

Nickel-Catalyzed Intramolecular [3 + 2 + 2] Cycloadditions of Alkylidenecyclopropanes. A Straightforward Entry to Fused 6,7,5-Tricyclic Systems

Lucía Saya,[†] Israel Fernández,[‡] Fernando López,^{*,†,§} and José L. Mascareñas^{*,†}

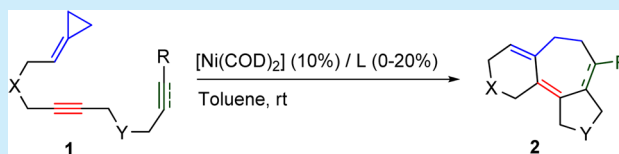
[†]Centro Singular de Investigación en Química Biológica y Materiales Moleculares (CIQUS) and Departamento de Química Orgánica, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain

[‡]Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense Madrid, 28040-Madrid, Spain

[§]Instituto de Química Orgánica General (CSIC), Juan de la Cierva, 3, 28006 Madrid, Spain

S Supporting Information

ABSTRACT: A highly diastereo- and chemoselective intramolecular nickel-catalyzed cycloaddition of alkene- and alkyne-tethered alkynylidenecyclopropanes is reported. The method constitutes the first fully intramolecular [3 + 2 + 2] alkylidenecyclopropane cycloaddition occurring via a proximal cleavage of the cyclopropane and makes it possible to build relevant 6,7,5-tricyclic frameworks in a single-pot reaction. Importantly, the reaction outcome is highly dependent on the characteristics of the nickel ligands.



Modern organic synthesis is increasingly demanding the development of sustainable transformations that allow readily available precursors to be converted into complex, target-relevant products.¹ In this context, transition-metal-catalyzed multicomponent cycloadditions are particularly appealing because they allow the assembly of cyclic systems from simpler acyclic precursors.² Along these lines, Saito³ and de Meijere⁴ have developed several Ni-catalyzed [3 + 2 + 2] intermolecular cycloadditions of alkylidenecyclopropanes with alkynes and/or alkenes (Scheme 1, a,b). Although the reactions yield synthetically appealing cycloheptene systems, their success is associated with the use of specifically activated alkylidenecyclopropanes

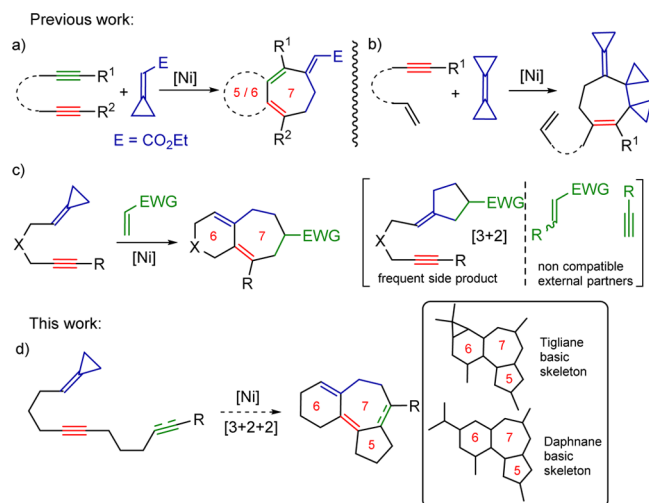
(ACPs). We have demonstrated that alkynylidenecyclopropanes can react with activated alkenes in the presence of Ni(COD)₂ to give 6,7-bicyclic systems (Scheme 1, c).^{5,6} While the reaction works well with acrylates, it fails with β -substituted alkenes and alkynes and is often accompanied by the competitive formation of cycloadducts arising from intermolecular [3 + 2] annulations.

Considering the wide occurrence and enormous relevance of bioactive diterpenes featuring 6,7,5-tricyclic skeletons and the well-known difficulties to assemble these types of skeletons using current synthetic methodologies,⁷ we investigated the viability of a fully intramolecular [3 + 2 + 2] annulation (Scheme 1, d).

Herein we describe an efficient and chemoselective intramolecular [3 + 2 + 2] cycloaddition reaction that allows 6,7,5-tricyclic skeletons to be built in a single step. The method constitutes the first intramolecular [3 + 2 + 2] cycloaddition involving ACPs that proceeds by proximal cleavage of the cyclopropane ring.⁸ We also provide DFT calculations that qualitatively explain the experimental results and shed light on the reaction mechanisms.

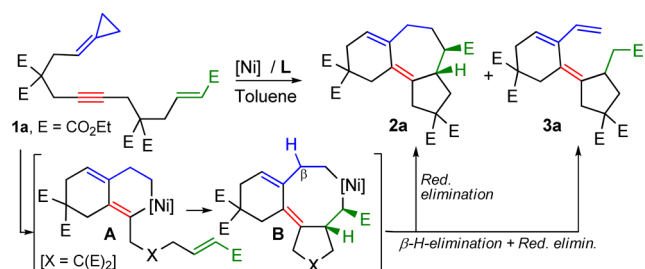
The feasibility of the cycloaddition was assessed with alkynylidenecyclopropane **1a** (Table 1). Gratifyingly, treatment of a toluene solution of **1a** with Ni(COD)₂ (10%), at rt for 24 h, led to the desired [3 + 2 + 2] cycloadduct **2a**, which was isolated in 85% yield (Table 1, entry 1). The reaction was completely diastereoselective, providing exclusively the isomer that retains the *trans* stereochemistry of the parent alkene, and could be significantly accelerated by slight heating at 40 °C (83% yield after 2 h, entry 2). Moreover, the catalyst loading could be decreased down to 5% without significantly compromising the

Scheme 1. Ni-Catalyzed [3 + 2 + 2] Cycloadditions



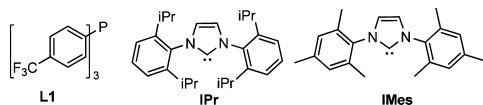
Received: August 1, 2014

Published: September 18, 2014

Table 1. Preliminary Screening of the Intramolecular Cycloaddition


entry ^a	[Ni] (10%)	L (mol %)	t (°C)	time (h)	2a (%)	3a (%)
1	Ni(cod) ₂		rt	24	85	0
2	Ni(cod) ₂		40	2	83	0
3 ^b	Ni(cod) ₂		40	4	80	0
4	Ni(cod) ₂	PPh ₃ (20)	40	2	0	86
5	Ni(cod) ₂	PPh ₃ (10)	40	24	0	39 ^{c,d}
6	Ni(cod) ₂	PCy ₃ (20)	40	4	0	85
7	Ni(cod) ₂	L1 (20)	40	2	9 ^{c,e}	5 ^c
8	Ni(cod) ₂	dppe (10)	40	24	76 ^{c,f}	1 ^c
9	Ni(cod) ₂	dppp (10)	40	24	86 ^{c,g}	2 ^c
10	Ni(cod) ₂	IPr (20)	40	24	23 ^{c,h}	1 ^c
11	Ni(cod) ₂	IMes (20)	40	24	67 ^{c,i}	1 ^c

^a1a (0.2 M in toluene), [Ni(COD)₂] (10%), L (%), at 40 °C. Full conversions (determined by ¹H NMR) and isolated yields of 2a and 3a, unless otherwise noted. ^bCarried out with Ni(COD)₂ (5%). ^cYield determined by ¹H NMR with internal standard. ^d89% conversion. ^e67% conversion. ^f86% conversion. ^g90% conversion. ^h38% conversion. ⁱ77% conversion.

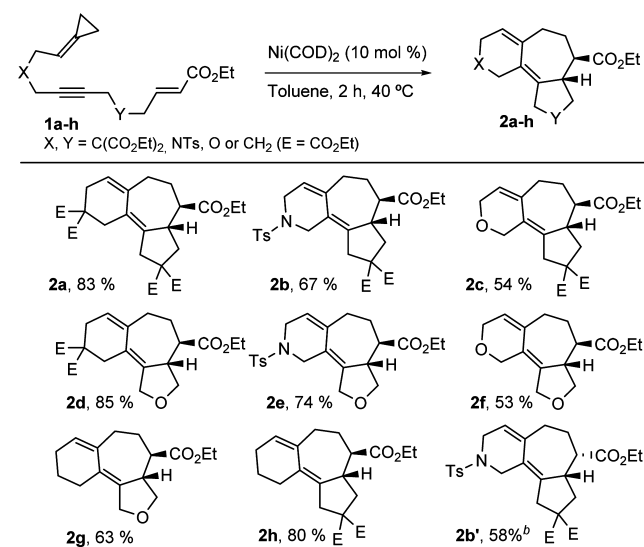


rate and yield of the process (entry 3). In an attempt to further understand the catalytic system, we analyzed the influence of external ligands. Curiously, and in contrast to the intermolecular processes,⁵ the use of PPh₃ (20%) in combination with Ni(COD)₂ (10%) did not inhibit the reaction; however, instead of providing the expected cycloadduct 2a, the reaction gave the bicyclic triene 3a in 86% yield, (entry 4).

The formation of this triene can be rationalized in terms of a β -hydride elimination step occurring on a hypothetical nickelacyclooctene intermediate of type B, which could alternatively evolve to the desired cycloadduct 2a through a reductive elimination step (Table 1). The use of equimolar amounts of Ph₃P and Ni(COD)₂ led to a significant decrease of the reaction rate (39% yield after 24 h), although the selectivity toward the triene 3a was preserved (entry 5). A more donating phosphine such as PCy₃ (20%) also favored the formation of 3a, which in this case was isolated in 85% yield after 4 h (entry 6). On the other hand, a less donating phosphine such as (*p*-CF₃Ph)₃P partially restored the [3 + 2 + 2] cycloaddition pathway, providing a 1:5.7 mixture of 2a and 3a in 60% overall yield (entry 7). Interestingly, the β -hydride elimination pathway could be completely suppressed by using bidentate phosphines such as dppe or dppp; however, full conversions were not reached even after 24 h at 40 °C when using these phosphines (entries 8 and 9). The ability of the bisphosphine ligands to inhibit the β -hydride elimination pathway is consistent with the lack of vacant sites at the metal owing to the bidentate coordination of the ligand.⁹ Curiously, and contrary to the performance of Ni(0)/

PR₃ catalysts (entries 4, 6, 7), the use of *N*-heterocyclic carbene ligands such as IPr or IMes led to the exclusive formation of the [3 + 2 + 2] cycloadduct 2a, although the reaction rates were significantly lower than that observed with just Ni(COD)₂ (entries 10 and 11 vs 2). The inhibition of the β -hydride elimination pathway in these cases might be related to the particular geometry of these bulky NHC ligands, which could impede the adoption of the required *syn*-coplanar disposition of the Ni and β -H atoms in the nickelacyclooctene intermediate of type B.¹⁰

Using Ni(COD)₂ as the optimal catalytic system, we found that ACP precursors 1b–1h, containing oxygen-, nitrogen-, or carbon-based tethers participate in the reaction to give the expected cycloadducts 2b–2h with complete diastereoselectivity and good or excellent yields (Scheme 2).

Scheme 2. Scope of the Intramolecular [3 + 2 + 2] Cycloaddition Reaction^a

^a1, 0.2 M in toluene. Full conversions determined by ¹H NMR. Isolated yields of 2. ^bObtained from *Z*-1b.

Importantly, in all cases the cycloadditions were completely chemoselective since no traces of potentially competitive [3 + 2] adducts,^{5,11} or of other side products, were detected. Particularly relevant are the cycloadditions of precursors that incorporate a saturated hydrocarbon linkage between the ACP and the alkyne (1g and 1h), as they generate tricyclic scaffolds (2g and 2h) reminiscent of those present in naturally occurring diterpenes.⁷ Of mechanistic significance, the reaction proved to be stereospecific, as the cycloaddition of a substrate containing a *cis*-alkene, *Z*-1b, afforded 2b', the complementary diastereoisomer to that obtained from 1b. The structure and stereochemical assignment of the adducts was performed by NMR, and in the case of 2e, further verification was obtained by X-ray diffraction analysis (Figure 1).

We then analyzed the viability of using 2 π -reactants other than alkenyl esters as reaction components. While electronically unactivated alkenes or allenes failed to participate in the process, the alkyne-containing precursors 1i and 1j did react in the presence of Ni(COD)₂ (10%) but instead of leading to the expected tricycles, we obtained the cyclooctatetraenes 4i and 4j in modest yields (Table 2, entries 1 and 2).¹² Notably, the use of Ph₃P (20%) in combination with Ni(COD)₂ (10%) switches

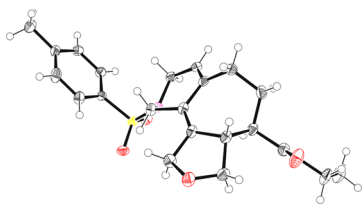
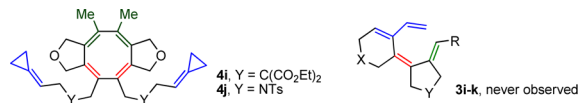


Figure 1. X-ray structure of 2e.

Table 2. Use of Alkynes as Third Cycloaddition Components^a

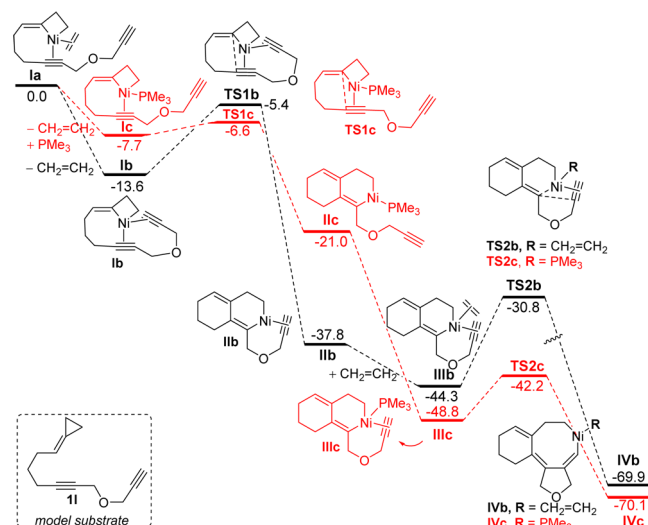
entry	R, 1	X	Y	L (mol %)	time (h)	2, (%)	4, (%)
1	Me, 1i	C(E) ₂	O		1.5		4i, 44
2	Me, 1j	NTs	O		1.5		4j, 34
3	Me, 1i	C(E) ₂	O	PPh ₃ (20)	1.5	2i, 50	4i, 10
4	Me, 1j	NTs	O	PPh ₃ (20)	1.5	2j, 36	4i, 2
5	Me, 1i	C(E) ₂	O	IPr (20)	1.5	2i, 65	
6	Me, 1j	NTs	O	IPr (20)	2	2j, 60	
7	H, 1k	C(E) ₂	O	PPh ₃ (20)	3	2k, 74	

^aConditions: **1** (0.2 M in toluene), [Ni(COD)₂] (10%), **L** (%). Full conversions after the indicated time. Isolated yields of **2** and **4**. E = CO₂Et.



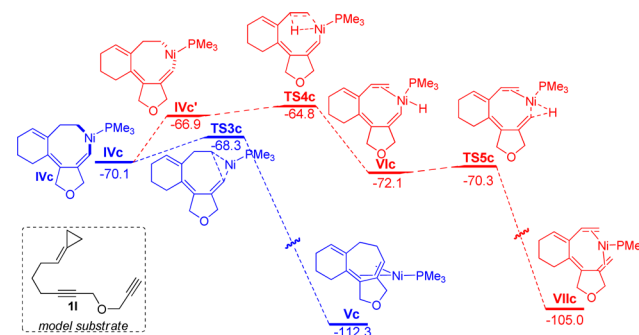
completely the outcome of the reaction, restoring the [3 + 2 + 2] cycloaddition process. Thus, under these conditions, **1i** and its NTs counterpart **1j** provided, after 1.5 h at rt, the expected tricycles in 50% and 36% yield, respectively, together with traces of the cyclooctatetraene products **4** (entries 3 and 4). Gratifyingly, the use of the NHC ligand IPr allowed the yields of the [3 + 2 + 2] cycloadducts to be improved to 65% and 60%, respectively (entries 5 and 6).¹³ On the other hand, the cycloaddition could also be achieved employing a terminal alkyne as third component (e.g., **1k**, entry 7). It is worth mentioning that in the reactions of entries 3–7 the β -hydride elimination products **3i–k** were never detected by NMR of the corresponding crude mixtures.

The above examples, besides proving a robust catalytic method for the synthesis of 6,7,5-fused tricycles, represent a new demonstration of the power of ligand tuning in metal-catalyzed reactions. To get information on the reaction mechanism and, in particular, to gain insights into the effect of the external ligand in the [3 + 2 + 2] cycloaddition of enediynes like **1i–k**, we carried out a DFT study using the substrate **1l** and Ni(CH₂=CH₂)₂ and PMe₃ as model reactants (Scheme 3).¹⁴ The computational data support a mechanism initiated by insertion of the nickel complex into the proximal C–C bond of the cyclopropane to give the nickelacyclobutane intermediate **Ia**, which readily evolves to **Ib** by exergonic coordination of the terminal alkyne or to **Ic** if coordinated to PMe₃.¹⁵ Interestingly, the following carbometallation steps that provide the nickelacyclohexenes of type **II** and the subsequent nickelacyclooctenes **IV** are significantly more favored when the nickel bears a coordinated phosphine. Indeed, analysis of the activation barriers for the first carbometallation leading to intermediates of type **II** shows a preference for the

Scheme 3. Calculated Profile for the Reaction of **1l** and [Ni(CH₂=CH₂)₂], with or without PMe₃¹⁴

pathway through transition state **TS1c** [$\Delta\Delta G^\ddagger = 7.1$ kcal·mol^{−1}], whereas the second carbometallation, through transition states of type **TS2**, shows again a lower energy barrier when occurring via **TS2c** [$\Delta\Delta G^\ddagger = 6.9$ kcal·mol^{−1}]. Thus, the presence of the external phosphine ligand seems to clearly favor the migratory insertion steps, thereby reducing the overall energetic barrier of the [3 + 2 + 2] process, a result that is in consonance with the experimental observations.¹⁶

The final reductive elimination step (**IVc** → **Vc**) proceeds via **TS3c** with a very low activation barrier of 1.8 kcal·mol^{−1} (Scheme 4, blue profile). The analogue step from **IVb** is similarly feasible ($\Delta G^\ddagger = 1.2$ kcal·mol^{−1}; Supporting Information, Scheme S1).

Scheme 4. Calculated Reductive and β -H Elimination Pathways for **IVc**¹⁴

We also calculated a plausible pathway involving a β -hydride elimination to give a tetraene of type **3** (Scheme 4, red profile). In consonance with the experimental results for the cycloaddition of **1k** (Table 2, entry 7), the process leading to **VIIc** (which proceeds via **IVc'**, a rotamer of **IVc** that has the required *syn*-disposition for the β -H elimination) is kinetically [$\Delta\Delta G^\ddagger = 3.5$ kcal·mol^{−1}] and thermodynamically [$\Delta\Delta G^\ddagger = 7.3$ kcal·mol^{−1}] disfavored over that forming the cycloadduct **Vc** (Scheme 4, blue profile). In contrast, we have found that the pathways leading to the products **2g** and **3g** are clearly competitive (Supporting Information, Scheme S2). This is in qualitative agreement with the experimental observation of products arising from a β -H elimination pathway, when the reaction of a diene like **1a** is

carried out in the presence of monodentate phosphines (Table 1, entries 4–6).

In summary, we have developed a Ni(0)-catalyzed [3 + 2 + 2] cycloaddition between an alkynylidenecyclopropane and a tethered alkene or alkyne. The cycloaddition, which proceeds via proximal cleavage of the cyclopropane and takes place with excellent chemo- and stereoselectivity, generates three new C–C bonds and provides a straightforward approach to synthetically appealing 6,7,5-fused tricyclic systems. Importantly, the results demonstrate that the reaction rate and outcome depends on the nickel ligands and that it is even possible to switch among different products by changing their electronic characteristics and denticity. These interesting ligand effects might be relevant to other nickel-catalyzed processes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data, including X-ray structures and further DFT calculations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: fernando.lopez@csic.es.

*E-mail: joseluis.mascareñas@usc.es.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Spanish MINECO (SAF2010-20822-C02-01/02, CTQ2010-20714-C02-01/BQU, CTQ2013-44303-P and CSD2007-00006, Consolider-Ingenio), the ERDF, the Xunta de Galicia (GRC2010/12, GR2013-041, INCITE09 209084PR), and the ERC (Adv. Grant. 340055). We thank Dr. G. Bhargava (Punjab Technical University) for initial work and the Orfeo-Cinca network.

■ REFERENCES

- (1) Wender, P. A.; Miller, B. L. *Nature* **2009**, *264*, 197.
- (2) (a) Inglesby, P. A.; Evans, P. A. *Chem. Soc. Rev.* **2010**, *39*, 2791. (b) Balme, G.; Bouyssi, G.; Monteiro, N. In *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005; pp 224–276. (c) Heller, B.; Hapke, M. *Chem. Soc. Rev.* **2007**, *36*, 1085. (d) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (e) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467. (f) Kumar, P.; Louie, J. Nickel-Mediated Cycloaddition, [2 + 2 + 2] and [2 + 2 + 1] Cycloaddition. In *Transition-Metal-Mediated Aromatic Ring Construction*; Tanaka, K., Ed.; John Wiley & Sons Ltd.: Chichester, 2012.
- (3) (a) Komagawa, S.; Wang, C.; Morokuma, K.; Saito, S.; Uchiyama, M. *J. Am. Chem. Soc.* **2013**, *135*, 14508. (b) Saito, S.; Komagawa, S.; Azumaya, I.; Masuda, M. *J. Org. Chem.* **2007**, *72*, 9114. (c) Maeda, K.; Saito, S. *Tetrahedron Lett.* **2007**, *48*, 3173. (d) Komagawa, S.; Saito, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2446.
- (4) Zhao, L.; de Meijere, A. *Adv. Synth. Catal.* **2006**, *348*, 2484.
- (5) Saya, L.; Bhargava, G.; Navarro, M. A.; Guliás, M.; López, F.; Fernández, I.; Castedo, L.; Mascareñas, J. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 9886.
- (6) For selected examples of Ni-catalyzed multicomponent cycloadditions, see: (a) Kumar, P.; Zhang, K.; Louie, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 8602. (b) Kumar, P.; Troast, D. M.; Cella, R.; Louie, J. *J. Am. Chem. Soc.* **2011**, *133*, 7719. (c) Saito, S.; Maeda, K.; Yamasaki, R.; Kitamura, T.; Nakagawa, M.; Kato, K.; Azumaya, I.; Masu, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 1830. (d) Wender, P. A.; Christy, J. P.; Lesser, A. B.; Gieseler, M. T. *Angew. Chem., Int. Ed.* **2009**, *48*, 7687.

- (7) (a) Rigby, J. H. *Stud. Nat. Prod. Chem.* **1993**, *12*, 233. (b) Wender, P. A.; Rice, K. D.; Schnute, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 7897. (c) Ovaska, T. V.; Reisman, S. E.; Flynn, M. A. *Org. Lett.* **2001**, *3*, 115. (d) Paquette, L.; Gallou, F.; Zhao, Z.; Young, D. G.; Liu, J.; Yang, J.; Friedrich, D. *J. Am. Chem. Soc.* **2000**, *122*, 9610. (e) Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976. (f) Jackson, S. R.; Johnson, M. G.; Mikami, M.; Shiokawa, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2694.

- (8) Previously reported Pd- and Rh-catalyzed intramolecular [3 + 2 + 2] cycloadditions of ACPs proceed through distal opening: (a) Bhargava, G.; Trillo, B.; Araya, M.; López, F.; Castedo, L.; Mascareñas, J. L. *Chem. Commun.* **2010**, *46*, 270. For Rh, see: (b) Evans, P. A.; Inglesby, P. A. *J. Am. Chem. Soc.* **2008**, *130*, 12838. (c) Evans, P. A.; Inglesby, P. A.; Kilbride, K. *Org. Lett.* **2013**, *15*, 1798. (d) Araya, M.; Guliás, M.; Fernández, I.; Bhargava, G.; Castedo, L.; Mascareñas, J. L.; López, F. *Chem.—Eur. J.* **2014**, *20*, 10255. For a review on cycloaddition strategies to seven-membered carbocycles, see: (e) Battiste, M. A.; Pelphrey, P. M.; Wright, D. L. *Chem.—Eur. J.* **2006**, *12*, 3438.

- (9) Bidentate bisphosphine ligands have also been shown to suppress β -H elimination processes in different types of transition-metal-catalyzed cycloadditions: (a) Jiao, L.; Lin, M.; Yu, Z.-X. *Chem. Commun.* **2010**, *46*, 1059. (b) Jiao, L.; Lin, M.; Yu, Z.-X. *J. Am. Chem. Soc.* **2011**, *133*, 447. (c) Lin, M.; Kang, G.-Y.; Guo, Y.-A.; Yu, Z.-X. *J. Am. Chem. Soc.* **2012**, *134*, 398.

- (10) Hong, X.; Liu, P.; Houk, K. N. *J. Am. Chem. Soc.* **2013**, *135*, 1456.

- (11) [3 + 2] Side products are also typically observed in intramolecular Pd-catalyzed [3 + 2 + 2] cycloadditions of ACPs; see ref 8a. For [3 + 2] cycloadditions of ACPs, see: (a) Delgado, A.; Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9282. (b) Durán, J.; Guliás, M.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2005**, *7*, 5693. (c) Trillo, B.; Guliás, M.; López, F.; Castedo, L.; Mascareñas, J. L. *Adv. Synth. Catal.* **2006**, *348*, 2381.

- (12) (a) Related [2 + 2 + 2 + 2] cycloadditions of non-symmetrical bisdiynes had been previously described by Wender et al. using [(dme)NiBr₂]/Zn as catalyst, although the reported regioselectivity was complementary to that of **4i** and **4j**; see ref 6d and Wender, P. A.; Christy, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 13402. (b) 1,6-Enynes have also been shown to participate in Ni-catalyzed [2 + 2 + 2 + 2] cycloadditions; see: Chai, Z.; Wang, H.-F.; Zhao, G. *Synlett* **2009**, 1785. Under the current conditions we did not observe these potential side products. (c) The structure of **4j** was also confirmed by X-ray analysis; see the Supporting Information.

- (13) The structure of **2j** could also be confirmed by X-ray analysis; see the Supporting Information.

- (14) Calculations carried out at the PCM(toluene)-M06/def2-SVP//B3LYP/def2-SVP level using the Gaussian 09 rev. B.01. See the Supporting Information for details. Free energies (ΔG_{298}) are given in kcal mol⁻¹.

- (15) The initial step from **11** to **1a**, not shown in Scheme 3, is identical to that previously published in ref 5.

- (16) (a) The presence of these external ligands might also disfavor the [2 + 2 + 2 + 2] pathway by impeding the coordination of the second diyne. (b) The first carbometallation step was also calculated from species **1a** and, eventually, led to **IIIb** through a similar activation barrier than that from **1b**. See the Supporting Information for details.