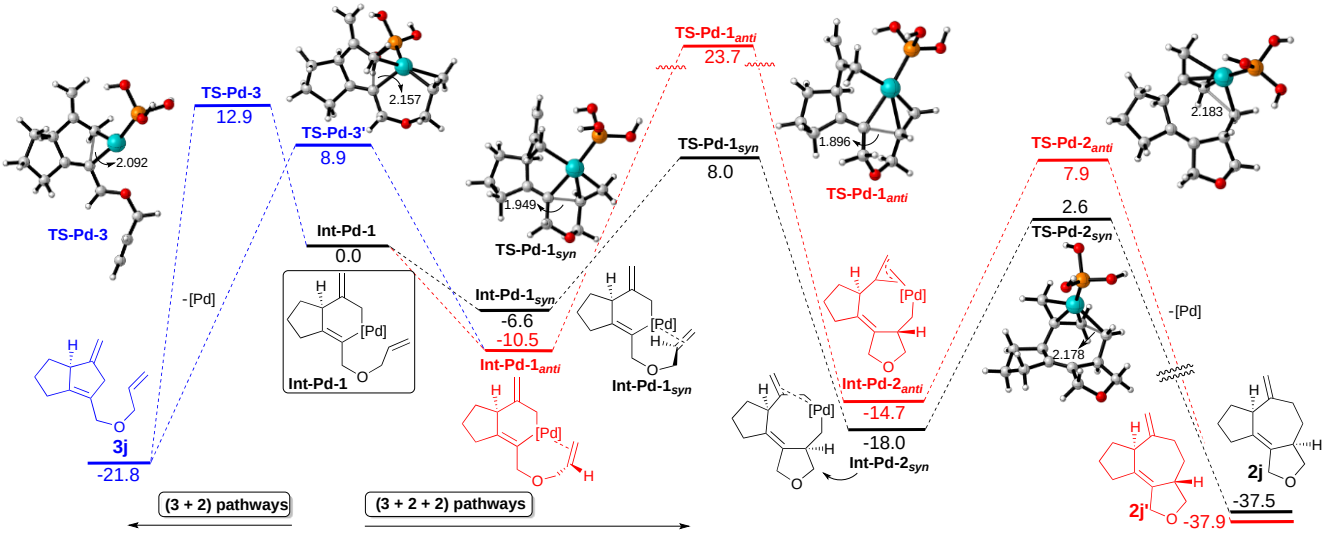


Figure 3. Computed reaction profile with a model Pd catalyst. [Pd] = Pd[P(OH)$_3$]. See caption for Figure 2 for additional details.

In conclusion, we have developed an intramolecular Rh-catalyzed (3 + 2 + 2) cycloaddition of ACPs alkenes and alkynes that affords synthetically relevant 5,7,5-fused tricyclic systems with moderate or good yields, good versatility and high diastereoselectivities. In contrast to related Pd-catalyzed cycloadditions that provide mixtures of (3 + 2) and (3 + 2 + 2) cycloadducts, the current reaction only yields the desired cycloheptenyl adducts.

Acknowledgements

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Keywords: Cycloaddition • rhodium • alkylidenecyclopropane • carbocycle • catalysis

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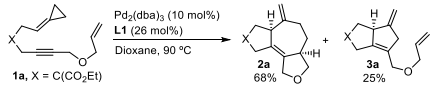
[8] The use 4% of [Rh(COD)Cl]$_2$ as originally reported by Evans,[5a] instead of 10% (entry 1), provided a poorer yield of **2a** (< 20%). Further attempts to increase the yield of **2a**, by introducing minor modifications of the reaction conditions (solvent, temperature or concentration) were not successful.

[9] The previously reported Pd-catalyzed (3+2+2) cycloaddition of **1a** afforded a 68% of the *syn*-(3+2+2) adduct **2a** and 25% yield of the competitive cyclopentene product **3a**. See reference [3b].



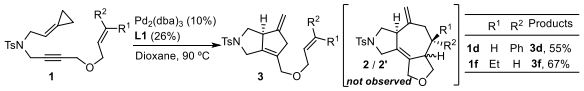
[10] A less electron-donating phosphine like (pCF$_3$Ph)$_3$P might facilitate the coordination of the alkene to the Rh and decrease the energy barrier of the reductive elimination. See, for instance: a) J. F. Hartwig, *Inorg. Chem*. **2007**, *46*, 1936 – 1947. For the synthesis of [(pCF$_3$Ph)$_3$P]$_3$RhCl, see: b) H-Ch. Wu, Sh. Hamid, J-Q. Yu, J. Spencer, *J. Am. Chem. Soc*. **2009**, *131*, 9604 – 9605.

[11] The absence of (3+2) adducts in the cycloaddition of **1b** and **1c** sharply contrasts with the poor selectivities of their Pd-catalyzed cycloadditions [(3+2+2)/(3+2) = 1.4 : 1 for **1b** and 1.2 : 1 for **1c**], see reference [3b].

[12] CCDC 986263 contains the crystallographic data of **2c**, which can be obtained via www.ccdc.cam.ac.uk/data_request/cif.

[13] CCDC 986265 contains the crystallographic data of **2d**, which can be obtained via www.ccdc.cam.ac.uk/data_request/cif.

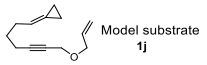
[14] Indeed, the Pd-catalyzed cycloadditions of **1d** and **1f**, under previously reported conditions,[3b] did not afford the corresponding (3+2+2) adducts. Instead, the (3+2) cycloadducts **3d** and **3f** were isolated in moderate yields.



[15] a) X-ray analysis of a pure sample of **2c'**, obtained by crystallization of the 1:7 mixture of **2c** and **2c'** resulting from the reaction, confirmed the *anti* configuration of the hydrogen atoms at the rings fusions. See Figure S3. CCDC 986264 contains the crystallographic data of **2c'**, which can be obtained via www.ccdc.cam.ac.uk/data_request/cif.

[16] Analysis of the enantioselectivity of **2c** and **2c'** by chiral HPLC revealed a 30 % ee for **2c** and a 20% ee for **2c'**, which suggests the viability of developing enantioselective variants with chiral phosphorous ligands.

[17] All the calculations were carried out at the B3LYP/def2-SVP level using the Gaussian 09 rev. B.01 suite of programs. See the Supp. Info. for details.



[18] For a theoretical study on Pd-catalyzed (3+2) cycloadditions of alkynylidenecyclopropanes including these initial steps, until **Int-Pd-1**, see: a) R. García-Fandiño, M. Gulías, L. Castedo, J. R. Granja, J. L. Mascareñas, D. J. Cárdenas, *Chem. Eur. J.* **2008**, *14*, 272 – 281; b) R. Garcia-Fandiño, M. Gulías, J. L. Mascareñas, D. J. Cárdenas, *Dalton Trans* **2012**, *41*, 9468– 9481.

[19] Theoretical calculations performed with the Rh-phosphite model catalyst $RhCl(P(OH)_3)_3$, also showed a significant preference for the (3+2+2) cycloaddition over the 3+2 counterpart (DDG = 12.3 Kcal·mol-1)

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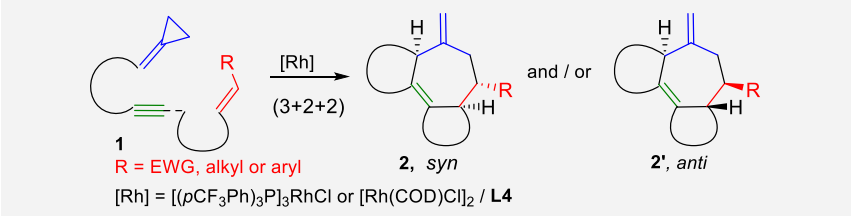
Rhodium-catalyzed Intramolecular (3 + 2 + 2) Cycloadditions between Alkylidenecyclopropanes, Alkynes and Alkenes



A Rh-catalyzed intramolecular (3 + 2 + 2) cycloaddition is reported. The cycloaddition affords synthetically relevant 5,7,5-fused tricyclic systems of type **2** from readily available dienyne precursors. The transformation takes place with moderate or good yields, high diastereoselectivity, and total chemoselectivity.