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Ruthenium-Catalyzed (2 + 2) Intramolecular Cycloaddition of Allenenes

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Supporting Information

ABSTRACT: We report a ruthenium-catalyzed (2 + 2) intramolecular cycloaddition of allenes and alkenes. We have found that the use of the ruthenium complex $RuH_2Cl_2(P^iPr_3)_2$, which has previously gone unnoticed in catalytic applications, is crucial for the observed reactivity. The reaction proceeds under mild conditions and is fully diastereoselective, providing a practical entry to a variety of bicyclo[3.2.0]heptane skeletons featuring cyclobutane rings.

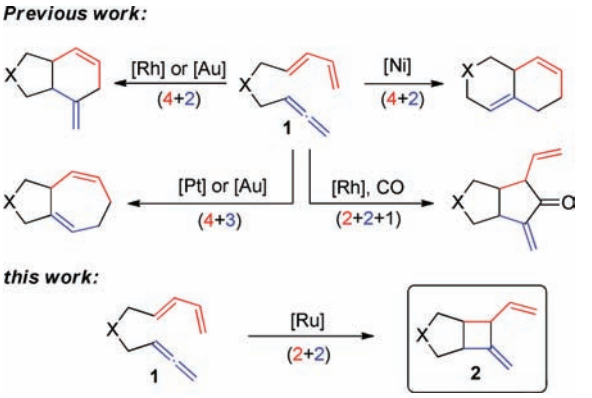
The extraordinary expansion of transition-metal catalysis during the last decades has opened the door to the development of a wide variety of cycloaddition reactions that otherwise could not be accomplished.[1,2] In some cases, it is even possible to choose different cycloaddition channels for the same substrate by just changing the metal complex that is used as the catalyst. This is the case for allenedienes of type **1**, which can participate in different types of (4 + 2), (4 + 3), or (2 + 2 + 1) intramolecular annulations depending on the choice of Rh,[3,4] Ni,[4] Au,[5] or Pt[6] catalysts (Scheme 1).

Herein we report a new type of intramolecular cycloaddition of allenedienes, namely, a ruthenium-catalyzed [2C + 2C] annulation process. The reaction proposes a new way of making fused cyclobutanes and represents a significant addition to the existing cycloaddition toolbox because of the scarcity of catalytic (2 + 2) intramolecular annulations of nonactivated systems.[7,8] Indeed, the only reported examples of intramolecular (2 + 2) cycloadditions between allenes and alkenes have been restricted to the use of arylalkenes and rely on gold catalysis.[7c,g,h]

This research arose in the context of recent findings on the stoichiometric reactivity of the complex $RuH_2Cl_2(P^iPr_3)_2$ with allenes.[9] We reasoned that tethering the allene to another unsaturated unit (e.g., a conjugated diene) could offer opportunities for annealing both partners in a catalytically productive manner.[10] A preliminary experiment was carried out using allendiene **1a**, a type of precursor that was recently used by us in Pt- and Au-catalyzed cycloaddition reactions.[5a,c,6] Gratifyingly, treatment of this substrate with 10 mol % $RuH_2Cl_2(P^iPr_3)_2$ in toluene at 45 °C afforded the (2 + 2) cycloadduct **2a** as a single diasteroisomer, although in a modest 30% yield (Scheme 2, conditions *a*). After a brief optimization, we found that the use of $(CH_2)_2Cl_2$ as the solvent and a higher dilution increased the yield up to 52% (conditions *b*). Importantly, other cycloadducts, such as the potentially competitive (4 + 2) product **3a**, were not detected.

To check the importance of the nature of the Ru catalyst, we browsed the performance of other Ru complexes previously used in different types of cycloadditions, such as Cp*RuCl(COD), $[Cp^*Ru(CH_3CN)_3]PF_6$, and $RuCl_2(PPh_3)_3$.[11] In each case, however, we observed either no reactivity or very low conversion to the desired (2 + 2) adduct **2a**. Thus, the scope of the cycloaddition process was further investigated using $RuH_2Cl_2(P^iPr_3)_2$ as the catalyst (Table 1).

Scheme 1. Annulations of Allenedienes



Scheme 2. Intramolecular (2 + 2) Cycloaddition

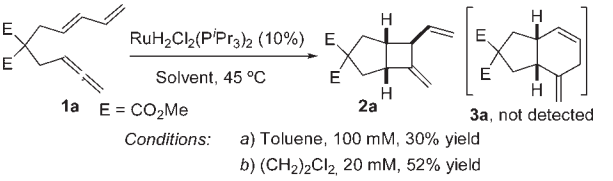


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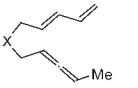
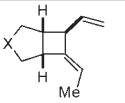
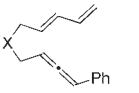
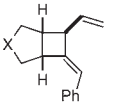
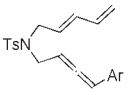
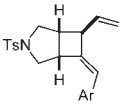
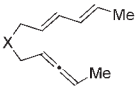
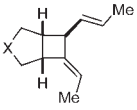
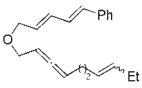
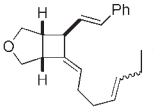
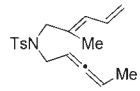
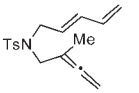
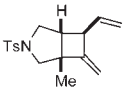
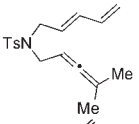
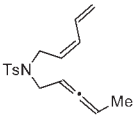
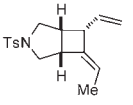
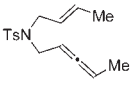
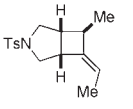
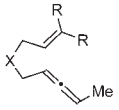
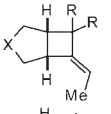
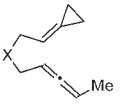
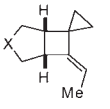
Table 1. Scope of the Ru-Catalyzed (2 + 2) Cycloaddition[a]

Entry	Substrate (**1**)	Product (**2**)	**2**, Yield
1	 **1b**, X= $C(CO_2Me)_2$		**2b**, 86%
2	**1c**, X= NTs		**2c**, 84%
3	**1d**, X=O		**2d**, 72%[b]
4	 **1e**, X= $C(CO_2Me)_2$		**2e**, 64%
5	 **1f**, Ar = *p*-CF_3Ph		**2f**, 60%
6	 **1g**, X= $C(CO_2Me)_2$		**2g**, 82%
7	 **1h**		**2h**, 80%
8	 **1i**	-	**2i**, -
9	 **1j**		**2j**, 42%[c]
10	 **1k**	-	**2k**, -
11	 (*Z*)-**1c**		**2c'**, 45%[d]
12[e]	 **1l**		**2l**, 52%[d]
13	 **1m**, R = H X =$C(CO_2Et)_2$		**2m**, 78%
14	**1n**, R = Me X =$C(CO_2Et)_2$		**2n**, -
15	 **1o**, X = $C(CO_2Et)_2$		**2o**, 63%

[a] Conditions: $RuH_2Cl_2(P^iPr_3)_2$ (10 mol %), DCE (20 mM), 45 °C, 2−6 h. The relative stereochemistries of the products were determined by nuclear Overhauser effect (NOE) NMR experiments. Some structures were also solved by X-ray crystallographic analysis. See the Supporting Information for details. [b] Yield was not optimized because of volatility of the product. [c] $RuH_2Cl_2(P^iPr_3)_2$ (20 mol %) was used. [d] Some of the side products that could be detected in the reaction mixture most probably arose from competitive β-hydride elimination processes. [e] The substrate was contaminated by a small proportion of the cis isomer.

Interestingly, substitution at the terminal position of the allene by a methyl group led a cleaner reaction and a significant increase in the reaction efficiency.[12] Therefore, precursors **1b**−**d** featuring different connecting tethers between the allene and the diene gave the expected adducts in good yields and complete selectivity with regard to the exo geometry of the double bond (Table 1, entries 1−3). Allenedienes **1e** and **1f** equipped with aromatic substituents at the allene terminus also participated in the cycloaddition, providing the corresponding (2 + 2) adducts as single isomers in 64 and 60% yield, respectively (entries 4 and 5). The reaction also worked with substituted dienes **1g** and **1h**, providing the corresponding adducts **2g** and **2h** in good yields of 82 and 80%, respectively (entries 6 and 7). Substrate **1i** bearing a methyl group at the most internal position of the diene did not react, but precursor **1j** with a methyl group at the internal position of the allene underwent the cycloaddition. Although the yield was moderate, this reaction provides an entry to important bicyclo[3.2.0]heptane systems with one quaternary stereocenter at the ring fusion (entry 9).

Mechanistically meaningful allenene **1k** bearing two methyl substituents at the distal position of the allene afforded only traces of the desired product, even after several hours at 45 °C. Indeed, most of the starting material was recovered unreacted from the resulting reaction mixture. On the other hand, substrate (*Z*)-**1c** featuring an internal cis alkene afforded **2c′** (entry 11), a cycloadduct that is epimeric to **2c** at the stereocenter incorporating the vinyl group. This result confirmed that the cycloaddition is stereospecific with regard to the diene stereochemistry.

Having browsed the scope with conjugated dienes, we next investigated whether the presence of the conjugated alkene is a strict requirement for the cycloaddition. Remarkably, allenene **1l** did also participate in the process, providing the expected cycloadduct in 52% yield (entry 12). Meanwhile, allenene **1m** containing an unsubstituted alkene underwent an efficient (2 + 2) cycloaddition (78% yield; entry 13). Interestingly, while substrate **1n** containing a dimethylalkene did not react even at higher temperatures, the alkylidenecyclopropane analogue **1o** gave the expected cycloadduct in good yield (entry 15).[13]

In order to gain mechanistic insights, we studied the transformation using density functional theory (DFT) calculations (B3PW91/LANL2DZ/6-31G**) with **1p** as a model substrate (Scheme 3 and Figure 1). These DFT calculations suggested that the catalytic cycle is initiated by the unsaturated species $RuCl_2(P^iPr_3)$ (**A**),[14] which arises from the dissociation of molecular hydrogen and one triisopropylphosphine ligand from the ruthenium precursor (Scheme 3). Coordination of the conjugated diolefin unit and the internal allenic double bond of the substrate to the metal center of **A** generates complex **B**, which evolves into the ruthenabicycle **C** by oxidative cyclometalation. Intermediate **C** might be represented as two main rotameric species $\mathbf{C_1}$ and $\mathbf{C_2}$, depending on the spatial disposition of the isopropylphosphine (see the Supporting Information). A σ- to π-allyl transformation of **C** affords **D**, which also exhibits two low-energy phosphine rotamers ($\mathbf{D_1}$ and $\mathbf{D_2}$). Intermediate **D** eliminates the (2 + 2) product by migration of the metalated carbon atom of the alkenyl unit to the internal site of the allyl moiety. The calculations suggest that formation of **C** rather than the final reductive elimination is the rate-determining step.[15] Indeed, reductive elimination from intermediate **D** (C−Ru−C angle 61.6°) is rather easy and much more favored than an alternative direct transformation of **C** into the product (C−Ru−C angle 104.0°). The proximity of the carbon atoms in **D** seems to facilitate this reductive step.

We also carried out calculations on substrate **1d**, which was experimentally tested, and the results suggest a similar energy profile (see the Supporting Information for details). On the other hand, calculations with allenenes instead of allenedienes

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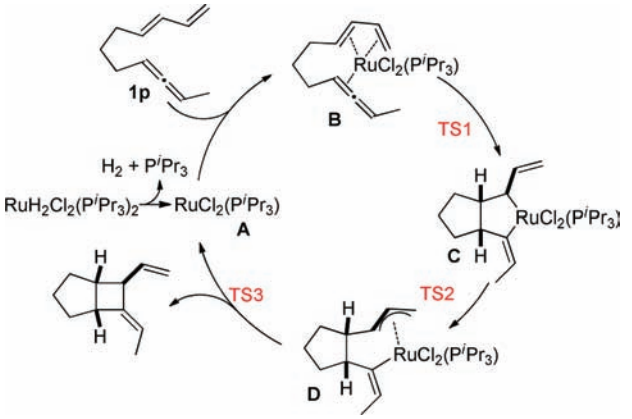
Scheme 3. Mechanistic Proposal



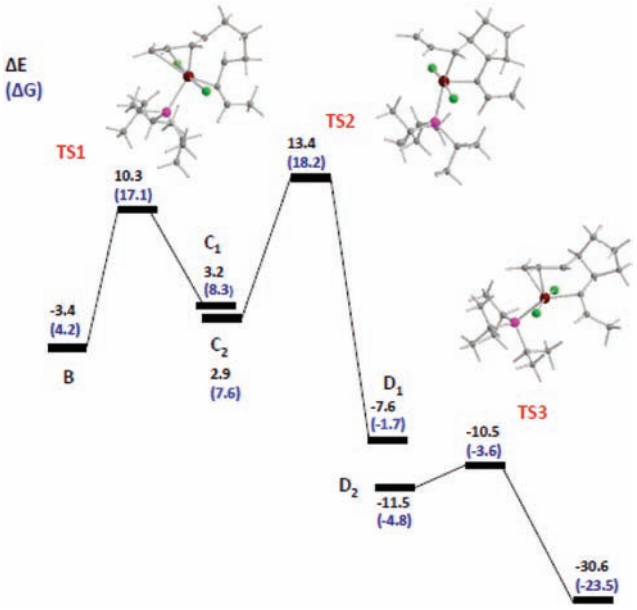
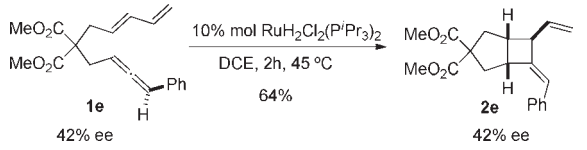


Figure 1. Energy profile (kcal mol^{-1}; ΔG values at 1 atm and 298.15 K are given in parentheses).

Scheme 4. Cycloaddition of Enantioenriched 1e



indicated a similar pathway, although the reductive elimination from an intermediate related to **C** but lacking the pendant vinyl group is more difficult, causing that step to become rate-determining.

This mechanism is fully consistent with the stereospecificity and diastereoselectivity observed experimentally. It is also concordant with the high sensitivity of the transformation to disubstitution of the distal carbon of the allene (such as in **1k**), as this introduces a serious steric congestion between one of the allene's groups and the isopropyl groups of the phosphine ligand.

Also in agreement with this mechanism, we found that treatment of an enantioenriched sample of allenediene **1e** (42% ee)[16] under the reaction conditions produced the expected cycloadduct **2e** with the same degree of enantiopurity (Scheme 4). In view of the ample number of possibilities for preparing optically active allenes, the methodology presents an interesting alternative to ensemble fused cyclobutanes in an enantioselective manner.[17]

In conclusion, we have developed a new type of metal-catalyzed (2 + 2) intramolecular cycloaddition of allenes and alkenes that represents the first catalytic application of $RuH_2Cl_2(P^iPr_3)_2$. The reaction proceeds under mild conditions and is fully diastereoselective, providing a new practical entry to bicyclic structures featuring cyclobutanes.[18]

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectroscopic data, crystallographic information files, additional calculations, and energies and Cartesian coordinates of optimized geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Kobayashi, S.; Jorgensen, K. A. *Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002.
(2) For a comprehensive review of metal-catalyzed cycloadditions, see: Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49–92.
(3) (a) Wender, P. A.; Croatt, M. P.; Deschamps, N. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2459–2462. (b) For a discussion of the "diene effect", see: Croatt, M. P.; Wender, P. A. *Eur. J. Org. Chem.* **2010**, 19–32.
(4) Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843–1844.
(5) (a) Trillo, B.; López, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *Chem.—Eur. J.* **2009**, *15*, 3336–3339. (b) Mauleón, P.; Zeldin, R. M.; González, A. Z.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 6348–6349. (c) Alonso, I.; Trillo, B.; López, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2009**, *131*, 13020–13030.
(6) Trillo, B.; López, F.; Gulías, M.; Castedo, L.; Mascareñas, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 951–954.
(7) For transition-metal-catalyzed intramolecular (2 + 2) cycloadditions, see: (a) Oh, C. H.; Gupta, A. K.; Park, D. I.; Kim, N. *Chem. Commun.* **2005**, *45*, 5670–5672. (b) Jiang, X.; Cheng, X.; Ma, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 8009–8013. (c) Luzung, M. R.; Mauleón, P.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12402–12403. (d) Kim, S. M.; Park, J. H.; Kang, Y. K.; Chung, Y. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 4532–4535. (e) Saito, N.; Tanaka, Y.; Sato, Y. *Organometallics* **2009**,

28, 669–671. (f) Saito, N.; Tanaka, Y.; Sato, Y. *Org. Lett.* **2009**, *11*, 4124–4126. (g) Alcarazo, M.; Stork, T.; Anoop, A.; Thiel, W.; Fürstner, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 2542–2546. Also see:(h) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804–16805.

(8) For recent reviews of (2 + 2) cycloadditions, see: (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Soc. Rev.* **2010**, *39*, 783–816. (b) Ma, S. *Chem. Rev.* **2005**, *105*, 2829–2872.

(9) Collado, A.; Esteruelas, M. A.; López, F.; Mascareñas, J. L.; Oñate, E.; Trillo, B. *Organometallics* **2010**, *29*, 4966–4974.

(10) For a preliminary use of this complex in a dehalogenation reaction, see: Esteruelas, M. A.; Herrero, J.; Oliván, M. *Organometallics* **2004**, *23*, 3891–3897.

(11) For selected recent examples of Ru-catalyzed cycloadditions of nonactivated unsaturated systems, see: (a) Garcia-Rubin, S.; Varela, J. A.; Castedo, L.; Saá, C. *Chem.—Eur. J.* **2008**, *14*, 9772–9778 and references therein. (b) Grecian, S.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 8285–8287. (c) Trost, B. M.; Hu, Y.; Horne, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 11781–11790. (d) Villeneuve, K.; Tam, W. *Organometallics* **2006**, *25*, 843–848. (e) López, F.; Delgado, A.; Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 10262–10263.

(12) Probably the presence of a substituent at the allene terminus avoids competitive side reactions of the allene moiety, and therefore, the cycloaddition pathway becomes preferential.

(13) Substrate **1o** undergoes an intramolecular (3 + 2) cycloaddition when treated with appropriate Pd catalysts. See: Trillo, B.; Gulías, M.; López, F.; Castedo, L.; Mascareñas, J. L. *Adv. Synth. Catal.* **2006**, *348*, 2381–2384. On the other hand, it has also been shown that related alkylidenecyclopropanes can participate in Ru-catalyzed intramolecular (3 + 2) cycloadditions to alkynes (see ref 11e).

(14) Barriers higher than 30 kcal mol^{-1} were found using $RuCl_2(P^iPr_3)_2$ as the active species for the first step of the process.

(15) Preliminary calculations suggested that the (4 + 2) pathway is more costly than the (2 + 2) route. See the Supporting Information for more details.

(16) The synthesis of this enantioenriched allenediene **1d** (42% ee) was carried out following a procedure similar to that described in the following reference: Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089–2090.

(17) For a review of the synthesis and use of chiral cyclobutanes, see: Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449–1484.

(18) For some examples of naturally occurring cyclobutanes and their applications, see: (a) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485–1538. (b) Sergeiko, A.; Poroikov, V. V.; Hanus, L. O.; Dembitsky, V. M. *Open Med. Chem. J.* **2008**, *2*, 26–37.