

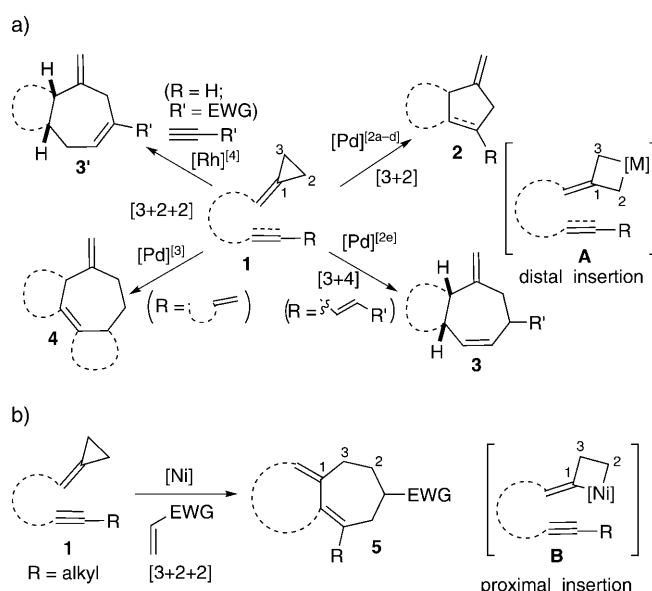
# Nickel-Catalyzed [3+2+2] Cycloadditions between Alkynylidenecyclopropanes and Activated Alkenes\*\*

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Dedicated to Professor José Barluenga on the occasion of his 70th birthday

Owing to the simultaneous presence of a coordinating double bond and a strained carbocycle, methylene- and alkylidenecyclopropanes (ACPs) undergo a number of interesting metal-assisted transformations.<sup>[1]</sup> In this context, over the last few years, we have developed a variety of [3+*n*] palladium-catalyzed intramolecular cycloadditions of alkylidenecyclopropanes (such as **1**), which provide practical entries to a variety of interesting bicycles (**2** and **3**, Scheme 1a).<sup>[2]</sup> Very recently, we also showed that the introduction of an additional two-carbon partner into the system makes it possible to accomplish intramolecular [3+2+2] annulation reactions that lead to cycloheptane-containing tricycles of type **4**.<sup>[3]</sup> In related studies, Evans and co-workers have elegantly demonstrated the possibility of using rhodium catalysts to induce intermolecular [3+2+2] processes ( $\rightarrow$ **3'**, Scheme 1a).<sup>[4]</sup> All of these reactions take place with cleavage of the distal bond of the ACP (C2–C3), and most probably proceed through the formation of 2-alkylidene metallacyclobutane intermediates of type **A**, resulting from a distal insertion of the metal in the ACP (Scheme 1a).<sup>[4,2f]</sup>

On the other hand, it has been shown that nickel complexes can promote alternative [3+2] and [3+2+2] annulations of ACPs, which involve the cleavage of a



**Scheme 1.** a) Previously reported metal-catalyzed [3+2] [3+2+2] and [4+3] cycloadditions involving ACP distal-bond cleavage, and b) our nickel-catalyzed cycloaddition involving proximal-bond cleavage. EWG = electron-withdrawing group.

proximal bond of the cyclopropane (C1–C2/3), instead of the distal one.<sup>[5]</sup> However, this chemistry is so far restricted to the use of methylenecyclopropane,<sup>[6]</sup> cyclopropylidene acetates,<sup>[7]</sup> or bicyclopropylidene,<sup>[8]</sup> as three-carbon (3C) partners. As part of our ongoing research on the development of metal-catalyzed cycloaddition reactions, we wondered about the behavior of substrates like **1** in the presence of nickel catalysts, envisaging that they could perform differently than with palladium and rhodium complexes.

Herein, we report a new type of nickel-catalyzed cycloaddition of ACPs that provides products resulting from the formal cleavage of the cyclopropane proximal bond (C1–C2). In particular, we demonstrate that ACPs of type **1**, when treated with [Ni(cod)<sub>2</sub>] (cod = 1,5-cyclooctadiene) and an electron-deficient alkene, participate in a novel [3C+2C+2C] cycloaddition reaction to give 6,7-fused bicyclic systems of type **5** (Scheme 1b). In addition, we present DFT calculations which, combined with experimental data, suggest that the catalytic cycle involves the initial formation of 1-alkylidene-nickelacyclobutane intermediates like **B**.

Initial assays were carried out with ACP **1a**. As shown in Table 1, this compound remained unchanged in the presence

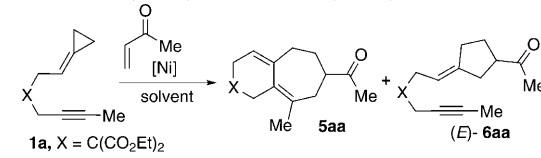
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**Table 1:** Preliminary assays of nickel-catalyzed cycloadditions of **1a**.



Entry <sup>[a]</sup>	MVK [equiv]	[Ni] (mol %)	Solvent	T [°C]	5 aa/6 aa <sup>[b]</sup>	Yield <sup>[c]</sup>
1	0	[Ni(cod) <sub>2</sub> ] (10)	toluene	RT	—	0 <sup>[d]</sup>
2	0	[Ni(cod) <sub>2</sub> ] (10)	toluene	90	—	0 <sup>[d]</sup>
3	2	[Ni(cod) <sub>2</sub> ] (10)	toluene	RT	74:26	40 <sup>[e]</sup>
4	2	[Ni(cod) <sub>2</sub> ] (10)	toluene	40	64:36	50 <sup>[f]</sup>
5	2	[Ni(cod) <sub>2</sub> ] (10)	toluene	90	72:28	58 <sup>[g]</sup>
6	10	[Ni(cod) <sub>2</sub> ] (10)	toluene	40	71:29	80
7	10	[Ni(cod) <sub>2</sub> ] (10)	DMF	40	67:33	49
8	10	[Ni(cod) <sub>2</sub> ] (10)	dioxane	40	67:33	73
9	10	[Ni(cod) <sub>2</sub> ] (10)	THF	40	65:35	75
10	10	[Ni(cod) <sub>2</sub> ]/PPh <sub>3</sub> (10)	toluene	40	—	0

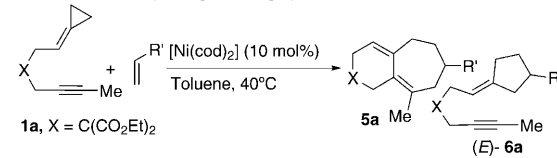
[a] Conditions: **1a** (0.2 M in toluene), 10 mol % [Ni(cod)<sub>2</sub>], MVK (0–10 equiv) for 3–12 h. [b] Based on the <sup>1</sup>H NMR spectrum of the crude reaction mixture. [c] Combined yield of **5aa** and **6aa** after full conversion, unless otherwise noted. [d] Compound **1a** was recovered after 12 h. [e] 88% conversion. [f] 66% conversion. [g] 65% conversion. DMF = *N,N*-dimethylformamide, THF = tetrahydrofuran.

of [Ni(cod)<sub>2</sub>] (10 mol %), even when heated in toluene at 90°C (Table 1, entries 1 and 2). However, **1a** did react at room temperature with the same nickel complex when it was treated with 2 equivalents of methyl vinyl ketone (MVK), thereby providing a 74:26 mixture of the [3+2+2] and [3+2] cycloadducts **5aa** and **6aa**, which were isolated in a 40% combined yield (Table 1, entry 3). Raising the temperature to 40°C, or even to 90°C, led only to a marginal increase in the efficiency of the process (Table 1, entries 4 and 5). Conversely, increasing the amount of methyl vinyl ketone up to 10 equivalents allowed for full conversions after 3 hours at 40°C, and cycloadducts **5aa** and **6aa** were isolated in a good 80% combined yield (ratio 71:29; Table 1, entry 6).<sup>[9,10]</sup> The reaction could also be performed in other solvents, such as *N,N*-dimethylformamide, dioxane, or tetrahydrofuran; however, the products were obtained in somewhat lower yields and selectivities (Table 1, entries 7–9). Interestingly, the addition of an external ligand, such as PPh<sub>3</sub>, completely inhibited the cycloaddition (Table 1, entry 10), whereas other sources of nickel(0), such as [NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>]/Et<sub>2</sub>Zn or Ni(acac)<sub>2</sub>/Et<sub>2</sub>Zn proved to be ineffective.<sup>[10]</sup>

The electronic and structural requirements of the alkene component were studied next (Table 2). Gratifyingly, cycloaddition reactions of **1a** with ethyl acrylate, acrolein, or phenyl vinyl sulfone were also efficient, thus providing the desired [3+2+2] adducts **5ab–5ad** with moderate selectivities and good overall yields (Table 2, entries 1–4). The presence of the electron-withdrawing group on the alkene seems to be mandatory, as the reactions with nonactivated alkenes, such as styrene or methyl-5-hexenoate, led to recovery of **1a** (Table 2, entries 5 and 6).<sup>[11]</sup>

Envisaging that the electronic properties of the alkyne could play an important role in determining the selectivity

**Table 2:** Nickel-catalyzed [3+2+2] cycloadditions of **1a** and alkenes.



Entry <sup>[a]</sup>	Alkene	5/6 (ratio) <sup>[b]</sup>	Yield <sup>[c]</sup>
1		<b>5aa/6aa</b> (71:29)	80
2		<b>5ab/6ab</b> (76:24)	70
3		<b>5ac/6ac</b> (80:20)	51
4		<b>5ad/6ad</b> (83:17)	40 <sup>[d]</sup>
5		—	—
6		—	—

[a] Conditions: **1a** (0.2 M in toluene), 10 mol % [Ni(cod)<sub>2</sub>], 10 equiv of alkene unless otherwise noted, for 3 h. [b] Based on the <sup>1</sup>H NMR spectrum of the crude reaction mixture. [c] Combined yield of **5a** and **6a** after full conversion. [d] 1.2 equiv of the alkene was employed.

and efficiency of the cycloaddition, we evaluated the reactivity of derivative **1b**, which features an electron-withdrawing ester substituent on the alkyne. The formation of [3+2+2] adducts of type **5** was now found to be clearly favored, and the competitive [3+2] cycloadducts (**6**) were not detected (Table 3, entries 1–4). However, the transformations suffered from moderate conversion,<sup>[12]</sup> probably because of catalyst inhibition by the product.<sup>[13]</sup> In any case, when phenyl vinyl sulfone was used as an intermolecular two carbon (2C) partner, the [3+2+2] cycloadduct could be obtained in up to 68% yield (Table 3, entry 4).

In search of a compromise to favor the [3+2+2] annealing process while avoiding the potential deactivation of the catalyst, we analyzed the performance of enynes equipped with other activating substituents on the alkyne group. Remarkably, substrate **1c**, which bears a CH<sub>2</sub>OAc substituent, provided full conversion using 10 mol % of catalyst, and gave higher [3+2+2]/[3+2] ratios (80:20) than those obtained from the cycloaddition of the nonactivated analogue **1a** (71:29; Table 3, entry 5 vs. Table 1, entry 6).

Replacing the acetyl residue in **1c** with a *tert*-butyldimethylsilyl group (**1d**) led to improved selectivity without eroding the catalyst efficiency. Indeed, the cycloaddition between **1d** and methyl vinyl ketone at 40°C, in the presence of [Ni(cod)<sub>2</sub>] (10 mol %), exclusively gave the desired [3+2+2] cycloaddition product **5da**, which was isolated in an excellent 89% yield (Table 3, entry 6). The cycloaddition of **1d** was also carried out with other alkenes, including ethyl acrylate, acrolein, and phenyl vinyl sulfone. In all of these cases, the reaction was complete after 12 hours and the [3+2+2] cycloadducts were obtained in good to excellent yields (Table 3, entries 7–9).<sup>[14]</sup> Importantly, the presence of a germinal diester in the connecting chain of **1d** is not mandatory, as the cycloaddition of the ether (**1e**) or *N*-tosyl derivatives (**1f**) led to comparable yields and also complete selectivities in favor of the desired [3+2+2] adducts (Table 3, entries 10–13).

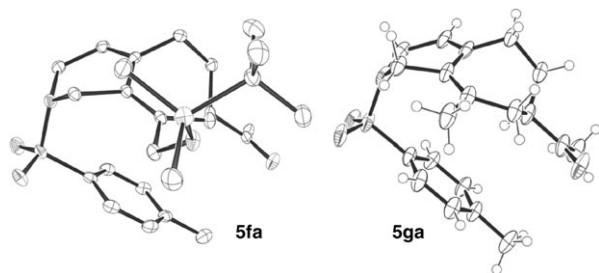
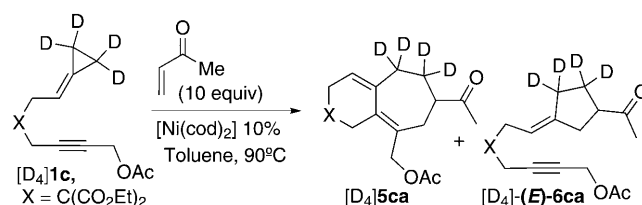
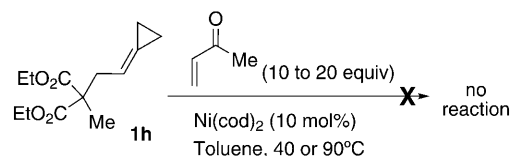
**Table 3:** Ni-catalyzed [3+2+2] cycloadditions of **1b–g** and alkenes.

Entry <sup>[a]</sup>	<b>1</b>	X	R	Alkene	<b>5/6</b> <sup>[b]</sup>	<b>5</b> , yield [%] <sup>[c]</sup>
1	<b>1b</b>	C(CO <sub>2</sub> Et) <sub>2</sub>	CO <sub>2</sub> Et <sup>[h]</sup>		100:0	<b>5ba</b> 44 <sup>[d]</sup>
2	<b>1b</b>	C(CO <sub>2</sub> Et) <sub>2</sub>	CO <sub>2</sub> Et <sup>[h]</sup>		100:0	<b>5bb</b> 50 <sup>[e]</sup>
3	<b>1b</b>	C(CO <sub>2</sub> Et) <sub>2</sub>	CO <sub>2</sub> Et <sup>[h]</sup>		100:0	<b>5bc</b> 24 <sup>[f]</sup>
4	<b>1b</b>	C(CO <sub>2</sub> Et) <sub>2</sub>	CO <sub>2</sub> Et <sup>[h]</sup>		100:0	<b>5bd</b> 68 <sup>[g]</sup>
5	<b>1c</b>	C(CO <sub>2</sub> Et) <sub>2</sub>	CH <sub>2</sub> OAc <sup>[h]</sup>		80:20	<b>5ca</b> 72
6	<b>1d</b>	C(CO <sub>2</sub> Et) <sub>2</sub>	CH <sub>2</sub> OTBS		100:0	<b>5da</b> 89
7	<b>1d</b>	C(CO <sub>2</sub> Et) <sub>2</sub>	CH <sub>2</sub> OTBS		100:0	<b>5db</b> 84
8	<b>1d</b>	C(CO <sub>2</sub> Et) <sub>2</sub>	CH <sub>2</sub> OTBS		100:0	<b>5dc</b> 45
9	<b>1d</b>	C(CO <sub>2</sub> Et) <sub>2</sub>	CH <sub>2</sub> OTBS		100:0	<b>5dd</b> 72
10	<b>1e</b>	O	CH <sub>2</sub> OTBS		100:0	<b>5ea</b> 71
11	<b>1f</b>	NTs	CH <sub>2</sub> OTBS		100:0	<b>5fa</b> 69
12	<b>1f</b>	NTs	CH <sub>2</sub> OTBS		100:0	<b>5fb</b> 62
13	<b>1f</b>	NTs	CH <sub>2</sub> OTBS		100:0	<b>5fd</b> 96
14	<b>1g</b>	NTs	Me		80:20	<b>5ga</b> 91

[a] Conditions: **1a** (0.2 M in toluene), 10 mol% [Ni(cod)<sub>2</sub>], 10 equiv of alkene, 12 h at 40°C, unless otherwise noted. [b] Based on the <sup>1</sup>H NMR spectrum of the crude reaction mixture. [c] Yield of pure **5**. Full conversion unless otherwise noted. [d] 69% conversion. [e] 66% conversion. [f] 25% conversion. [g] 71% conversion. [h] Reaction carried out at 90°C. Ac = acetyl, TBS = *tert*-butyldimethylsilyl.

The reaction of the N-tosyl derivative **1g** provided the corresponding cycloadducts in a 91% combined yield, and in an 80:20 ratio, analogous to the outcome with **1a**. Cycloadduct **5ga** as well as the homologous **5fa** were characterized by X-ray crystallographic analysis, after recrystallization from a mixture of diethyl ether/hexanes (Figure 1).<sup>[15]</sup>

In order to gain an insight into the reaction mechanism, we performed a control experiment using tetradeuterated **1c** ([D<sub>4</sub>]**1c**; Scheme 2). Analysis of the products revealed the incorporation of the deuterated methylene groups in neigh-

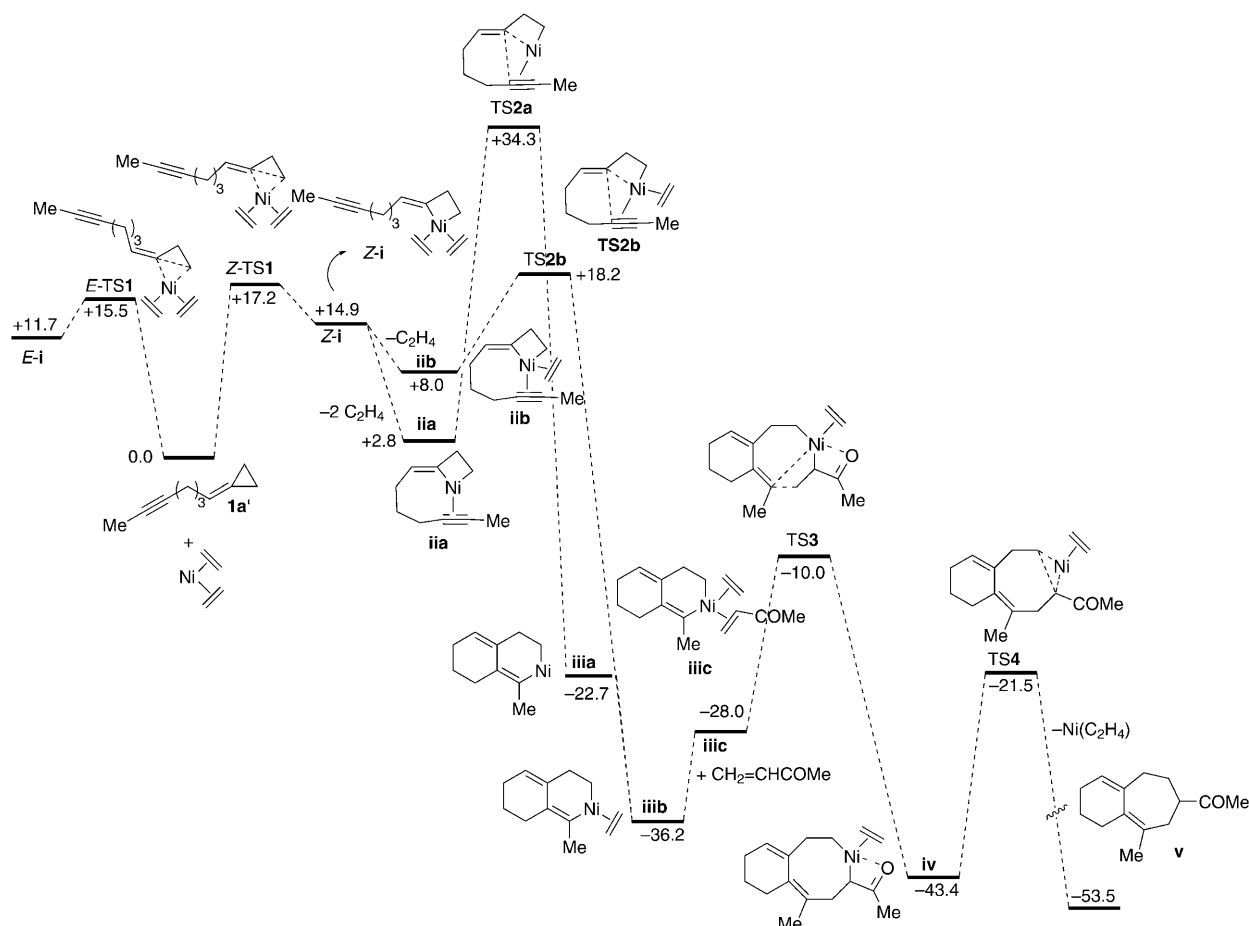
**Figure 1.** X-ray diffraction of cycloadducts **5fa** and **5ga** (hydrogen atoms in **5fa** are omitted for clarity).**Scheme 2.** Nickel-catalyzed cycloaddition of [D<sub>4</sub>]**1c**.**Scheme 3.** Control reaction with alkylidenecyclopropane **1h**.

*Z*-**i** and *E*-**i**, the *E* isomer being 3.2 kcal mol<sup>−1</sup> more stable (Scheme 4). However, intramolecular coordination of the alkyne to the nickel is only possible in the *Z* isomer (*Z*-**i**), thus leading to intermediates **ii**a or **ii**b.<sup>[17]</sup> Whilst a migratory

boring positions, which confirms that both the [3+2+2] and [3+2] cycloaddition reactions took place by cleavage of a proximal bond of the cyclopropane ring.

It was also interesting to find that the presence of the alkyne unit tethered to the ACP was not only essential for the [3+2+2] process but also for the [3+2] cycloaddition. Indeed, ACP **1h**, which lacked an alkyne moiety, failed to give any cycloaddition product, and only starting material was recovered even after several hours at high temperature or using higher amounts of alkene (Scheme 3). Performing this reaction in the presence of different amounts of an external alkyne, such as 2-hexyne, did not bring any difference, thus confirming that the tethered alkyne is critical for both annulation processes.

In order to obtain more mechanistic information, we performed preliminary DFT calculations using substrate **1a'** and Ni(CH<sub>2</sub>=CH<sub>2</sub>)<sub>2</sub> as model reactants.<sup>[16]</sup> The computational data indicated that the reaction starts with a proximal insertion of the nickel complex into the cyclopropane ring. This insertion might lead to two different isomers



**Scheme 4.** Calculated reaction profile (B3LYP/def2-SVP level) for the reaction between **1'** and  $[\text{Ni}(\text{CH}_2=\text{CH}_2)_2]$ . Free energies ( $\Delta G_{298}$ ) are given in  $\text{kcal mol}^{-1}$ .

insertion into the alkyne from **iia** into **iiia** has a rather high activation barrier, the same process from the coordinatively saturated intermediate **iib** is much easier (energy barrier of  $10.2 \text{ kcal mol}^{-1}$ ).

Intermediate **iib** might evolve by different pathways. Of all the possibilities studied,<sup>[10]</sup> the favored pathway consists of an initial coordination of the methyl vinyl ketone to the nickel center, followed by insertion into the  $\text{C}_{\text{sp}^2}\text{-Ni}$  bond to provide intermediate **iv** (overall energy barrier of  $26.2 \text{ kcal mol}^{-1}$ ). This transformation is kinetically favored over other alternative reaction pathways<sup>[10]</sup> owing to the stabilizing coordination of the carbonyl group of the ketone to the nickel moiety in the saddle point **TS3** (and in intermediate **iv**). An alternative process, which would also eventually afford products of type **5**, could involve the insertion of the methyl vinyl ketone into the  $\text{C}_{\text{sp}^3}\text{-Ni}$  bond of **iiib**. However, the corresponding transition state for this process turned out to be  $12.2 \text{ kcal mol}^{-1}$  higher in energy, making that pathway very unlikely.<sup>[10,18,19]</sup> Intermediate **iv** produces the final adduct after a reductive elimination step, with an energy barrier of  $21.9 \text{ kcal mol}^{-1}$ .<sup>[20]</sup>

In conclusion, we have developed the first nickel-catalyzed  $[3\text{C}+2\text{C}+2\text{C}]$  cycloaddition involving nonactivated ACPs. Contrary to previous palladium- and rhodium-catalyzed cycloadditions of alkynylidenecyclopropanes,<sup>[2-4]</sup> which

provided cycloadducts arising from the distal opening of the cyclopropane, the current method provides complementary, synthetically useful 6,7-fused bicyclic systems, resulting from cleavage of the proximal bond of the ring. According to DFT calculations, the reaction involves the formation of a nickel-acyclobutane species (like **iib**) as the key intermediate.

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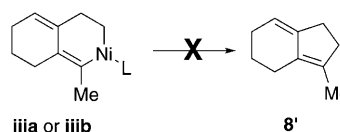
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- [10] For further details, see the Supporting Information.
- [11] Similarly, alkenes with substituents at their  $\beta$  position, such as ethyl 2-butenate, failed to participate in the cycloaddition reaction.
- [12] Slow addition (5 h) of the reactants (**1b** and MVK) to a solution of [Ni(cod)<sub>2</sub>] (20 mol %) did not improve the conversion.
- [13] Performing the cycloaddition between **1b** and MVK (10 equiv) in the presence of 20 mol % of cycloadduct **5ba** afforded 30% conversion. Increasing the amount of **5ba** to up to 90% led to an even lower conversion (18%). Comparison of these results with those of Table 3 (entry 1) suggests that the cycloadduct **5ba** inhibits the cycloaddition, probably by coordinating to the nickel catalyst.
- [14] Substrates with terminal alkyne groups led to recovery of the majority of the starting material.
- [15] CCDC 791310 (**5ga**) and 782973 (**5fa**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
- [16] All the calculations were carried out at the B3LYP/def2-SVP level using the Gaussian 03 rev.D.01 suite of programs. For computational details, see the Supporting Information.
- [17] Nickelacyclobutane *E-i* could be involved in the formation of the [3+2] cycloaddition products of type **6**, as the alkene moiety of these cycloadducts exhibits *E* stereochemistry. However, the requirements of the intramolecularly linked alkyne (Scheme 3) suggests that alternative mechanisms, probably involving alkyne-stabilized nickelacyclopentenes, might be operating.<sup>[7]</sup> It is possible that the higher selectivity observed for **1d** in comparison to **1c** (Table 2, entries 5 and 6) might be related to a greater difficulty in producing such intermediates owing to steric reasons.
- [18] Despite extensive investigation, a transition state corresponding to a reductive elimination from **iiia** or **iiib**, to afford an intramolecular [3+2] cycloadduct, could not be located computationally. This result is in agreement with experimental results, as these types of 6,5-bicyclic systems were never detected.



- [19] DFT calculations on a substrate bearing an ester group instead of the methyl group at the alkyne moiety revealed lower energy barriers for the migratory-insertion steps eventually leading to the [3+2+2] adducts. This result is consistent with the higher [3+2+2]/[3+2] selectivity observed experimentally for this type of precursor (**1b**).
- [20] Regioisomers of type **9** were never observed. In agreement with this results, DFT calculations showed that the corresponding pathway leading to these products is more energetic than that affording **5**.

