ABSTRACT: A highly diastereo- and chemoselective intramolecular nickel-catalyzed cycloaddition of alkene- and alkyne-tethered alkylidenecyclopropanes 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 (ACP). 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-tricarbocycles 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-tricarbocyclic 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...
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 intramolecular 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 24 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 sym-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).

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 alkyn (1g and 1h), as they generate tricarbocyclic scaffolds (2g and 2h) reminiscent of those present in naturally occurring diterpenes.7 Of mechanistic significance, the reaction proved to be stereo-specific, 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 2π-reactants other than alkenyl esters as reaction components. While electronically unactivated alkenes or allenes failed to participate in the process, the alkyn-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

<table>
<thead>
<tr>
<th>entry</th>
<th>[Ni] (10%)</th>
<th>L (mol %)</th>
<th>t (°C)</th>
<th>time (h)</th>
<th>2a (%)</th>
<th>3a (%)</th>
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<td>0</td>
</tr>
<tr>
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<td>4</td>
<td>80</td>
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<td>0</td>
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<tr>
<td>4</td>
<td>Ni(cod)2</td>
<td>PPh3 (20)</td>
<td>40</td>
<td>2</td>
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<td>86</td>
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<tr>
<td>5</td>
<td>Ni(cod)2</td>
<td>PPh3 (10)</td>
<td>40</td>
<td>24</td>
<td>0</td>
<td>93c,d</td>
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<td>6</td>
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<td>4</td>
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<td>85</td>
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<td>7</td>
<td>Ni(cod)2</td>
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<td>2</td>
<td>9e,f,g</td>
<td>5c</td>
</tr>
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<td>8</td>
<td>Ni(cod)2</td>
<td>dppe (10)</td>
<td>40</td>
<td>24</td>
<td>76f,g</td>
<td>1c</td>
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<td>9</td>
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<td>86f,g</td>
<td>2c</td>
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<tr>
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<td>Ni(cod)2</td>
<td>IPr (20)</td>
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<td>24</td>
<td>23f,g,i</td>
<td>1c</td>
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<tr>
<td>11</td>
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<td>IMes (20)</td>
<td>40</td>
<td>24</td>
<td>67f,g,i</td>
<td>1c</td>
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“1a. 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.5 Carried out with Ni(COD)2 (5%). Yield determined by 1H NMR with internal standard.6 89% conversion.6 67% conversion.8 86% conversion.8 90% conversion.8 97% conversion.8

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

4i, 0.2 M in toluene. Full conversions determined by 1H NMR. Isolated yields of 2.6 Obtained from Z-1b.
organic Letters

Figure 1. X-ray structure of 2e.

Table 2. Use of Alkynes as Third Cycloaddition Components

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>I</th>
<th>X</th>
<th>Y</th>
<th>L (mol %)</th>
<th>time (h)</th>
<th>2 (%)</th>
<th>4 (%)</th>
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<td></td>
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<td>C(E)₂</td>
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<td>i</td>
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<td>2j, 36</td>
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<td>i</td>
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<td>i</td>
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<td>IPr (20)</td>
<td>2</td>
<td>2j, 60</td>
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<tr>
<td>7</td>
<td>H</td>
<td>1k</td>
<td>C(E)₂</td>
<td>PPh₃ (20)</td>
<td>3</td>
<td>2k, 74</td>
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</table>

"Conditions: 1 (0.2 M in toluene), [Ni(COD)₂] (10%), L (mol %). 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, Ii and its NTs counterpart Ij 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). 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 enediyynes like 1a–k, we carried out a DFT study using the substrate 1i and Ni(Ch₃–CH₂)₂ and PMe₃ as model reactants (Scheme 3). 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 1a, which readily evolves to 1b by exergonic coordination of the terminal alkyne or to 1c if coordinated to PMe₃. Interestingly, the following carbometalation 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 carbometalation leading to intermediates of type II shows a preference for the pathway through transition state TS1c [ΔΔΔ<sup>‡</sup> = 7.1 kcal·mol⁻¹], whereas the second carbometalation, through transition states of type TS2, shows again a lower energy barrier when occurring via TS2c [ΔΔΔ<sup>‡</sup> = 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.

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 [ΔΔΔ<sup>‡</sup> = 1.2 kcal·mol⁻¹; Supporting Information, Scheme S1].

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 [ΔΔΔ<sup>‡</sup> = 3.5 kcal·mol⁻¹] and thermodynamically [ΔΔΔG<sup>‡</sup> = 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 dieneyne 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 alkynylideneacyclopentane 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.mascarenas@usc.es.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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■ REFERENCES

(12) Related [2 + 2 + 2 + 2] cycloadditions of non-symmetrical biisynes had been previously described by Wender et al. using [(dme)Nih2/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//BSLYP/def2-SVP level using the Gaussian 09 rev. B.01. See the Supporting Information for details. Free energies (Dg298) are given in kcal mol−1.
(15) The initial step from II to Ia, not shown in Scheme 3, is identical to that previously published in ref 5.
(16) (a) The presence of these external ligands might also disfavour the [2 + 2 + 2 + 2] pathway by impeding the coordination of the second diyne. (b) The first carbometallation step was also calculated from species Ia and, eventually, led to IIb through a similar activation barrier than that from Ib. See the Supporting Information for details.