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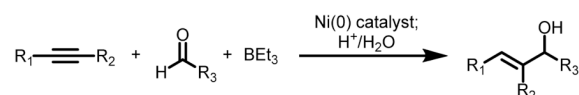
Mechanism and Transition State Structures for Nickel-Catalyzed Reductive Alkyne-Aldehyde Coupling Reactions

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Regio- and enantiocontrolled reductive coupling reactions catalyzed by transition metals provide an efficient route to highly functionalized synthons from a diverse range of inexpensive, readily available commercial starting materials, such as aldehydes, ketones, imines, epoxides with alkynes, allenes, and alkenes.¹ The exact mechanism of many of these processes is still unknown and varies heavily on the metal, substrates, and reducing agent. In particular, nickel-catalyzed reductive couplings of an alkyne with an aldehyde afford access to synthetically important allylic alcohols² with the use of various reducing agents, including organozincs,³ silanes,⁴ organoboranes,⁵ vinylzirconium reagents,⁶ and chromium(II) chloride.⁷ The couplings of alkene with aldehyde or ketone are more difficult and were achieved recently only through the use of stronger Lewis acids such as AlMe₃ or silyl triflates.⁸ Here, we establish the mechanism and nature of rate-, regio- and stereoselectivity determining transition states for alkyne-aldehyde couplings catalyzed by Ni(0)-phosphine catalyst and borane reductant.



Four different mechanisms have been proposed for metal-catalyzed reductive coupling reactions:^{2c,d,9} a) the most widely proposed mechanism is oxidative cyclization of alkyne and aldehyde to form a metallacycle intermediate, followed by transmetalation of the reductant and subsequent reductive elimination of the product³ (Scheme 1); b) a similar mechanism but with the metal bonded to the reductant in the oxidative cyclization;⁹ c) oxidative addition of the reductant to the metal and subsequent insertion of the two π components; d) oxidative addition to one π component (alkyne or aldehyde) and subsequent insertion of the second component. We have investigated the mechanisms of this process with density functional theory.¹⁰ Mechanism a) (Scheme 1) is found to be favored for the model system involving reaction of acetylene and acetaldehyde with PMe₃ ligand and BEt₃ as reductant.¹¹

The catalyst resting state is the 16e⁻ alkyne(bisphosphane)-nickel(0) complex **3**. All 18e⁻ complexes are more than 5 kcal/mol less stable than the 16e⁻ complex **3**. Aldehyde complexation in place of one phosphine gives η^1 -complex **4** or η^2 -complex **5**, which are 10.6

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Supporting Information Available: Free energy surface of the full catalytic cycle, details of the calculations on alternative mechanisms b, c, and d, optimized Cartesian coordinates and energies, and complete reference of Gaussian 03. This material is available free of charge via the Internet at <http://pubs.acs.org>.

and 8.2 kcal/mol less stable, respectively, while only the η^2 -complex leads to product. Complex **5** is trigonal planar with five low-energy d orbitals to accommodate the ten d electrons on Ni (Figure 1). Upon oxidative cyclization, **5** is transformed to the T-shaped metallacycle **6** with four low-energy d orbitals, instead of the five present in **5**, accommodating the eight d electrons in the Ni(II) intermediate **6**. The transformation from **5** to **6** involves electron transfer from the filled metal $d_{x^2-y^2}$ orbital to the in-plane π^*_{\parallel} orbitals of alkyne and aldehyde. In **TS1-A** and **6**, the planar geometry also enabled the back-donation from the filled metal d_{xz} orbital to the out-of-plane alkyne π^*_{\perp} orbital.

The $d \rightarrow \pi^*_{\perp}$ back-donation stabilizes the transition state **TS1-A** and intermediate **6**. In the oxidative cyclization of ethylene and acetaldehyde, no such back-donation is possible due to the lack of out-of-plane π orbitals. The oxidative cyclization transition state **TS1-A'** and intermediate **6'** involving ethylene are 7.6 and 8.6 kcal/mol less stable than those of the reaction with acetylene, respectively (Figure 2b). This explains the inertness of alkene in the oxidative cyclization with aldehyde and Ni(0) when no Lewis acid is present.^{8,12}

We also investigated an alternative pathway, in which the BEt_3 reductant coordinates with the aldehyde oxygen as a Lewis acid to stabilize the negative charge building up in the oxidative cyclization transition state (Path **B**, Scheme 1). For the reaction with acetylene, coordination of BEt_3 to the aldehyde oxygen destabilizes the reactant π complex **7** and the oxidative cyclization transition state **TS1-B** by 14.2 and 2.4 kcal/mol, respectively, in terms of free energies (Figure 2a). However, BEt_3 coordination slightly stabilizes the cyclization transition state of ethylene and acetaldehyde by 0.8 kcal/mol. This suggests that coordination with weak Lewis acid BEt_3 slightly accelerates the oxidative cyclization of aldehyde with alkene, but not with alkyne. The stronger Lewis acid AlMe_3 strongly favors coordination with aldehyde oxygen (path **B**) for both ethylene and acetylene, lowering the activation free energies by 19.2 and 16.0 kcal/mol, respectively. This acceleration effect makes the oxidative cyclization with alkene a feasible process in the presence of strong Lewis acids.^{8, 13}

For the reaction with acetylene, the transformation from the catalyst resting state **3** to the BEt_3 complexed metallacycle **8** is only slightly exergonic, while the subsequent steps are very exergonic with low activation barriers. Ethyl migration from BEt_3 to the Ni (**TS2**) requires activation energy of 9.9 kcal/mol. β -Hydrogen elimination from the ethyl on nickel and reductive elimination of the product are found to be a concerted process (**TS3**) with a low barrier of only 3.8 kcal/mol. The π -complex **10** then dissociates to liberate the borinic acid ether product and coordinates with reactants to enter the next catalytic cycle.¹⁴ Oxidative cyclization (**TS1-A**) is the rate-determining step, and controls the regio- and enantioselectivity of this reaction.¹⁵

Based on these calculations, the aforementioned oxidative cyclization mechanism has such a low barrier that it would be difficult for other processes to compete. In mechanism b, the reactant and the oxidative cyclization transition state are all much less stable when Ni is bonded to BMe_3 in place of PMe_3 . The transition state and product of the oxidative addition of BEt_3 to the metal (mechanism c) cannot be located. The reactant complex of this mechanism, the borane(bisphosphine)nickel complex is 3.6 kcal/mol higher energy than **TS1-A**. Thus, oxidative addition of BEt_3 is not likely to occur. The activation barriers of oxidative addition to acetylene or acetaldehyde (mechanism d) are 33.7 and 40.8 kcal/mol, respectively, both much higher than the oxidative cyclization mechanism.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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14. See Supporting Information for the free energy profile of the full catalytic cycle.
15. For experimental regio- and enantioselectivities, see refs 4d,5b,c,g,h,i.

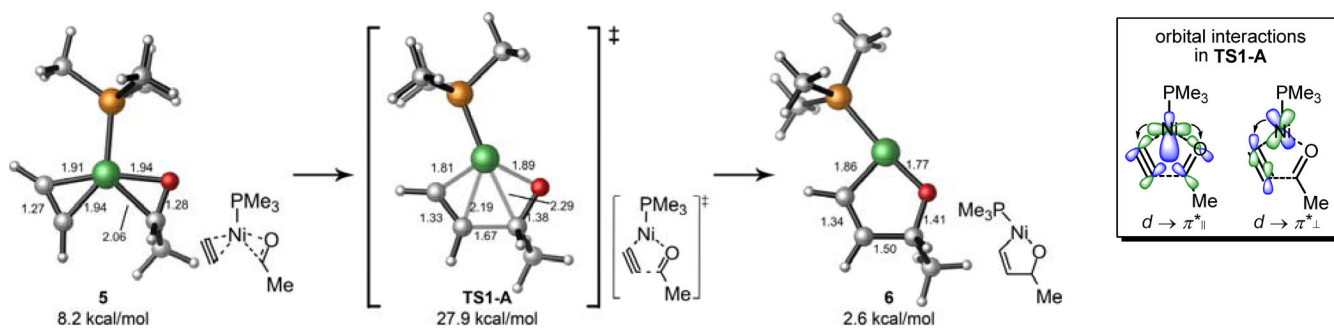
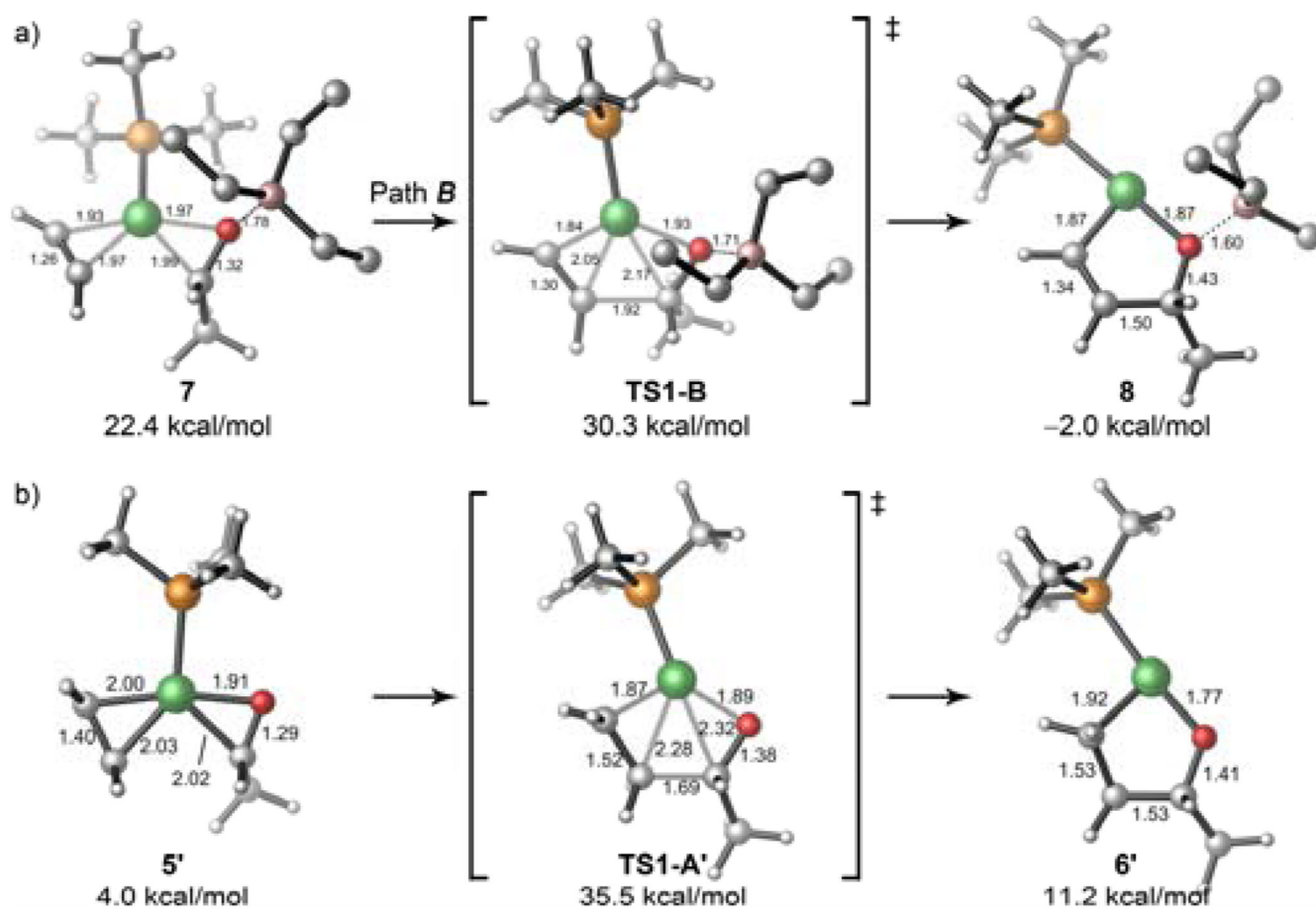
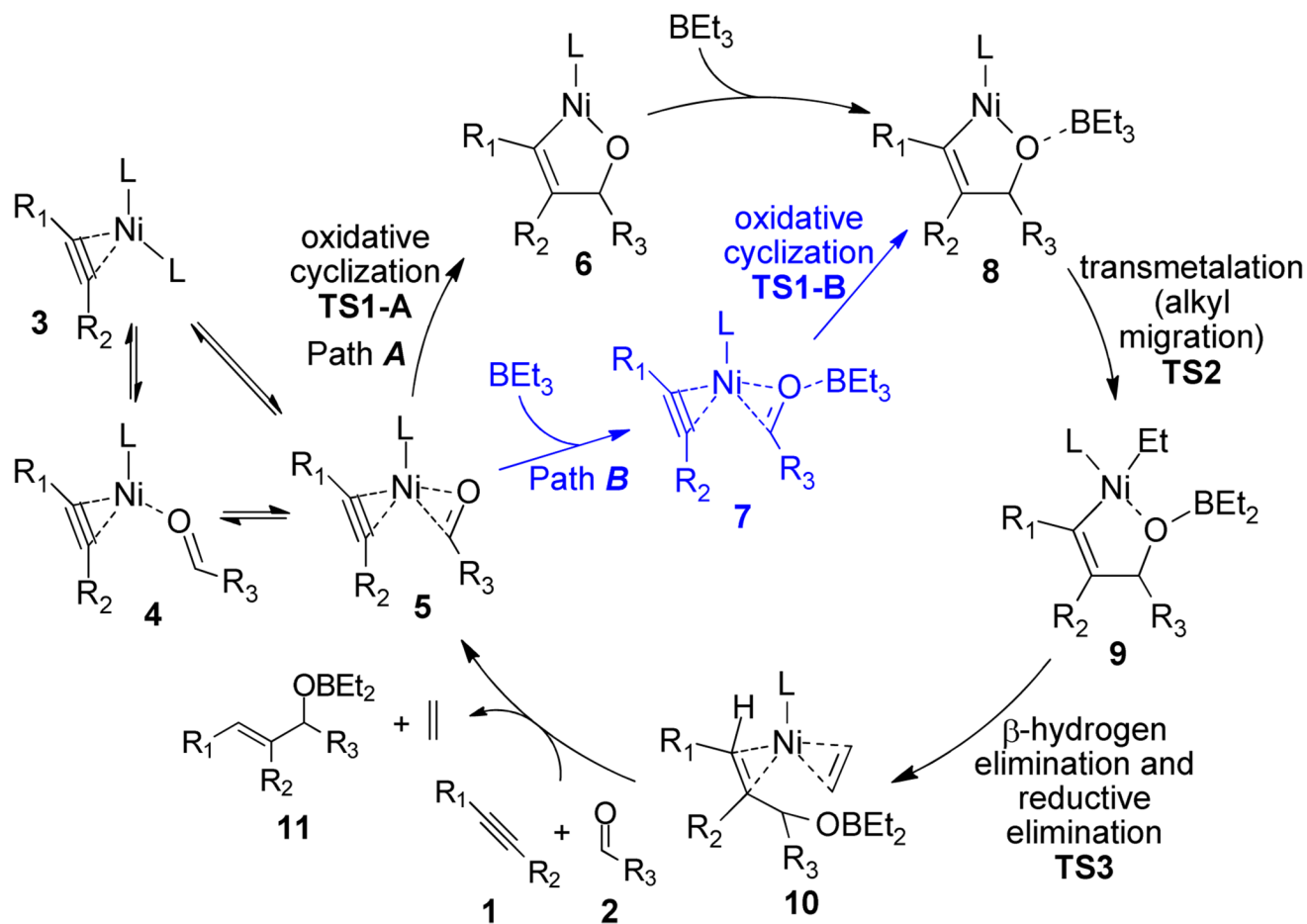


Figure 1. Oxidative cyclization of alkyne and aldehyde. Bond lengths are in Å. Energies are with respect to the catalyst resting state **3**.

**Figure 2.**

a) An alternative pathway of alkyne-aldehyde oxidative cyclization: borane coordination to the aldehyde oxygen. Bond lengths are in Å. Energies are with respect to the catalyst resting state **3**. Hydrogens in BEt_3 are not shown. b) Oxidative cyclization of ethylene and acetaldehyde. Bond lengths are in Å. Energies are with respect to the catalyst resting state alkene(bisphosphane)nickel(0) complex **3'**.

**Scheme 1.**

The oxidative cyclization mechanism of Ni-catalyzed reductive coupling between alkynes and aldehydes.