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

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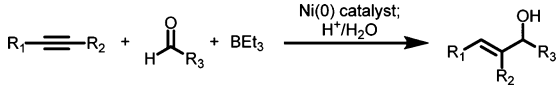
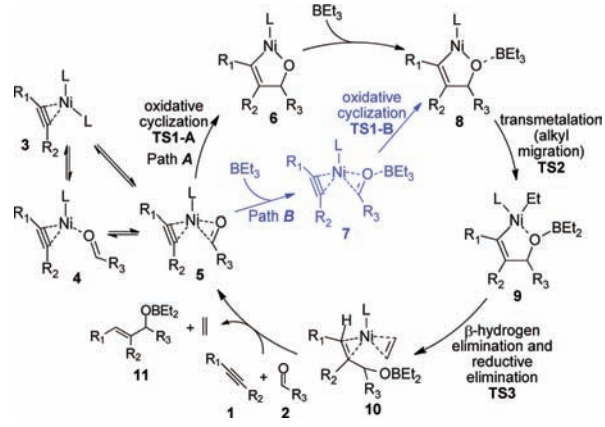
Regio- and enantiocontrolled reductive coupling reactions catalyzed by transition metals provide an efficient route to highly functionalized synthons from a diverse range of inexpensive, readily available commercial starting materials, such as aldehydes, ketones, imines, and epoxides reacting with alkynes, allenes, and alkenes.[1] The exact mechanism of many of these processes is still unknown and depends strongly 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 alcohols[2] 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 alkenes with aldehydes or ketones are more difficult and were achieved recently only through the use of stronger Lewis acids, such as $AlMe_3$ or silyl triflates.[8] Here we establish the mechanism and nature of the rate- and 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) oxidative cyclization of alkyne and aldehyde to form a metallacycle intermediate, followed by transmetalation of the reductant and subsequent reductive elimination of the product[3] (this is the most widely proposed mechanism and is shown in black in 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; and (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 the reaction of acetylene and acetaldehyde with PMe_3 ligand and BEt_3 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 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 10 d electrons on Ni (Figure 1). Upon oxidative cyclization, **5** is transformed into the T-shaped metallacycle **6**, which has four low-energy d orbitals

Scheme 1. Oxidative Cyclization Mechanism of Ni-Catalyzed Reductive Coupling between Alkynes and Aldehydes



(instead of the five present in **5**) that accommodate 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 $\pi^*_{\parallel}$ orbitals of the alkyne and aldehyde. In **TS1-A** and **6**, the planar geometry also enables back-donation from the filled metal d_{xz} orbital to the out-of-plane alkyne $\pi^*_{\perp}$ orbital.

The d → $\pi^*_{\perp}$ 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 because of 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, respectively, than those for the reaction with acetylene (Figure 2b). This explains the inertness of alkenes in the oxidative cyclization with aldehydes 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 built 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 energy (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 the weak Lewis acid BEt_3 slightly accelerates the oxidative cyclization of aldehydes with alkenes but not with alkynes. The stronger Lewis acid $AlMe_3$ strongly favors coordination with the 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 alkenes a feasible process in the presence of strong Lewis acids.[8,13]

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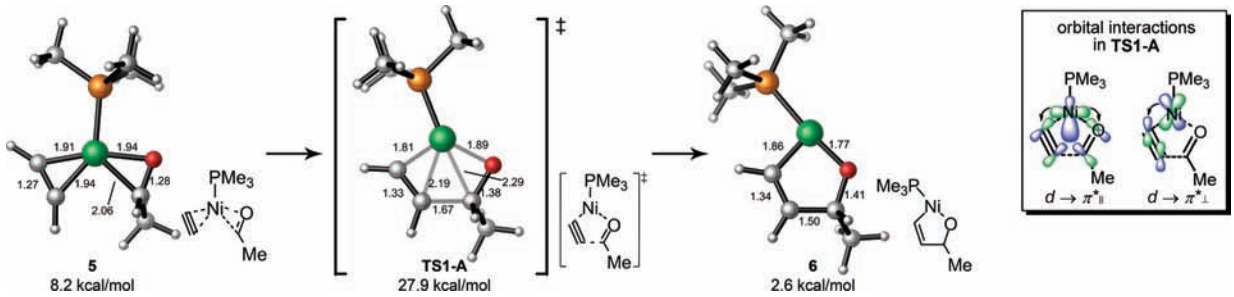

Figure 1. Oxidative cyclization of acetylene and acetaldehyde. Bond lengths in Å. Energies relative to **3**.

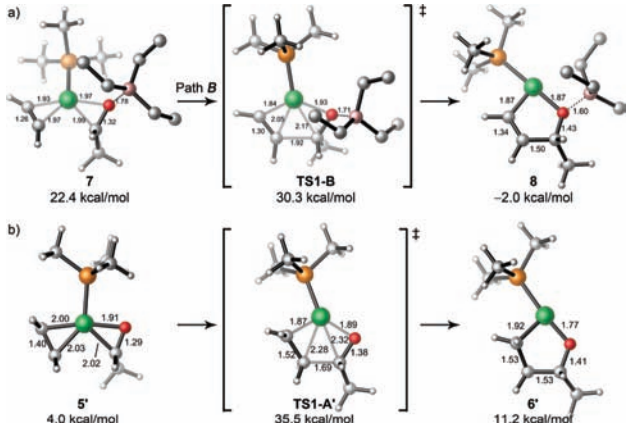

Figure 2. (a) Alternative pathway of alkyne−aldehyde oxidative cyclization: borane coordination to the aldehyde oxygen. Bond lengths in Å. Energies relative to **3**. Hydrogens in BEt_3 have been omitted. (b) Oxidative cyclization of ethylene and acetaldehyde. Bond lengths in Å. Energies relative to the catalyst resting state, alkene(bisphosphane)nickel(0) complex **3′**.

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 Ni (**TS2**) requires an activation free 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.[15]

On the basis of 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 complex 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 in energy than **TS1-A**. Thus, oxidative addition of BEt_3 is not likely to occur. The activation barriers for oxidative addition to acetylene and acetaldehyde (mechanism d) are 33.7 and 40.8 kcal/mol, respectively, both of which are much higher than that for the oxidative cyclization mechanism.

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Supporting Information Available: Free-energy surface for the full catalytic cycle, details of the calculations on alternative mechanisms b−d, optimized Cartesian coordinates and energies, and complete ref 10. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Previous theoretical studies on Ni-catalyzed alkyne−*enone* reductive coupling reactions with $ZnMe_2$ reductant in a *ligand-free* system suggested that $ZnMe_2$ is bonded to nickel in the oxidative cyclization transition state. See: Hratchian, H. P.; Chowdhury, S. K.; Gutierrez-Garcia, V. M.; Amarasinghe, K. K. D.; Heeg, M. J.; Schlegel, H. B.; Montgomery, J. *Organometallics* **2004**, *23*, 4636.
(10) All of the geometry optimizations and frequency calculations were performed with the B3LYP functional implemented in Gaussian 03 (Frisch, M. J.; et al. *Gaussian 03*, revision D.01; Gaussian, Inc.: Pittsburgh, PA, 2004). The LANL2DZ basis set was used for nickel and the 6-31G(d) basis set for the other atoms.
(11) Calculations on a real system (R_1 = Ph, R_2 = Me, R_3 = *i*-Pr, L = PEt_3) suggested that its transition-state geometries and activation energies are similar to those of the model system (see the Supporting Information for details).
(12) The oxidative cyclization of alkyne and aldehyde can proceed without the presence of Lewis acid. See: Ogoshi, S.; Arai, T.; Ohashi, M.; Kurosawa, H. *Chem. Commun.* **2008**, 1347.
(13) (a) When phosphine ligand is present, $ZnMe_2$ also coordinates with the aldehyde oxygen and accelerates the oxidative cyclization (see the Supporting Information for details). (b) $ZnMe_2$ can also accelerate the oxidative cyclization of enone and alkyne in a ligand-free system (see ref 9).
(14) See the Supporting Information for the free-energy profile of the full catalytic cycle.
(15) For experimental regio- and enantioselectivities, see refs 4d and 5b, c, g−i, l.

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