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Mechanistic Origin of Chemo- and Regioselectivity of Nickel-Catalyzed [3 + 2 + 2] Cyclization Reaction

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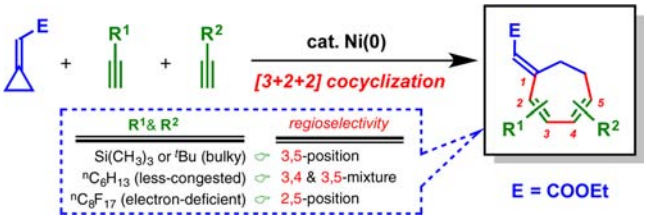
Supporting Information

ABSTRACT: A density functional theory (DFT) study was performed to elucidate the mechanism of the Ni-catalyzed [3 + 2 + 2] cyclization reaction of cyclopropylideneacetate with two alkynes. A systematic search showed that the nature of the alkynes determines the choice between two reaction pathways and hence the regioselectivity. Strongly electron-deficient acetylenes preferentially afford 2,5-disubstituted products via nickelacyclopentadienes generated by [2 + 2] cocyclization, whereas normal alkynes afford 3,4- or 3,5-products via an unprecedented pathway involving a [3 + 2] nickelacycle intermediate.

Seven-membered carbocycles are a key structural feature in many natural products, and regio- and chemoselective construction of these structures has been one of the central issues in organic synthesis because of the difficulty of the ring-closing reaction due to enthalpic/entropic factors.[1] Transition-metal-catalyzed multicomponent coupling reactions for the construction of medium-sized carbocycles have revolutionized this field.[2,3] For example, one of our group has developed a nickel-catalyzed [3 + 2 + 2] cyclization of one cyclopropylideneacetate (CPA) with two alkynes to afford seven-membered rings (Scheme 1).[4] This reaction is now general for a wide range of alkyne substrates and has been developed as a three-component reaction ($R_1 \neq R_2$)[5] that provides high regioselectivity in many cases. It has also been developed as an intramolecular reaction to afford bicyclic compounds[6a] and a [4 + 3 + 2] reaction to give nine-membered ring compounds.[6b,c] Nevertheless, the reaction mechanism remains incompletely understood.

Scheme 1. Ni-Catalyzed [3 + 2 + 2] Cyclization of Cyclopropylideneacetate (CPA) and Two Alkynes



Recently, a DFT study on the [3 + 2 + 2] cocyclization reaction was reported, in which the key step is oxidative cyclization of Ni(0) with two molecules of alkynes to generate a nickelacyclopentadiene (NCP).[7] Although the NCP mechanism can explain the experimental results of many Ni(0)-catalyzed cocyclizations,[8,9] it cannot account for several features of the [3 + 2 + 2] cocyclization. In particular, the regioselectivity of [3 + 2 + 2] cocyclization depends markedly on the substituents of the alkynes (Scheme 1), *and this cannot be explained in terms of the NCP mechanism (vide infra)*. Hence, in the present work, we used the recently developed AFIR (artificial force induced reaction) method[10] with density functional theory (DFT) to systematically determine possible reaction pathways and the origin of the regioselectivity of the Ni(0)-catalyzed [3 + 2 + 2] cocyclization, as well as to clarify the structural and electronic features of Ni(0) complexes with various alkynes and/or CPA.[11,12]

At first, we focused on the reaction of CPA with ethyne in the presence of the Ni(0)/PMe_3 catalyst as a minimum chemical model, and two possible routes were identified (Schemes 2 and 3). Path A leads to the NCP **CP3A-1a** through two transition states (TSs), **TS1A-1a** and **TS2A-1a**, with reasonable activation barriers (Scheme 2), in good agreement with the previous calculation.[7] However, a second, unprecedented route, Path B (*via* nickelacycle **CP3B-1a**), turned out to be kinetically and thermodynamically more favorable (Scheme 3i). The initial π-complexation of Ni(PMe_3)$_2$ with CPA (**CP0-2a**) is likely to occur preferentially to that with ethyne (**CP0-1a**), being favored by ca. 5 kcal/mol due to the potent electron-accepting ability of CPA.[13] Oxidative double Ni−C bond formation from **CP1B-1a** gives an intermediate **CP2B-1a** with an activation energy of 13.9 kcal/mol. The intermediate **CP2B-**

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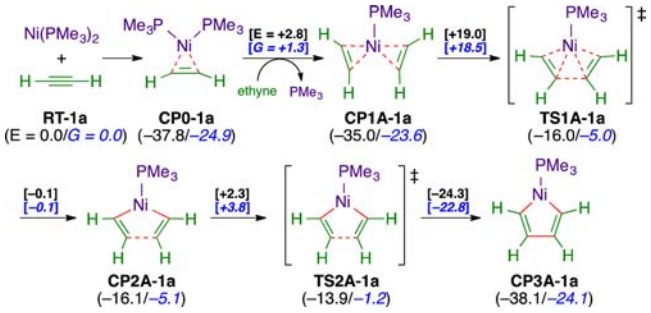
Scheme 2. Oxidative Cyclization Section of Path A[a]



[a]Energy changes at the level of M06/LANL2DZ&6-31+G* are shown in kcal/mol.

1a is located on a shallow energy minimum and takes a distorted pentagonal structure (C2−Ni1−C5 128.7°). **CP2B-1a** is easily converted to **CP3B-1a** with a very small energy barrier. **CP3B-1a** then forms a π-complex **CP4B-1a** with the second alkyne (Scheme 3ii), and insertion of the alkyne proceeds with a small barrier of 3.1 kcal/mol to give a seven-membered nickelacycle intermediate **CP5B-1a**, which, with simultaneous ring opening of cyclopropane and reductive elimination, exothermically provides the complex **CP6B-1a** of the seven-membered carbocycle product and the Ni(0) catalyst, as shown Scheme 3iii, with high exothermicity. Finally **CP6B-1a** ejects the carbocycle product and regenerates the Ni(0) species with an energy loss of only 9.0 kcal/mol, which is compensated by the formation of the **CP0-2a** π-complex for the next catalytic cycle. The entire reaction profile is illustrated in Figure 1. The overall exothermicity is very large because of the formation of three C−C bonds and cleavage of the cyclopropane ring, and this provides the driving force of the reaction. As shown in Figure 1, the CPs and TSs in Path B are energetically more favorable than those in Path A, and the reaction is therefore much less likely to take place along Path A than along path B, at least in the case of using ethyne as the alkyne unit.

To elucidate the effects of different alkynes on the mechanism, we next focused on initial complexes **CP0** with various alkynes and applied energy decomposition analysis (Figure 2).[14] The optimized geometries of these complexes are similar to one another, but the energies are quite different

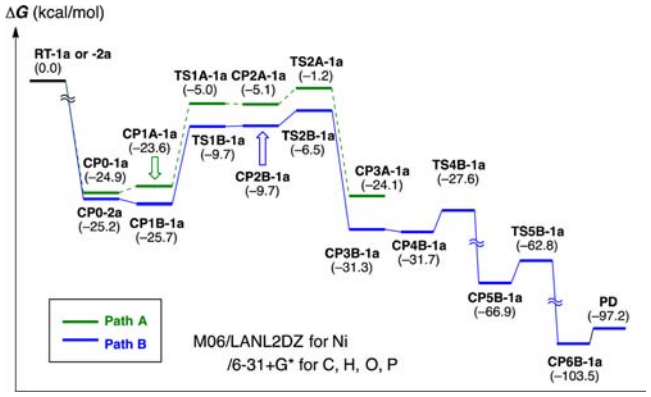


Figure 1. Comparison of the energy profiles (ΔG, kcal/mol) of Path A and Path B for reaction of alkyne **1a**.

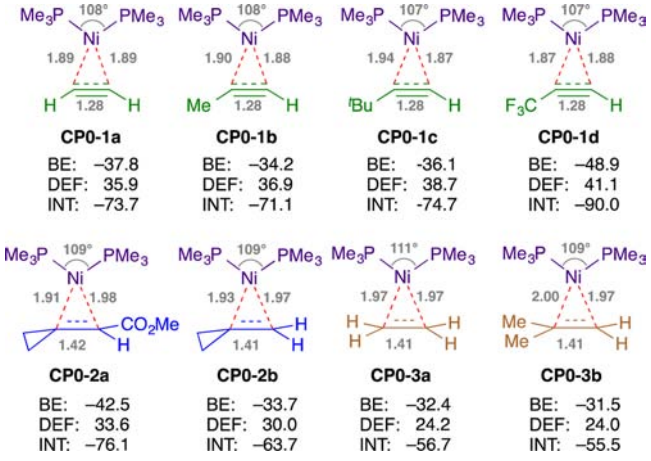
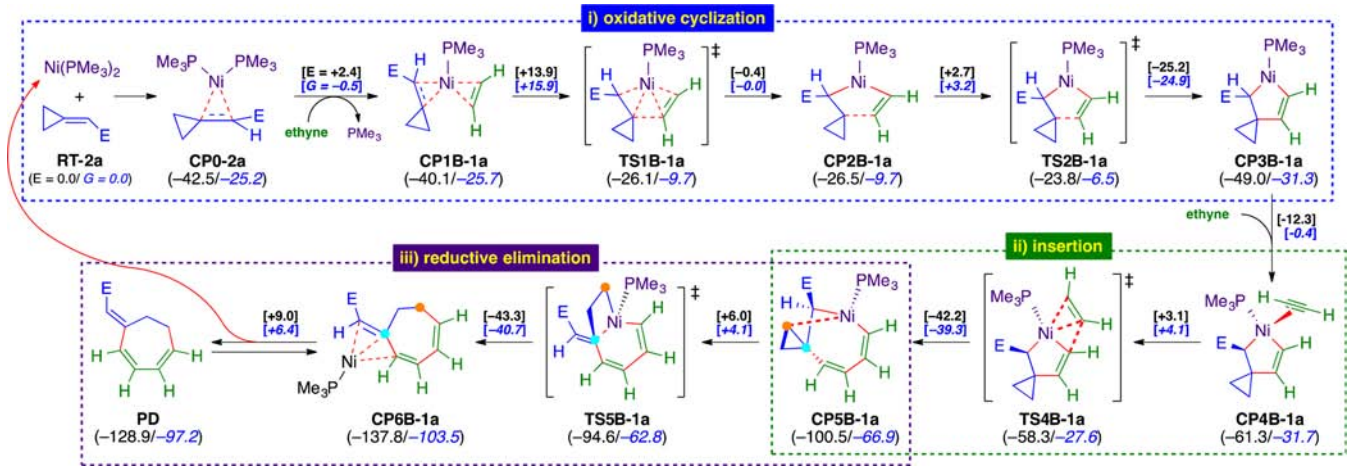


Figure 2. Bonding energies (BEs), deformation energies (DEFs), and interaction energies (INTs) of CP0s (M06/LANL2DZ&6-31+G*; energy: kcal/mol).

depending on the substituent on the acetylene unit. CPA forms a complex with Ni(0) species with a large interaction energy (INT) and consequently a large bonding energy (BE), due mainly to a potent back-donation interaction between high-lying d orbital of Ni(0) and lower-lying π^* orbital of CPA. This strongly suggests that the present [3 + 2 + 2] cocyclization would proceed via formation of **CP1B-1a** (Path B) for most

Scheme 3. Reaction Profile along Path B (M06/LANL2DZ&6-31+G*, energy changes in kcal/mol)



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alkynes. However, strongly electron-deficient alkynes, such as perfluoroalkylacetylene, should favor Path A over Path B if the d−π^* interaction plays a critical role. Indeed, with the CF_3 unit INT and thus BE of **CP0-1d** being more negative than those of **CP0-2a**, Path A should be the main route in this case. This change of reaction pathway should change the regioselectivity of the [3 + 2 + 2] cocyclization.

The reactions of CPA with propyne (**1b**, R = Me) and 3,3-dimethylbutyne (**1c**, R = *t*-Bu) as chemical models for less-congested and bulkier alkyl substituents on the acetylene unit were then examined to assess the origin of the regioselectivity in Path B. In this pathway, the regio-determining step has been found to be the acetylene insertion (Scheme 3ii) into the nickelacycle intermediate (see Schemes S1 and S2 of the Supporting Information). The optimized transition structures for the step are shown in Figure 3A. The activation energies

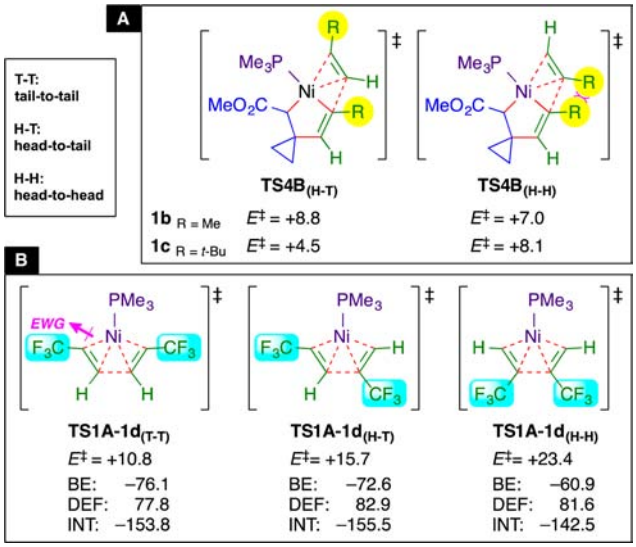

Figure 3. (A) Origin of regioselectivity; (B) Switching of the mechanism with electron-deficient alkynes (M06/LANL2DZ&6-31+G*; energy: kcal/mol).

from the prereaction complexes for **TS4B-1b**$_{(H-T)}$, **TS4B-1b**$_{(H-H)}$, **TS4B-1c**$_{(H-T)}$, and **TS4B-1c**$_{(H-H)}$ are 8.8, 7.0, 4.5, and 8.1 kcal/mol, respectively. The results are fully consistent with the experimental observations: the barrier for the 3,5-regioisomer (**TS4B-1c**$_{(H-T)}$) is lower than that for the 3,4-substituted product (**TS4B-1c**$_{(H-H)}$) in the case of the bulky alkyne due to steric hindrance, while the energy difference for the less-congested alkyne (**TS4B-1b**$_{(H-T)}$, **TS4B-1b**$_{(H-H)}$) is very small.

We next investigated Path A using trifluoromethylacetylene (R = CF_3) as the simplest model of a strongly electron-deficient alkyne. Here, oxidative double Ni−C bond formation was found to be the regio-determining step (Figure 3B).[15] Although there are three regioisomers for the TSs (head-to-head, head-to-tail, and tail-to-tail), the TS **TS1A-1d**$_{(T-T)}$ that affords the 2,5-regioisomer is energetically more favorable than **TS1A-1d**$_{(H-T)}$ and **TS1A-1d**$_{(H-H)}$ by 3.5 and 15.2 kcal/mol, respectively, because the tail-to-tail configuration leads the least steric hindrance while retaining effective orbital interaction of Ni(0) with the acetylenes, judging from the values of DEF and INT of the TSs.[8a,9b,16] This view is fully consistent with previous reports.[8a,15,17] The activation energy from **CP1A-1d** for **TS1A-1d**$_{(T-T)}$, which affords the 2,5-disubstituted product, is 10.8 kcal/mol (see also Figure S7). This analysis is in good agreement with the experimental observation that the reaction with perfluoroalkylacetylene gave the 2,5-substituted product as a single isomer.[4b,c,18]

In summary, we have shown that the Ni-catalyzed [3 + 2 + 2] cyclization of cyclopropylideneacetate (CPA) with alkynes takes place through Path B as well as Path A, depending entirely on the nature of the alkynes (Figure 4). Normal alkynes, such

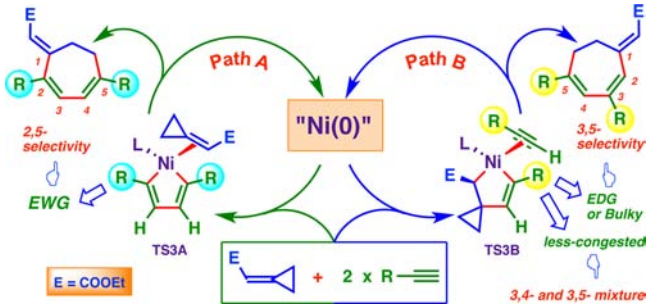

Figure 4. Summary of the reaction mechanism.

alkyl acetylenes, favor Path B over Path A, and the regioselectivity of the products is determined by the steric bulkiness of the alkyne at the second acetylene insertion step (**TS4B**). The use of strongly electron-withdrawing alkynes completely changes the reaction mode because of the facile complexation of Ni(0) with electron-deficient alkynes, and as a result, Path A becomes predominant and the formation of NCP becomes the regio-determining step. The present results indicate that appropriate selection of the combination of CPA and alkynes can provide efficient functionality with tunable regioselectivity and the reaction route. Hence, we believe this work provides a theoretical basis for designing new synthetic methods and strategies to construct medium- to large-sized rings in a controllable and diversified manner.

■ ASSOCIATED CONTENT

Supporting Information

Details of computational procedure, Cartesian coordinates, energy data, and full citation for calculation. 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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