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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Mechanistic Study of Nickel-Catalyzed Ynal Reductive Cyclizations through Kinetic Analysis

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S Supporting Information

ABSTRACT: The mechanism of nickel-catalyzed, silane-mediated reductive cyclization of ynals has been evaluated. The cyclizations are first-order in [Ni] and [ynal] and zeroth-order in [silane]. These results, in combination with the lack of rapid silane consumption upon reaction initiation, are inconsistent with mechanisms involving reaction initiation by oxidative addition of Ni(0) to the silane. Silane consumption occurs only when both the alkyne and aldehyde are present. Mechanisms involving rate-determining oxidative cyclization to a metallacycle followed by rapid reaction with the silane are consistent with the data obtained.

The nickel-catalyzed reductive and alkylative coupling of two π-components has been widely studied, with processes using aldehydes, ketones, enones, imines, alkynes, dienes, and allenes as the most commonly employed π-components.[1] A variety of reducing agents, including silanes, organozincs, organoboranes, organoaluminums, and alkenyl zirconium reagents, have been employed. Of these procedures, the reductive coupling of aldehydes and alkynes is one of the most extensively studied.[2] Numerous variants have appeared, and it is clear that the intra- or intermolecular nature of the process, the reducing agent involved, and the ligand structure employed must all be carefully matched depending on the specific application desired. The formation of a nickel metallacycle intermediate **1** derived from oxidative cyclization of Ni(0) with the aldehyde and alkyne is a central feature of the most commonly proposed mechanisms (Scheme 1). Cleavage of the Ni$-$O bond of this intermediate by the reducing agent then leads to product, typically with either silanes or boranes in reductive variants (H-atom installation, product **2**) or with organozincs in alkylative variants (alkyl group installation, product **3**).

The generation of a dimeric form of metallacycle **1** was documented by Ogoshi using benzaldehyde and 2-butyne as substrates.[3] This species was observed to undergo conversion to an alkylative cyclization product **3** upon exposure to dimethylzinc, although the rate of the organozinc addition was much slower than the overall rate of a typical catalytic process. For the Et_3B-based procedure,[2c] a detailed computational study by Houk and Jamison found that a metallacycle-based mechanism, followed by Ni$-$O bond cleavage by the borane, was operative.[4] A number of additional studies have provided mechanistic insights by examining various product-oriented mechanistic analyses, including regiochemical, stereochemical, and crossover-labeling probes.[2d,5] Despite the insights provided by the above studies, no quantitative rate studies have been reported, and considerable ambiguity remains in the operative pathway of silane-mediated reductive couplings. The ambiguity arises from the facility of alternate pathways involving the generation of nickel hydride intermediates that precede C$-$C bond formation.

The facility of Si$-$H oxidative addition to Ni(0), likely involved in Ni(0)-mediated hydrosilylation pathways for either carbonyl or alkyne substrates,[6] has often been proposed in various classes of nickel-catalyzed reductive couplings.[7] The oxidative addition of silane to a Ni(0) phosphine complex could afford silyl nickel hydride species **4** that then undergoes insertions of the aldehyde and alkyne (Scheme 2). Different possibilities for the timing of the sequential alkyne and aldehyde insertions through hydrometalation and/or silylmetalation pathways are depicted with intermediates **5a**, **5b**, and **5c**.[8] Alternatively, complexation of the aldehyde or alkyne to Ni(0) could facilitate addition of the silane to nickel prior to C$-$C bond formation (Scheme 2, intermediate **6** or **7**). An addition process of this type would then be followed by insertion of the remaining π-component. The metallacycle mechanism where silane σ-bond metathesis occurs as the last step (Scheme 1) differs fundamentally from mechanisms that involve silane addition at an early stage that preceeds C$-$C bond formation (Scheme 2).[9] The rational design of improved procedures, more effective catalysts, and enantioselective processes requires an understanding of the key mechanistic steps, in particular the central involvement of metallacycle or nickel hydride intermediates.

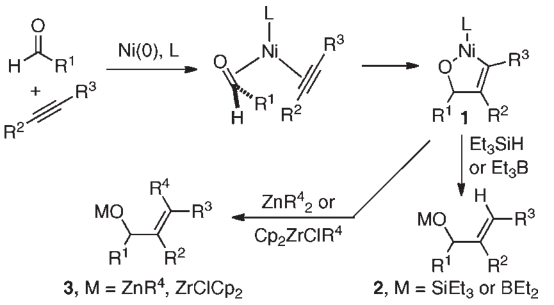
Complexities in distinguishing these mechanistic pathways (Schemes 1 and 2) have persisted throughout the development of numerous classes of nickel-catalyzed reductive couplings.[1,2,7,10] To address the long-standing questions of reaction mechanism and the role of silane in nickel-catalyzed, silane-mediated reductive couplings, this Communication describes a detailed rate analysis of a representative intramolecular coupling and the direct observation of silane depletion using various catalyst$-$substrate combinations. The involvement of metallacyclic intermediates (Scheme 1) is consistent with the data obtained, and evidence against mechanisms that involve initial addition of a nickel species to the silane (Scheme 2) is provided.

A rate study of the cyclization of ynal **8** with catalytic $Ni(COD)_2/PCy_3$ was carried out under synthetically relevant

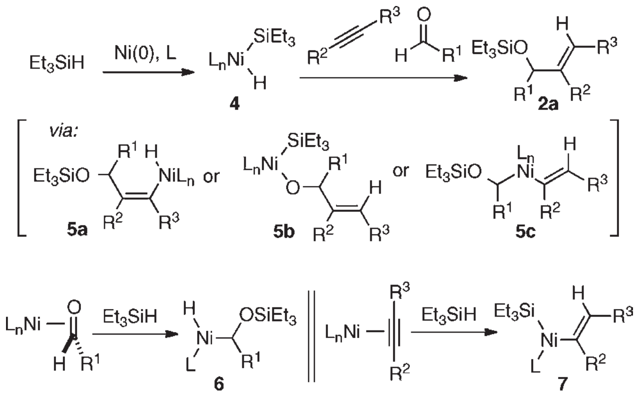
Received: January 28, 2011
Published: March 28, 2011

dx.doi.org/10.1021/ja200867d | *J. Am. Chem. Soc.* 2011, 133, 5728–5731

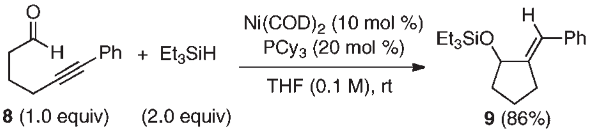
Scheme 1. Nickel-Catalyzed Aldehyde−Alkyne Couplings



Scheme 2. Mechanisms Initiated by Oxidative Addition to Et_3SiH



conditions using the method of initial rates in the production of **9** (eq 1).



(1)

In situ IR monitoring was used to measure reaction progressions in real-time. Due to the fast rate of intramolecular coupling, kinetic analyses were performed at −25 °C. A clear first-order dependence of reaction rate on [ynal **8**] was observed across all concentrations studied (Figure 1). The reaction rate was also shown to have a linear dependence on $[Ni(COD)_2]$ between 10 and 25 mol % catalyst loading, yielding catalyst turnover frequencies of 13.8−32.3 h^{-1}. These results could be consistent with either mechanism described above (Schemes 1 and 2). However, no significant change in reaction rate was observed with varying $[Et_3SiH]$ as silane stoichiometry was varied from 1.0 to 4.0 equiv (Figure 1).

To further distinguish between mechanisms, kinetic isotope effect studies and crossover experiments were undertaken to gain insight into the Si−H bond cleavage process (Scheme 3). Reductive cyclization of **8** in the presence of excess Et_3SiH and Et_3SiD yielded no significant kinetic isotope effect (k_H/k_D = 1.00), consistent with post-rate-limiting participation of the silane reducing agent.[11] In crossover experiments employing excess Et_3SiD and Pr_3SiH, ynal **8** was converted to products **9** and **10** with approximately 10% crossover. Thus, the primary mechanistic pathway proceeds without crossover, in contrast to the PBu_3-promoted process originally reported.[2d,12]

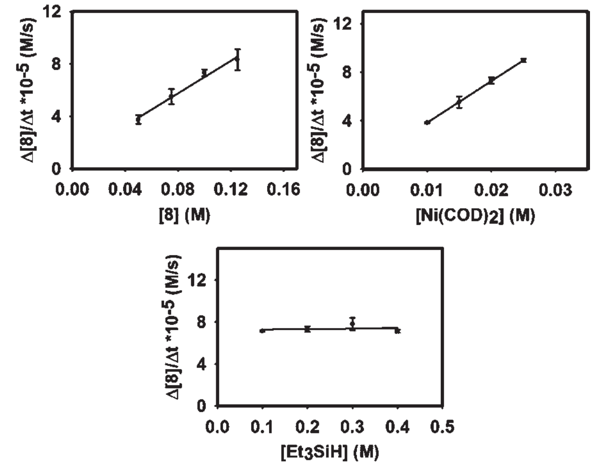
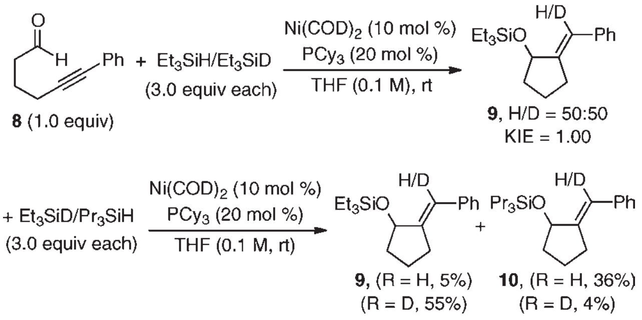


Figure 1. Determination of kinetic order of reaction components. (Top left) Linear dependence of initial reaction rate on [**8**]. (Top right) Linear dependence of initial reaction rate on $[Ni(COD)_2]$. (Bottom) Zeroth-order dependence of initial reaction rate on $[Et_3SiH]$. Reported values are given as the average of three or more experiments, with error bars representing the standard deviation between individual runs.

Scheme 3. Kinetic Isotope Effects and Crossover Experiments



The zeroth-order dependence on Et_3SiH in ynal reductive cyclizations and lack of kinetic isotope effect are inconsistent with rate-determining oxidative addition of Ni(0) to the Si−H bond (Scheme 2). For a mechanism involving the production of nickel hydride **4** to be consistent with the kinetic order studies, a fast reaction between a PCy_3 adduct of $Ni(COD)_2$ with Et_3SiH must occur, followed by a slow subsequent insertion step, in order for the first-order dependence on [Ni], first-order dependence on [ynal], and zeroth-order dependence on $[Et_3SiH]$ to be observed. To examine this possibility, 1.0 equiv of the catalyst derived from $Ni(COD)_2$ and PCy_3 was added to a solution of Et_3SiH with *in situ* IR monitoring, and no consumption or change of the silicon hydride stretch (2100 cm^{-1}) was observed on the time scale and temperature of productive catalytic reactions (Figure 2a). As noted above (Scheme 2, intermediate **6** or **7**), rate-determining complexation of either aldehyde or alkyne to Ni(0) could be followed by rapid consumption of silane, and thus be consistent with the rate data.[13] To examine this possibility, a solution of 1.0 equiv of the same catalyst was injected to a THF solution of Et_3SiH and hydrocinnamaldehyde at −25 °C, and no consumption of silane was observed as judged

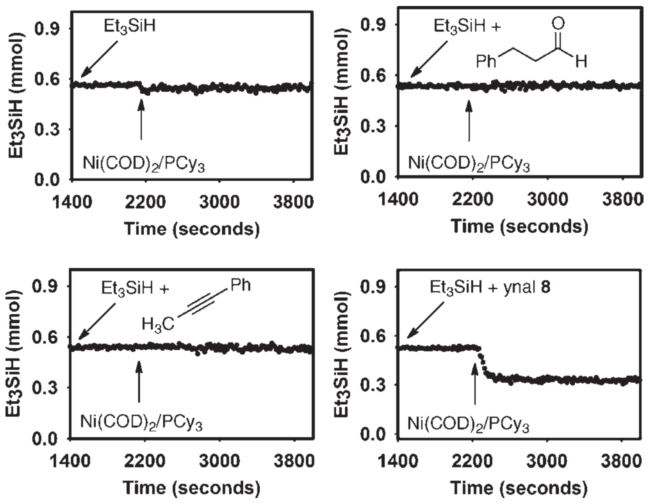


Figure 2. Experiments tracking silane depletion, with monitoring of silane IR stretch at 2100 cm^{-1}. (a, top left) Et$_3$SiH (1.0 equiv) at −25 °C, then a mixture of Ni(COD)$_2$ (1.0 equiv) and PCy$_3$ (2.0 equiv). (b, top right) Et$_3$SiH (1.0 equiv) and hydrocinnamaldehyde (1.0 equiv) at −25 °C, then a mixture of Ni(COD)$_2$ (1.0 equiv) and PCy$_3$ (2.0 equiv). (c, bottom left) Et$_3$SiH (1.0 equiv) and phenyl propyne (1.0 equiv) at −25 °C, then a mixture of Ni(COD)$_2$ (1.0 equiv) and PCy$_3$ (2.0 equiv). (d, bottom right) Et$_3$SiH (1.0 equiv) and ynal **8** (1.0 equiv) at −25 °C, then a mixture of Ni(COD)$_2$ (1.0 equiv) and PCy$_3$ (2.0 equiv).

by *in situ* IR analysis (Figure 2b).[14] Similary, injection of 1.0 equiv of the same catalyst to a solution of phenyl propyne and Et$_3$SiH at −25 °C resulted in no silane depletion (Figure 2c). However, adding 1.0 equiv of the same catalyst to a solution of ynal **8** and Et$_3$SiH at −25 °C led to productive formation of product **9** with steady depletion of silane (Figure 2d).

These experiments, coupled with the rate analysis and lack of silane kinetic isotope effect, are consistent with the metallacycle mechanism (Scheme 1) and provide strong evidence against mechanisms that involve addition of a Ni(0) species to silane (Scheme 2). Additionally, kinetically viable mechanisms that involve catalyst modification via the conversion of Ni(0) to a reactive Ni(II) hydride upon reaction initiation would involve rapid silane consumption at the level of nickel catalyst loading.[15] However, rapid silane consumption does not precede the beginning of ynal consumption or product formation. The intermediacy of metallacycle **1** followed by rapid reaction with Et$_3$SiH, is consistent with these observations. Metallacycle **1** is likely formed by oxidative cyclization of a Ni(0)−ynal complex following slow or reversible complexation of substrate.[16]

In summary, the kinetic behavior of a nickel-catalyzed silane-mediated reductive cyclization of ynals has been evaluated. This report represents the first such study across the many classes of related nickel-catalyzed reductive couplings that have been reported. The rate studies are consistent with a mechanism involving rate-determining oxidative cyclization to a metallacyclic intermediate, followed by rapid silane-mediated conversion to the protected allylic alcohol product. A number of mechanisms involving oxidative addition of silane to nickel can be ruled out on the basis of this analysis. Future work will be directed toward fully elucidating the nature of the steps that follow the rate-determining oxidative cyclization, as well as evaluating the generality of these results in intermolecular couplings and with other ligand systems.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Full experimental details, NMR spectra, and *in situ* IR kinetics data. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

The authors acknowledge receipt of NIH grant GM57014 (including GM57014-13S2) in support of this work. R.D.B. acknowledges receipt of a U.S. DOE GAANN Fellowship (P200A060119). We are especially grateful to Profs. Anne J. McNeil and Melanie S. Sanford and their research groups for helpful discussions. J.M. thanks the faculty of the Institute of Chemical Research of Catalonia (ICIQ) for hospitality during a sabbatical stay.

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(8) Hydrosilylation of ynals with Rh hydrosilylation catalysts provides the opposite regiochemistry for silane addition, producing alkenylsilane products. See:Ojima, I.; Tzamarioudaki, M.; Tsai, C. Y. *J. Am. Chem. Soc.* **1994**, *116*, 3643.

(9) In addition to the possibilities described in the text, alteration of the precatalyst oxidation state during reaction initiation would provide additional available mechanistic pathways. For example, the Ni(II)-catalyzed hydrosilylation of carbonyl compounds proceeds by nickel hydride generation by σ-bond metathesis of silane with a nickel

alkoxide. See:Tran, B. L.; Pink, M.; Mindiola, D. J. *Organometallics* **2009**, *28*, 2234.

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(11) The Ni(COD)$_2$/PCy$_3$ catalyst system studied in this Communication proceeded with an inverse kinetic isotope effect ($k_H/k_D = 0.75$) for the hydrosilylation of cinnamaldehyde at 45 °C in THF (heating at this temperature was required to achieve good conversion). For discussions of kinetic isotope effects observed in hydrosilylation reactions, see: (a) Parks, D. J.; Blackwell, J. M.; Piers, W. E. *J. Org. Chem.* **2000**, *65*, 3090. (b) Nolin, K. A.; Krumper, J. R.; Pluth, M. D.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 14684. (c) Schneider, N.; Finger, M.; Haferkemper, C.; Bellemin-Laponnaz, S.; Hofman, P.; Gade, L. H. *Chem. Eur. J.* **2009**, *15*, 11515.

(12) A study of the post-rate-limiting steps and origin of crossover is in progress and will be reported elsewhere.

(13) For studies of carbonyl hydrosilylation processes that describe various mechanisms for silane consumption, see ref 11 and the following:Ojima, I.; Kogure, T. *Organometallics* **1982**, *1*, 1390.

(14) The consumption of Et$_3$SiH via the hydrosilylation of cinnamaldehyde using a Ni(COD)$_2$/PCy$_3$ catalyst system in THF is observed but requires heating to 45 °C for several hours.

(15) Nickel hydride-catalyzed pathways typically involve electrophilic Ni(II) species. See ref 9 and the following: RajanBabu, T. V. *Synlett* **2009**, 853–885.

(16) The first-order dependence on ynal illustrates that the Ni(0) ynal complex is not the sole catalyst resting state.