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

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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 Et₃B-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

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Supporting Information Available: Full experimental details and copies of NMR spectral data and *in situ* IR kinetics data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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 hydrometallation and/or silylmallation 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, intermediates **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) fundamentally differs from mechanisms that involve silane addition at an early stage that precedes 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 manuscript 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/PCy₃ was carried out under synthetically relevant conditions using the method of initial rates in the production of **9** (eq 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 10–25 mol% catalyst loading, yielding catalyst turnover frequencies of 13.8 to 32.3 per hour. 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 [Et₃SiH] as silane stoichiometry was varied from 1.0 to 4.0 equiv (Figure 1).

(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 Et₃SiH and Et₃SiD 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}

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 $\text{Ni}(0)$ 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 $\text{Ni}(\text{COD})_2$ with Et_3SiH must occur, followed by a slow subsequent insertion step, in order for the first-order dependence on $[\text{Ni}]$, first-order dependence on $[\text{ynal}]$, and zeroth-order dependence on $[\text{Et}_3\text{SiH}]$ to be observed. To examine this possibility, 1.0 equiv of the catalyst derived from $\text{Ni}(\text{COD})_2$ 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 timescale and temperature of productive catalytic reactions (Figure 2a). As noted above (Scheme 2, intermediates **6** or **7**), rate-determining complexation of either aldehyde or alkyne to $\text{Ni}(0)$ 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 $-25\text{ }^\circ\text{C}$, and no consumption of silane was observed as judged by in situ IR analysis (Figure 2b).¹⁴ Similarly, injection of 1.0 equiv of the same catalyst to a solution of phenyl propyne and Et_3SiH at $-25\text{ }^\circ\text{C}$ resulted in no silane depletion (Figure 2c). However, adding 1.0 equiv of the same catalyst to a solution of ynal **8** and Et_3SiH at $-25\text{ }^\circ\text{C}$ 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 $\text{Ni}(0)$ species to silane (Scheme 2). Additionally, kinetically viable mechanisms that involve catalyst modification via the conversion of $\text{Ni}(0)$ to a reactive $\text{Ni}(\text{II})$ 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_3SiH , is consistent with these observations. Metallacycle **1** is likely formed by oxidative cyclization of a $\text{Ni}(0)$ -ynal complex following slow or reversible complexation of substrate.^{16,17}

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 towards 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. (a) Montgomery J. *Angew Chem Int Ed*. 2004; 43:3890.(b) Montgomery J, Sormunen GJ. *Top Curr Chem*. 2007; 279:1.(c) Malik HA, Baxter RD, Montgomery J, Bullock RM. *Nickel-Catalyzed Reductive Couplings and Cyclizations. Catalysis Without Precious Metals*. Wiley-VCH Weinheim, Germany 2010:181.(d) Moslin RM, Miller-Moslin K, Jamison TF. *Chem Commun*. 2007:4441.(d) Ikeda S. *Angew Chem Int Ed*. 2003; 42:5120. For related processes with other metals: (e) Skucas E, Ngai MY, Komanduri V, Krische MJ. *Acc Chem Res*. 2007; 40:1394. [PubMed: 17784728] (f) Jeganmohan M, Cheng CH. *Chem Eur J*. 2008; 14:10876.(g) Reichard HA, McLaughlin M, Chen MZ, Micalizio GC. *Eur J Org Chem*. 2010:391.
2. (a) Oblinger E, Montgomery J. *J Am Chem Soc*. 1997; 119:9065.(b) Tang XQ, Montgomery J. *J Am Chem Soc*. 1999; 121:6098.(c) Huang WS, Chan J, Jamison TF. *Org Lett*. 2000; 2:4221. [PubMed: 11150204] (d) Mahandru GM, Liu G, Montgomery J. *J Am Chem Soc*. 2004; 126:3698. [PubMed: 15038707] (e) Yang Y, Zhu SF, Zhou CY, Zhou QL. *J Am Chem Soc*. 2008; 130:14052. [PubMed: 18834121]
3. Ogoshi S, Arai T, Ohashi M, Kurosawa H. *Chem Commun*. 2008:1347.
4. McCarren PR, Liu P, Cheong PHY, Jamison TF, Houk KN. *J Am Chem Soc*. 2009; 131:6654. [PubMed: 19397371]
5. (a) Miller KM, Jamison TF. *J Am Chem Soc*. 2004; 126:15342. [PubMed: 15563136] (b) Moslin RA, Miller KM, Jamison TF. *Tetrahedron*. 2006; 62:7598.(c) Malik HA, Sormunen GJ, Montgomery J. *J Am Chem Soc*. 2010; 132:6304. [PubMed: 20394367]
6. (a) Chaulagain MR, Mahandru GM, Montgomery J. *Tetrahedron*. 2006; 62:7560.(b) Buchan ZA, Bader SJ, Montgomery J. *Angew Chem Int Edit*. 2009; 48:4840.
7. (a) Tamao K, Kobayashi K, Ito Y. *J Am Chem Soc*. 1989; 111:6478.(b) Sato Y, Takimoto M, Hayashi K, Katsuhara T, Takagi K, Mori M. *J Am Chem Soc*. 1994; 116:9771.(c) Sato Y, Takimoto M, Mori M. *J Am Chem Soc*. 2000; 122:1624. For a recent demonstration: (d) Zell T, Schaub T, Radacki K, Radius U. *Dalton Trans*. 2011; 40:1852. [PubMed: 21243148]
8. Hydrosilylation of ynals with Rh hydrosilylation catalysts provides the opposite regiochemistry for silane addition, producing alkenylsilane products. See: Ojima I, Tzamarioudaki M, Tsai CY. *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 BL, Pink M, Mindiola DJ. *Organometallics*. 2009; 28:2234.
10. For related classes of silane-mediated nickel-catalyzed reductive couplings, see reference 7 and: (a) Sato Y, Sawaki R, Mori M. *Organometallics*. 2001; 20:5510–5512.(b) Ng SS, Jamison TF. *J Am Chem Soc*. 2005; 127:7320. [PubMed: 15898774] (c) Saito N, Sugimura Y, Sato Y. *Org Lett*. 2010; 12:3494. [PubMed: 20590086]
11. The Ni(COD)₂/PCy₃ 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 DJ, Blackwell JM, Piers WE. *J Org Chem*. 2000; 65:3090. [PubMed: 10814201] (b) Nolin KA, Krumper JR, Pluth MD, Bergman RG, Toste FD. *J Am Chem Soc*. 2007; 129:14684. [PubMed: 17983224] (c) Schneider N, Finger M, Haferkemper C, Bellemin-Lapontaz S, Hofman P, Gade LH. *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 references 11 and the following: Ojima I, Kogure T. *Organometallics*. 1982; 1:1390.
14. The consumption of Et_3SiH via the hydrosilylation of cinnamaldehyde using a $\text{Ni}(\text{COD})_2/\text{PCy}_3$ catalyst system in THF is observed but requires heating to 45 °C for several hours.
15. Nickel hydride-catalyzed pathways typically involve electrophilic $\text{Ni}(\text{II})$ species. See reference 9 and RajanBabu TV. *Synlett*. 2009:853–885. [PubMed: 19606231]
16. The first order dependence on ynal illustrates that the $\text{Ni}(0)$ ynal complex is not the sole catalyst resting state.

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 **[Et₃SiH]**. Reported values are given as the average of three or more experiments with error bars representing the standard deviation between individual runs.

Figure 2. Experiments tracking silane depletion, with monitoring of silane IR stretch at 2100 cm^{-1}

(A) Top left: Et_3SiH (1.0 equiv) at -25°C , then a mixture of $\text{Ni}(\text{COD})_2$ (1.0 equiv) and PCy_3 (2.0 equiv). (B) Top right: Et_3SiH (1.0 equiv) and hydrocinnamaldehyde (1.0 equiv) at -25°C , then a mixture of $\text{Ni}(\text{COD})_2$ (1.0 equiv) and PCy_3 (2.0 equiv). (C) Bottom left: Et_3SiH (1.0 equiv) and phenyl propyne (1.0 equiv) at -25°C , then a mixture of $\text{Ni}(\text{COD})_2$ (1.0 equiv) and PCy_3 (2.0 equiv). (D) Bottom right: Et_3SiH (1.0 equiv) and ynal **8** (1.0 equiv) at -25°C , then a mixture of $\text{Ni}(\text{COD})_2$ (1.0 equiv) and PCy_3 (2.0 equiv).

Scheme 1.
Nickel-Catalyzed Aldehyde-Alkyne Couplings

Scheme 2.
Mechanisms Initiated by Oxidative Addition to Et₃SiH

Scheme 3.
Kinetic Isotope Effects and Crossover Experiments.