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Mechanism, Reactivity, and Selectivity of Nickel-Catalyzed [4 + 4 + 2] Cycloadditions of Dienes and Alkynes

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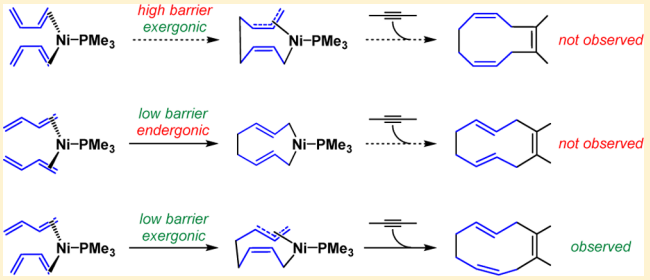
Supporting Information

ABSTRACT: Density functional theory (DFT) calculations with B3LYP and M06 functionals elucidated the reactivities of alkynes and *Z*/*E* selectivity of cyclodecatriene products in the Ni-catalyzed [4 + 4 + 2] cycloadditions of dienes and alkynes. The Ni-mediated oxidative cyclization of butadienes determines the *Z*/*E* selectivity. Only the oxidative cyclization of one *s-cis* to one *s-trans* butadiene is facile and exergonic, leading to the observed 1*Z*,4*Z*,8*E*-cyclodecatriene product. The same step with two *s-cis* or *s-trans* butadienes is either kinetically or thermodynamically unfavorable, and the 1*Z*,4*E*,8*E*- and 1*Z*,4*Z*,8*Z*-cyclodecatriene isomers are not observed in experiments. In addition, the competition between the desired cooligomerization and [2 + 2 + 2] cycloadditions of alkynes depends on the coordination of alkynes. With either electron-deficient alkynes or alkynes with free hydroxyl groups, the coordination of alkynes is stronger than that of dienes, and alkyne trimerization prevails. With alkyl-substituted alkynes, the generation of alkyne-coordinated nickel complex is much less favorable, and the [4 + 4 + 2] cycloaddition occurs.



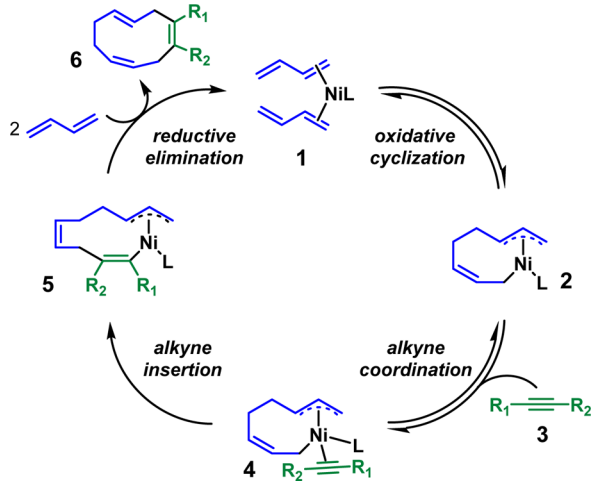
INTRODUCTION

As an ubiquitous and important family of molecules, terpenes, provide flavors, fragrances, medicines, and commercial products.[1] Although terpenes possess a seemingly endless variety of architectural complexities, nature is able to utilize simple five-carbon moieties to build the tens of thousands of different members of the terpene family.[2] The biosynthesis of terpenes often occurs in a unified fashion as a "two-phase" process:[3] (1) in the "cyclase" phase, small linear hydrocarbon phosphate building blocks are coupled together, followed by both enzymatic and nonenzymatic cyclizations and rearrangements; (2) in the "oxidase" phase, the oxidations of alkenes and carbon−hydrogen bonds result in large structural diversity.

Inspired by the early work on Ni-catalyzed diene oligomerizations from Wilke,[4] Heimbach,[5] and others,[6] the Baran group proposed a Ni-catalyzed diene/alkyne cooligomerization that could mimic Nature's cyclase approach to terpenes (Scheme 1).[7] From the nickel−butadiene complex **1**, the oxidative cyclization of dienes gives the nine-membered ring intermediate **2**. This intermediate, **2**, undergoes alkyne insertion to produce the 11-membered ring intermediate **5**. Subsequent reductive elimination generates the desired 10-membered ring product **6**.

Extensive experimental explorations of ligand, substrate, and other conditions led to successive butadiene/alkyne cooligomerizations with intriguing reactivities and selectivities:[7] (i) only the 1*Z*,4*Z*,8*E*-cyclodecatriene is generated, while the 1*Z*,4*E*,8*E*- and 1*Z*,4*Z*,8*Z*-isomers are not observed (Scheme 2a); (ii) the [2 + 2 + 2] cycloadditions of alkynes are competitive with electron-deficient alkynes or alkynes with free hydroxyl group (Scheme 2b, 2c).[8] In order to contribute to the future development of this methodology,[9] we explored the mechanism, reactivities, and selectivities of the Ni-catalyzed

Scheme 1. Proposed Ni-Catalyzed Diene/Alkyne Cooligomerization



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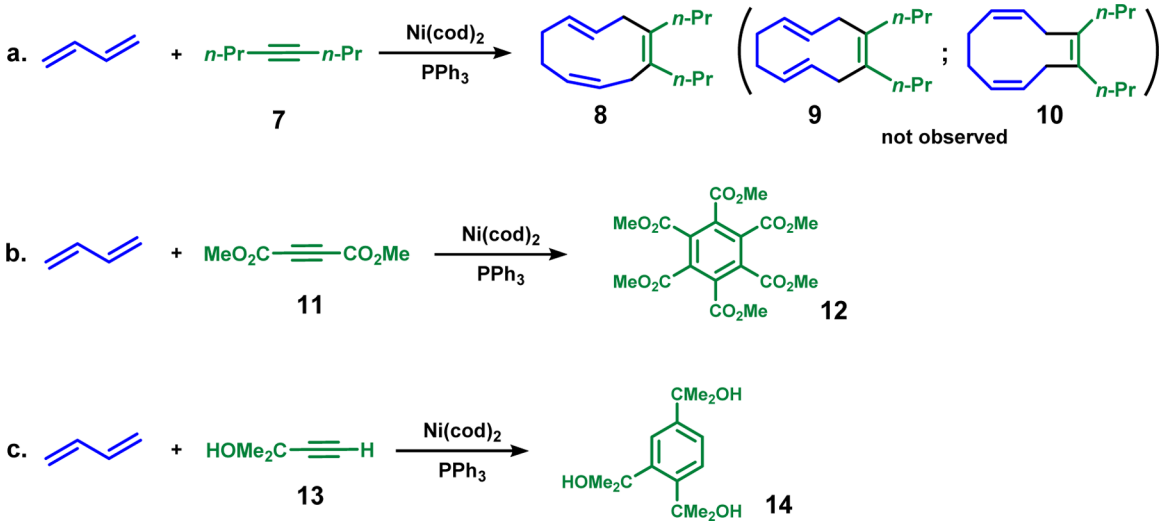
Scheme 2. Selected Examples of Ni-Catalyzed Butadiene/Alkyne Cooligomerization and Competitive [2 + 2 + 2] Cycloadditions of Alkynes



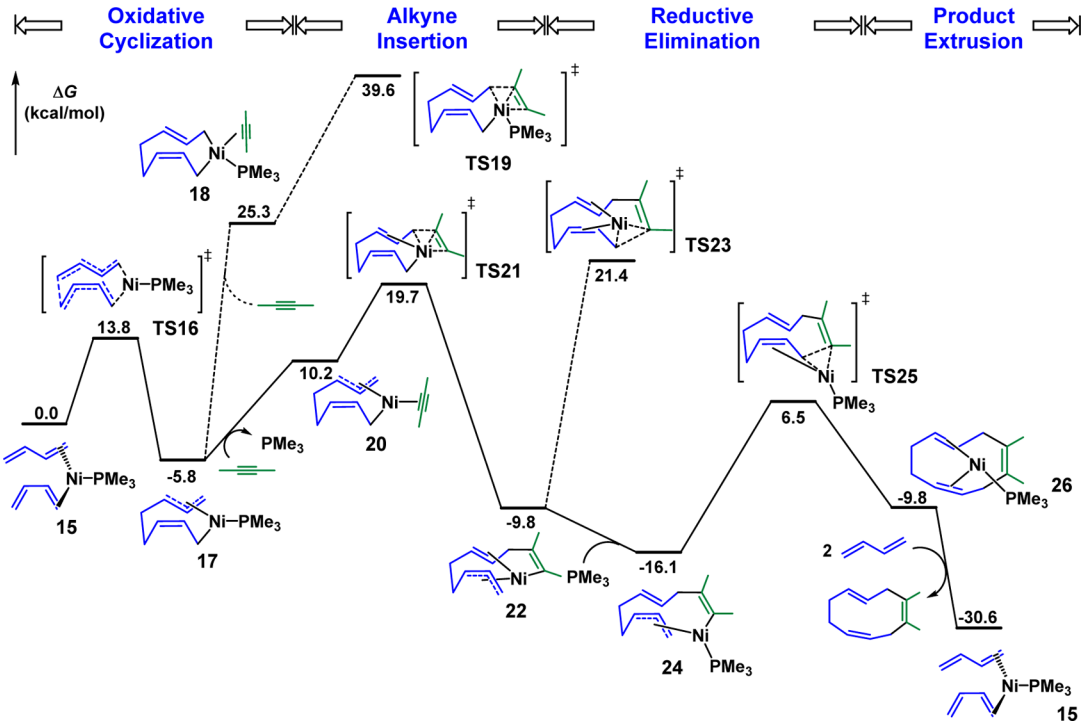


Figure 1. Gibbs free energy profile of [Ni(PMe$_3$)]-catalyzed butadiene/2-butyne cooligomerization (energies computed at the level of M06/6-311+G(2d,p),SDD//B3LYP/6-31G(d),SDD).

diene/alkyne cooligomerization with density functional theory (DFT) calculations.[10]

COMPUTATIONAL DETAILS

Geometry optimizations, vibrational frequencies, and thermal energy corrections were performed with the B3LYP functional, and a 6-31G(d) basis set for all main group elements and SDD basis set for nickel, as implemented in Gaussian 09.[11] Energies were evaluated with the M06 method[12] and a 6-311+G(2d,p) basis set for all main group elements and SDD basis set for nickel. All reported free energies involve zero-point vibrational energy corrections and thermal corrections to Gibbs free energy at 298 K.[13] Extensive conformational searches have been conducted to make sure that the most stable conformers are located, and only the most stable conformers are discussed in this work.

RESULTS AND DISCUSSION

1. Mechanism of Butadiene/Alkyne Cooligomerization. The mechanism of Ni-catalyzed diene/alkyne cooligomerization of butadiene and 2-butyne as the model substrates and PMe$_3$ as the model ligand was first explored.[14] The calculated free energy profile of the productive pathway is shown in Figure 1, and optimized structures of selected intermediates and transition states are shown in Figure 2. From the [(PMe$_3$)Ni(butadiene)$_2$] complex **15**, the facile oxidative cyclization of one *s-cis* and one *s-trans* butadiene via **TS16**

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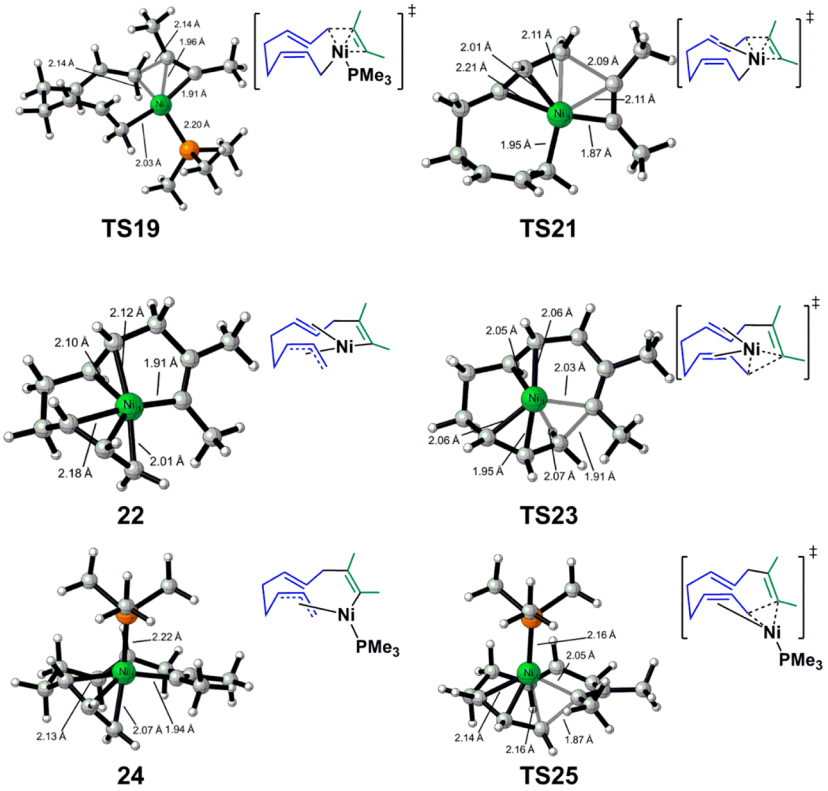

Figure 2. Optimized structures of selected intermediates and transition states of [Ni(PMe_3)]-catalyzed butadiene/2-butyne cooligomerization.

generates the nine-membered ring intermediate **17** (see later text for discussions on *Z*/*E* selectivity).[15] The coordination of 2-butyne produces the unstable tetracoordinate intermediate **18**, and the subsequent alkyne insertion via **TS19** is very unfavorable with a 45.4 kcal/mol overall barrier with respect to the intermediate **17**. Alternatively, a ligand exchange between 2-butyne and PMe_3 occurs to produce the intermediate **20**.[16] Despite the endergonic ligand exchange, the alkyne insertion via **TS21** only requires a 25.5 kcal/mol barrier with respect to **17**, generating the 11-membered ring intermediate **22**. From **22**, the reductive elimination through **TS23** is unfavorable with a barrier of 31.2 kcal/mol. The alternative reductive elimination with PMe_3 coordination via **TS25** is much more favorable, producing the cyclodecatriene-coordinated nickel complex **26**, and the product liberation regenerates the butadiene−nickel complex **15**. Therefore, the rate-determining step of the catalytic cycle is the alkyne insertion and the overall reaction barrier is 25.5 kcal/mol from the resting state **17** to the alkyne insertion transition state **TS21**. In addition, the ligand dissociation and recoordination are essential in this reaction. The phosphine ligand dissociates first in order to undergo a facile alkyne insertion via **TS21** and recoordinates to facilitate the reductive elimination through **TS25**.

2. Origins of *Z*/*E* Selectivity. Based on the productive pathway with one *s-cis* and one *s-trans* butadienes, we studied the *Z*/*E* selectivity of cyclodecatriene products when two *s-cis* or *s-trans* butadienes undergo the same cooligomerization with 2-butyne. The reaction with one *s-cis* and one *s-trans* butadiene produces the observed 1*Z*,4*Z*,8*E*-cyclodecatriene, and the other two pathways generate the *Z*/*E* isomers. The computed free energy profiles are shown in Figure 3. The first step of the catalytic cycle, Ni-mediated oxidative cyclization of butadienes, determines the *Z*/*E* selectivity. The oxidative cyclization with two *s-cis* butadienes (via **TS16-cc**) requires a 25.7 kcal/mol barrier, making this pathway unfavorable. In addition, the same cyclization with two *s-trans* butadienes is very endergonic, generating the unstable nine-membered ring intermediate **17-tt**. This leads to the 34.6 kcal/mol overall barrier for the subsequent alkyne insertion, making the reaction with two *s-trans* butadienes unfavorable. Only the oxidative cyclization with one *s-cis* and one *s-trans* butadienes is facile and exergonic, leading to a productive pathway.

Figure 4 shows the optimized structures and relative free energies of the transition states and nine-membered ring intermediates of the Ni-mediated oxidative cyclization step.[17] Comparing the transition states, **TS16-cc** is at least 10.1 kcal/mol less stable than the others. This results from the weak coordination of the dienes in **TS16-cc**. In order to form the terminal C−C bond in the oxidative cyclization, one of the coordinating double bonds of dienes in **TS16-cc** is distorted to be perpendicular to the $Ni_1-C_2-P_{10}$ plane (highlighted in green in **TS16-cc** of Figure 4). This distortion significantly weakens the coordination of this double bond and destabilizes the transition state.[18] In contrast, when the oxidative cyclization occurs with *s-trans* butadienes, **TS16** and **TS16-tt** maintain the planar coordination of both dienes and are much more stable than **TS16-cc**, leading to the achievable barriers. Comparing the generated nine-membered ring intermediates, **17-tt** is much less stable than **17** and **17-cc**. Because of the two trans-double bonds in the nine-membered ring of **17-tt**, this complex cannot maintain the η^3 coordination as in the other two intermediates. This makes **17-tt** much less stable than **17** and **17-cc**. Therefore, only the oxidative cyclization with one *s-cis* and one *s-trans* butadienes is facile and exergonic, leading to the productive pathway.

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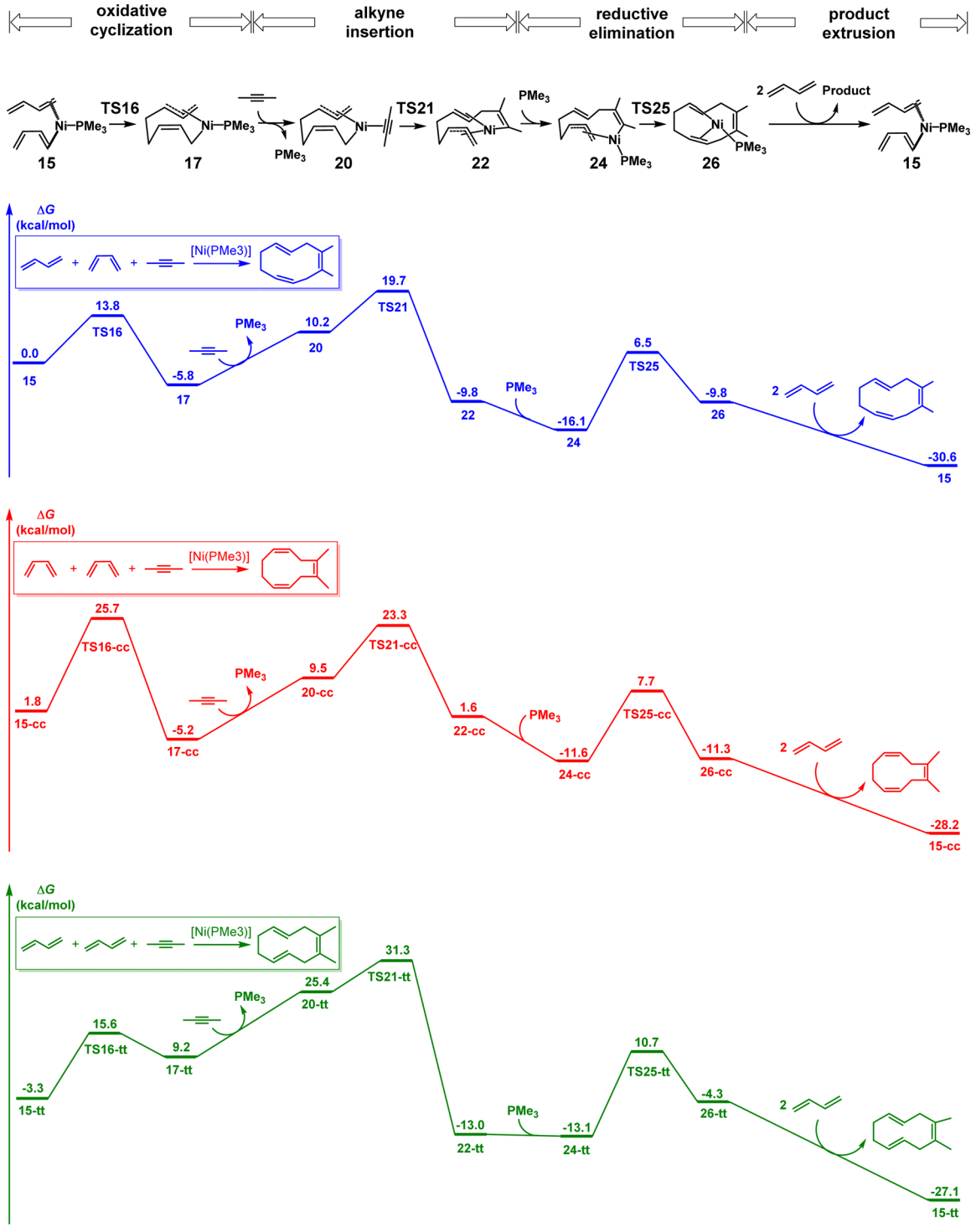

Figure 3. Gibbs free energy profiles of [Ni(PMe_3)]-catalyzed cooligomerization involving *s-cis* and *s-trans* butadienes and 2-butyne (Gibbs free energies in kcal/mol).

3. Competition with Alkyne Trimerization. We also studied the competing [2 + 2 + 2] cycloadditions of alkynes, using 2-butyne as the model substrate.[19,20] The free energies for the most favorable pathway are shown in Figure 5. From the nickel−diene complex **15**, the endergonic ligand exchange of alkynes generates the intermediate **27**. The oxidative cyclization of 2-butynes via **TS28** involves a 27.7 kcal/mol overall barrier with respect to **15**, producing the nickellacyclopentadiene intermediate **29**. From **29**, the coordination of 2-butyne and subsequent insertion through **TS31** are facile, generating the intermediate **32**. The reductive elimination via **TS33** only requires a barrier of 9.1 kcal/mol and produces the aryl ring-coordinated complex **34**. Therefore, the rate-limiting step of the [2 + 2 + 2] cycloaddition is the oxidative cyclization, and this trimerization of 2-butyne requires a 27.7 kcal/mol overall barrier, which is much less favorable than the [4 + 4 + 2] cycloaddition of butadienes and 2-butyne.

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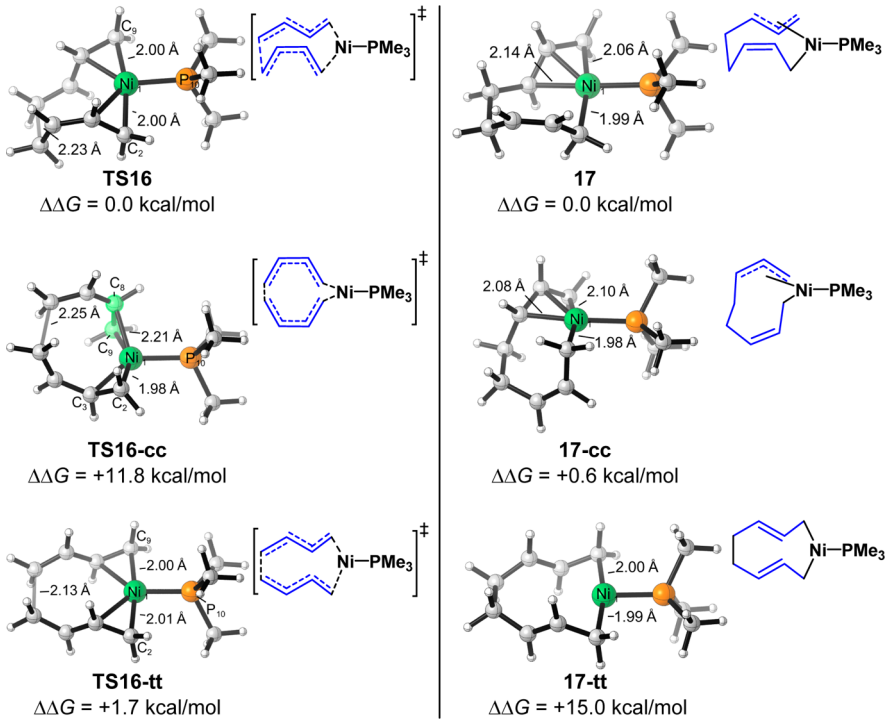

Figure 4. Optimized structures and relative free energies (transition states are compared to **TS16**, and intermediates are compared to **17**) of transition states and generated intermediates of [Ni(PMe_3)]-mediated oxidative cyclization of *s-cis* and *s-trans* butadienes.

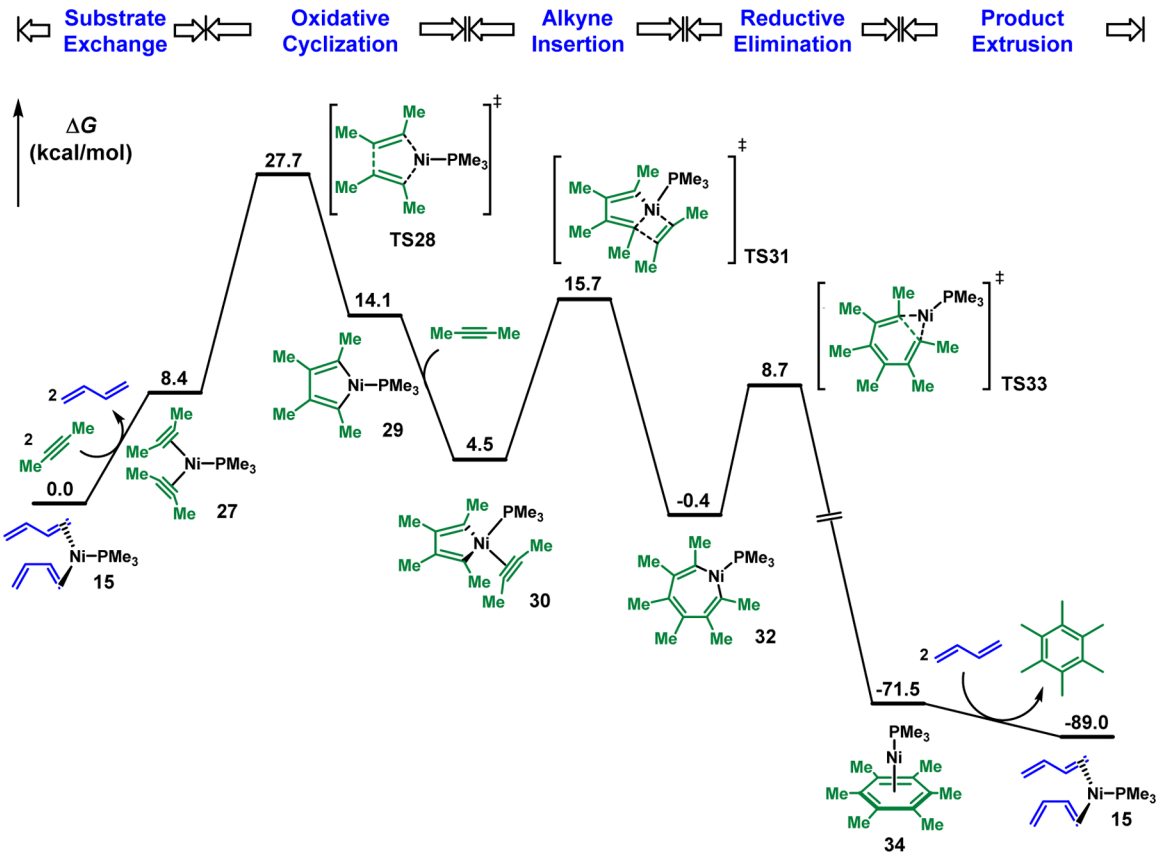

Figure 5. Free energy changes of the most favorable pathway of [Ni(PMe_3)]-catalyzed [2 + 2 + 2] cycloaddition of 2-butynes.

We studied the same trimerization reaction with electron-deficient alkyne (using dimethyl acetylene dicarboxylate as example) and alkyne with free hydroxyl group (using 2-methyl-3-butyn-2-ol as example), and the free energy changes are shown in Figure 6. The ligand exchange between alkynes and butadienes determines the competition between the [4 + 4 + 2]

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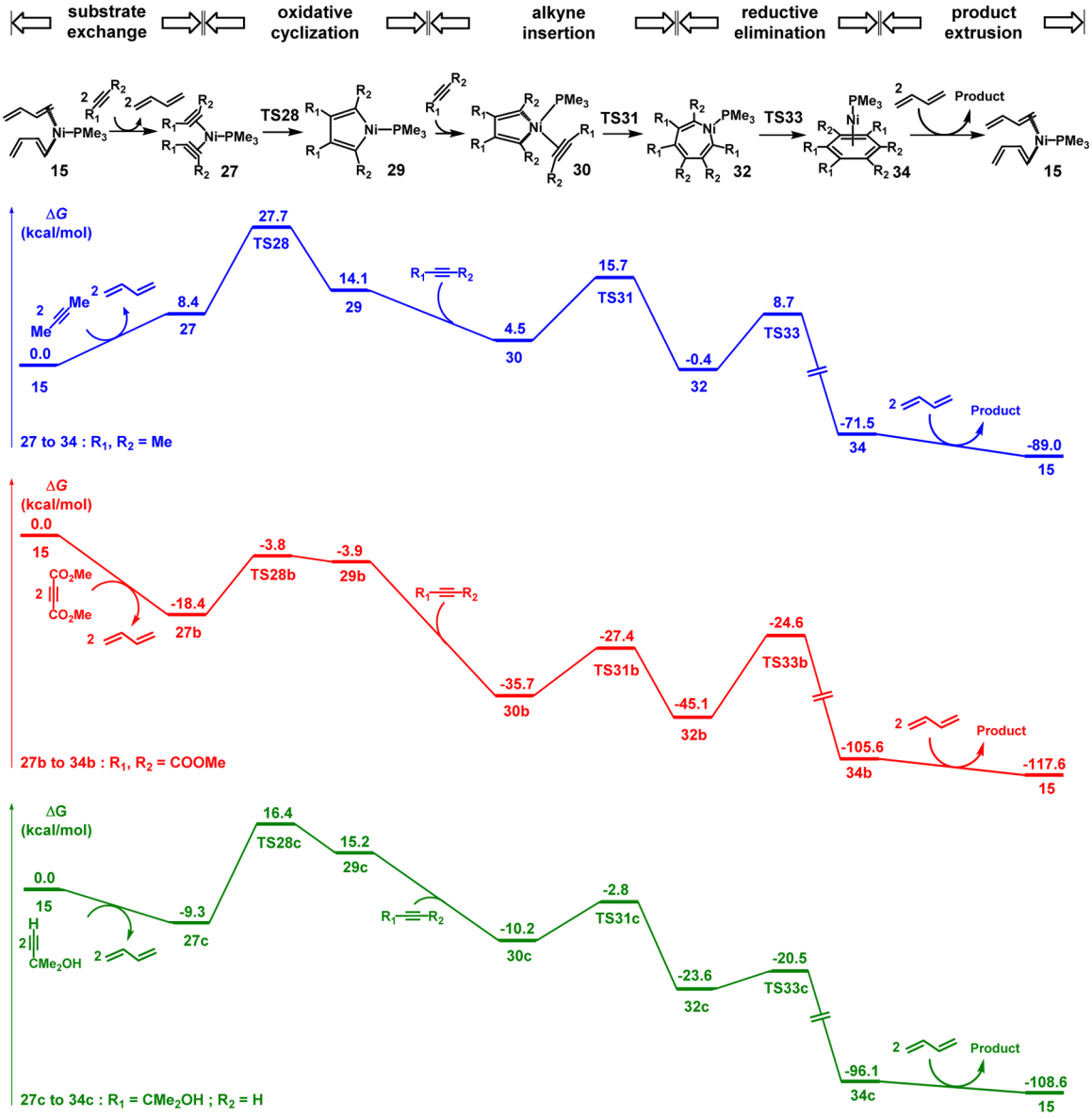

Figure 6. Gibbs free energy profiles of [Ni(PMe_3)]-catalyzed [2 + 2 + 2] cycloadditions with 2-butyne, dimethyl acetylene dicarboxylate, and 2-methyl-3-butyn-2-ol.

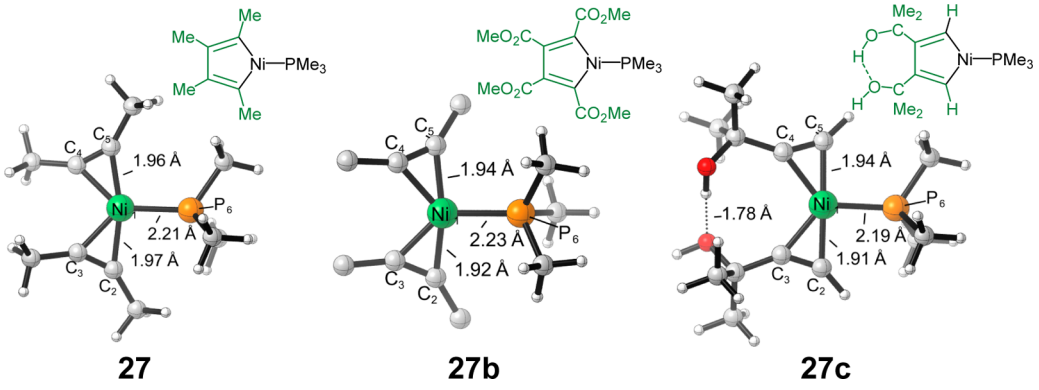

Figure 7. Optimized structures of [(PMe_3)Ni(alkyne)$_2$] complexes, **27** for 2-butyne, **27b** for dimethyl acetylene dicarboxylate, and **27c** for 2-methyl-3-butyn-2-ol (only the α-carbons of the ester groups in **27b** are shown for simplicity).

and [2 + 2 + 2] cycloadditions. With 2-butyne, the ligand exchange between alkynes and butadienes is endergonic by 8.4 kcal/mol, making the subsequent oxidative cyclization of alkynes much less favorable as compared to the cool-

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igomerization pathway with butadiene (Figure 1). In contrast, the same step is exergonic by 18.4 kcal/mol with dimethyl acetylene dicarboxylate and exergonic by 9.3 kcal/mol with 2-methyl-3-butyn-2-ol. These exergonic coordinations of alkynes make the [2 + 2 + 2] cycloadditions competitive, leading to the benzene derivatives, as found in the experiments.

Figure 7 shows the optimized structures of the alkyne-coordinated complexes, **27**, **27b**, and **27c**. Electron-deficient alkynes, such as dimethyl acetylene dicarboxylate in **27b**, have much stronger coordination to electron-rich nickel(0) as compared to 2-butyne. This strong coordination of electron-deficient alkynes makes the substrate exchange from **16b** to **27b** exergonic, leading to the favorable alkyne trimerization. In addition, when the alkyne has free hydroxyl group, there is an intramolecular hydrogen bond that stabilizes the complex **27c**. This makes the formation of **27c** favorable, also leading to the productive [2 + 2 + 2] cycloadditions. Therefore, when electron-deficient alkynes, or alkynes with a free hydroxyl group are used, the alkyne coordination of nickel is stronger than the diene coordination. This favorable coordination alters the energetics such that the [2 + 2 + 2] trimerization of alkynes competes with the [4 + 4 + 2] reaction.

CONCLUSIONS

We have studied the mechanism, reactivities, and selectivities of Ni-catalyzed [4 + 4 + 2] cycloadditions of dienes and alkynes through density functional theory (DFT) calculations. The reaction is found to proceed through the oxidative cyclization of dienes to form the nickel−phosphine complex. This nine-membered ring intermediate dissociates the phosphine ligand and then undergoes rate-determining alkyne insertion, affording the 11-membered ring intermediate. In order to undergo a facile reductive elimination, the phosphine ligand recoordinates to nickel and facilitates the formation of 1*Z*,4*Z*,8*E*-cyclodecatriene products.

We found that the *Z*/*E* selectivity of the cyclodecatriene products is determined by the diene oxidative cyclization step. Only the oxidative cyclization between one *s-cis* and one *s-trans* butadiene is facile and exergonic. The step with two *s-cis* butadienes requires much higher barrier due to the weak coordination of dienes, and the step with two *s-trans* butadienes generates high energy nine-membered ring intermediates. Therefore, the oxidative cyclization with two *s-cis* or *s-trans* butadienes are both much less favorable than the reaction with one *s-cis* and one *s-trans* butadienes either kinetically or thermodynamically, resulting in the 1*Z*,4*Z*,8*E*-cyclodecatriene products.

We also investigated the competing [2 + 2 + 2] cycloaddition of alkynes with [Ni(PMe_3)] as the same active catalyst and found that the alkyne coordination determines the feasibility of the trimerization of alkynes. With electron-deficient alkynes or alkynes with free hydroxyl groups, the coordination of alkynes is much stronger as compared to the coordination of dienes, and the side reaction prevails. In contrast, the alkyl-substituted alkynes coordinate more weakly, and the generation of alkyne-coordinated nickel complex is less favorable. In these cases, the [4 + 4 + 2] cycloaddition of dienes and alkynes occurs.

ASSOCIATED CONTENT

Supporting Information

Free energy profiles of unfavorable [2 + 2 + 2] cycloadditions with butadienes, Cartesian coordinates, and energies of DFT-computed stationary points and saddle points. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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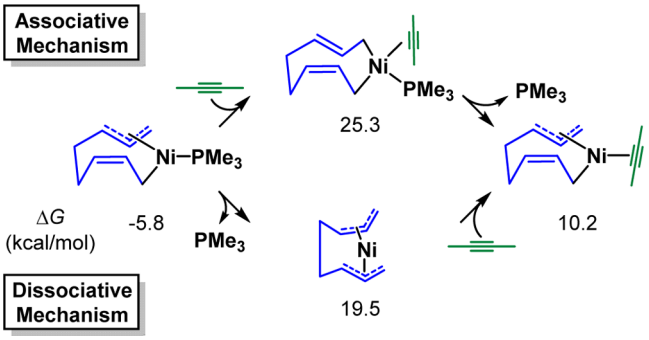

(17) The geometries of **TS16**, **TS16-cc**, and **TS16-tt** were also calculated with the B3LYP-D3 method, and the relative energies of the reoptimized geometries, **TS16′**, **TS16-cc′**, and **TS16-tt′**, are similar to those of the original geometries. ($\Delta\Delta G$(**TS16′**) = 0.0 kcal/mol, $\Delta\Delta G$(**TS16-cc′**) = 12.5 kcal/mol, and $\Delta\Delta G$(**TS16-tt′**) = 1.9 kcal/mol).
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