

# Highly Active Nickel Catalysts for C–H Functionalization Identified through Analysis of Off-Cycle Intermediates

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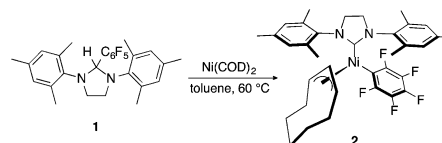
**S** Supporting Information

**ABSTRACT:** An inhibitory role of 1,5-cyclooctadiene (COD) in nickel-catalyzed C–H functionalization processes was identified and studied. The bound COD participates in C–H activation by capturing the hydride, leading to a stable off-cycle  $\pi$ -allyl complex that greatly diminished overall catalytic efficiency. Computational studies elucidated the origin of the effect and enabled identification of a 1,5-hexadiene-derived pre-catalyst that avoids the off-cycle intermediate and provides catalytic efficiencies that are superior to those of catalysts derived from Ni(COD)<sub>2</sub>.

Nickel catalysis is widely recognized as a low-cost and sustainable method for conducting a wide range of catalytic processes.<sup>1</sup> The use of nickel in C–H functionalization processes has received particular attention in recent years, with many unique transformations reported for the functionalization of sp<sup>2</sup> and sp<sup>3</sup> C–H bonds.<sup>2–4</sup> While cost and availability considerations make the use of nickel in catalysis highly attractive, relatively high catalyst loadings are commonly employed throughout the nickel literature.<sup>1</sup> Additionally, limitations in substrate scope and the high temperature requirements of many nickel-catalyzed C–H functionalizations limit the practicality of the otherwise highly promising methods. Important mechanistic insights have been provided on a number of the processes noted above, including the addition of arene C–H bonds to alkenes and alkynes<sup>5</sup> and the C–O/C–H cross-couplings of heteroaromatics.<sup>6</sup> However, little attention has been placed on the role of ancillary ligands on the nickel pre-catalyst and the potential for off-cycle intermediates that could impede efficient catalysis. In the vast majority of Ni(0)-catalyzed processes, Ni(COD)<sub>2</sub> is employed as the pre-catalyst. While a few reports noted synthetic implications of the presence of 1,5-cyclooctadiene (COD) in altering catalyst performance,<sup>7</sup> little understanding of the basis for these effects has been elucidated.<sup>8</sup> Here we describe a detailed analysis of the role of COD in nickel-catalyzed C–H activation processes and the importance of off-cycle intermediates that retain a COD unit and impede catalysis. The insights from this analysis enable the identification of conveniently prepared and highly active COD-free pre-catalysts for nickel-catalyzed C–H functionalization processes that proceed at room temperature (rt).

Initial insights into the role of COD in C–H functionalization processes were provided by an unexpected result while exploring the use of pentafluorobenzene (C<sub>6</sub>F<sub>5</sub>H)-derived

## Scheme 1. Formation of $\pi$ -Allyl Complex 2

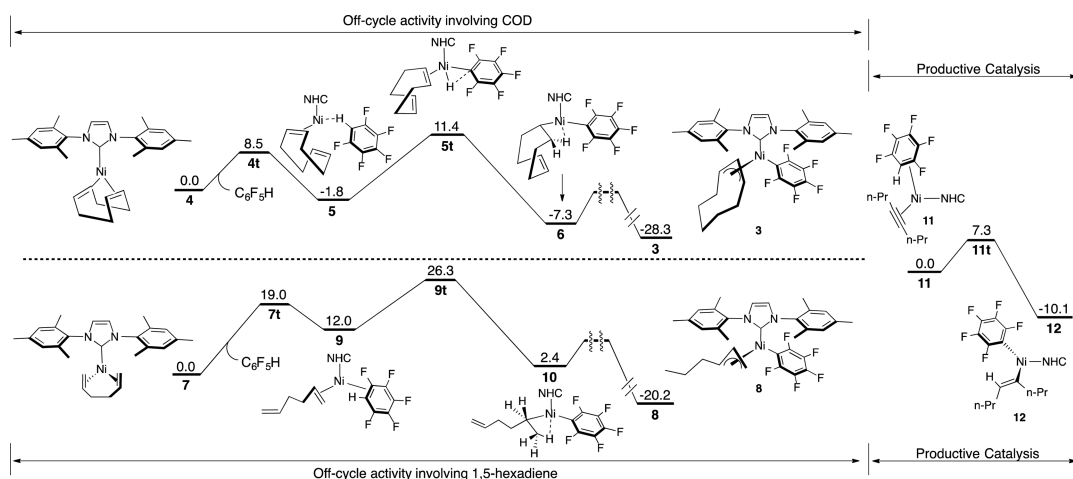


precursors to access Ni(0) *N*-heterocyclic carbene (NHC) complexes. Following the procedure described by Waymouth and Hedrick,<sup>9</sup> precursor **1** was treated with Ni(COD)<sub>2</sub>, anticipating extrusion of C<sub>6</sub>F<sub>5</sub>H and formation of the Ni(0) adduct of SIMes. To our surprise, stable Ni(II)  $\pi$ -allyl complex **2** was instead obtained (Scheme 1). It is likely that formation of the expected Ni(0)-SIMes complex along with an equivalent of C<sub>6</sub>F<sub>5</sub>H occurs, and then addition of the Ni-NHC complex to C<sub>6</sub>F<sub>5</sub>H proceeds via C–H activation. Hydride migration to bound COD followed by chain walking ultimately forms  $\pi$ -allyl complex **2**. Whereas an analogous  $\pi$ -allyl complex had previously been prepared from a Ni(0) complex of P(*i*-Pr)<sub>3</sub>,<sup>5d</sup> the direct capture of the fluoroarene extruded from an NHC precursor such as **1** is, to our knowledge, unprecedented.  $\pi$ -Allyl complex **3** (Figure 1) can be generated in a similar fashion by stirring C<sub>6</sub>F<sub>5</sub>H, IMes, and Ni(COD)<sub>2</sub>, in support of the mechanism postulated above. Although **2** was not characterized by X-ray diffraction, the structure of **3** was confirmed by X-ray analysis (Supporting Information (SI)). The rapid and efficient capture of low concentrations of C<sub>6</sub>F<sub>5</sub>H formed during generation of the Ni(0)-NHC complex raised the question of the impact of this process in arene C–H functionalizations. Thus, we set out to examine the implications of the formation of **3** in catalytic processes by both theoretical and experimental studies.

To elucidate the mechanism for the formation of **3**, reaction discovery methods developed in our laboratory were employed. These methods hypothesize and evaluate plausible elementary reaction steps,<sup>10</sup> providing detailed descriptions of thermodynamics and kinetics at a rapid pace.<sup>11</sup> The resulting mechanism predicted via this method (Figure 1) is initiated by dissociation of one of the bound alkenes of a Ni(COD)-NHC complex (**4**). This process has a low barrier of 8.5 kcal/mol (**4t**) to form structure **5**. Upon generation of an open coordination site, the oxidative addition of C<sub>6</sub>F<sub>5</sub>H takes place, followed by subsequent migratory insertion, termed ligand-to-ligand hydrogen transfer (LLHT), to form **6**, with a rate-limiting barrier of

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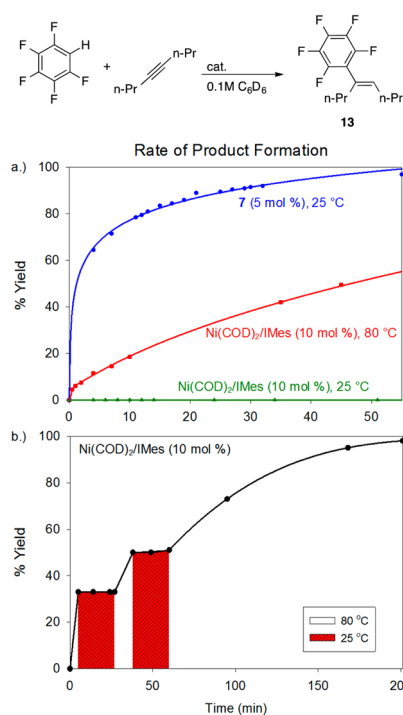


**Figure 1.** Gibbs free energies for the formation of **3**, **8**, and **12**. All energies are reported in kcal/mol ( $\omega$ B97X-D/cc-pVTZ).

11.4 kcal/mol (**5t**). This is proposed to arise from the back-bonding character of the alkene–nickel interaction, resulting in an electron-rich alkene ligand that mediates C–H activation. The observation of LLHT, instead of classical three-centered oxidative addition, is consistent with previously described DFT investigations for the mechanism of alkyne hydrofluoroarylation.<sup>5b</sup> The proposed mechanism is representative of the lowest energy pathway from **4** to **6**. From **6**, a straightforward series of  $\beta$ -hydride elimination/migratory insertion events (chain walking)<sup>12</sup> forms **3**, which was determined to be 28.3 kcal/mol downhill from starting structure **4** (Figure 1), suggesting that complexes analogous to **3** may be associated with an off-cycle resting state that diminishes productive catalysis.

Following the seminal precedent from Nakao and Hiya, the coupling of 4-octyne with  $C_6F_5H$  to generate product **13** was used as a test case, monitoring reactions using  $^{19}F$  NMR (Figure 2). When a catalyst derived from 10 mol%  $Ni(COD)_2$  and free IMes were used, the reaction was very slow at rt, resulting in a 2% yield after 1 h. Notably, characteristic  $^{19}F$  peaks associated with **3** were observed in low concentrations throughout the reaction (SI, S6). At 80 °C, product formation was observed, and a yield of 60% was obtained after 1 h (Figure 2a).  $\pi$ -Allyl complexes **2** and **3** as pre-catalysts for the coupling of 4-octyne and  $C_6F_5H$  were unreactive at rt but afforded an 80 and 83% yield, respectively, upon stirring at 80 °C for 3 h. We thus considered that forming **3** in reactions using  $Ni(COD)_2$ -derived catalysts might inhibit catalysis throughout the reaction; alternatively it may slowly release a more active form of the catalyst following an induction period. To address this question, the reaction using  $Ni(COD)_2/IMes$  was heated to 80 °C for 5 min to initiate catalysis. The  $^{19}F$  NMR spectrum illustrated a 33% yield, and after 20 min at rt, the yield remained unchanged (Figure 2b). This procedure was repeated for another heating/cooling period, and similar results were observed. Notably, no allyl- $C_6F_5H$  is observed that would result from reductive elimination of **3**. Given the high barrier for the reversion of **3** to **4**, the conversion of **3** to an active catalyst likely proceeds through a ligand substitution of the alkyne with an alternative intermediate. This outcome suggests that **3** is formed as an off-cycle resting state that persists throughout the entire reaction and that replacement of COD with an alternative ancillary ligand might increase overall reaction rates.

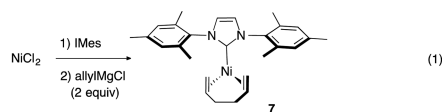
Other than  $Ni(COD)_2$ , there is an absence of commercially available  $Ni(0)$  compounds that lack either strong donors,



**Figure 2.** (a) Reaction progression plots showing the formation of product **13** over time. (b) Reaction progression using  $Ni(COD)_2/IMes$  with temperature cycles between 80 and 25 °C.

which lead to coordinatively saturated NHC complexes, or  $\pi$ -acidic ligands, which typically lead to considerably lower reactivity.<sup>7c</sup> *In situ* reduction of  $Ni(II)$  sources is commonly employed in nickel catalysis, but the limited solubility of nickel halides restricts solvent choice. The reactivity of the (*i*-Bu)<sub>2</sub>Al(acac) byproduct can also complicate catalytic reactions that utilize DIBAL-H reduction of  $Ni(acac)_2$ .<sup>13</sup> Furthermore, *in situ* reduction of  $Ni(II)$  and coordination of an NHC ligand result in poorly defined catalysts that are difficult to controllably generate. For these reasons, identifying a well-defined  $Ni(0)$ -NHC pre-catalyst that can be generated in the absence of COD, strong donor ligands, or strong  $\pi$ -acids is highly desirable for C–H activation processes.

With these criteria in mind, the 1,5-hexadiene-supported  $Ni(0)$ -NHC complexes developed by Hazari are an especially attractive catalyst class to consider (eq 1).<sup>14</sup> These catalysts



may be prepared by adding allylmagnesium bromide to a solution of ligand (i.e., NHC or phosphine) and  $\text{NiCl}_2$ , which generates the 1,5-hexadiene  $\text{Ni}(0)$  complex by reductive elimination of the  $\text{Ni}(\text{II})$  bis-allyl intermediate. The 1,5-hexadiene complexes span a range of NHCs, providing access to well-defined  $\text{Ni}(0)$ -NHC complexes. The IMes variant **7** was isolated and tested for catalytic activity. Interestingly, when **7** was used as a catalyst (5 mol%) for the coupling of  $\text{C}_6\text{F}_5\text{H}$  and 4-octyne, high yields at rt after 1 h were produced (Figure 2a). This significant increase in efficiency suggested that off-cycle activity involving the ancillary ligand was greatly diminished. As anticipated, COD plays an inhibitory role in catalytic reactions using pre-catalyst **7** (see SI).

In principle, a  $\pi$ -allyl complex analogous to **3** could form by direct insertion of 1,5-hexadiene (**8**, Figure 1). In an effort to determine the accessibility of **8**, the mechanism and feasibility of its formation were computationally examined. Following a path similar to that described for COD, the LLHT reaction has a net barrier of 26.3 kcal/mol (**9t**), suggesting that the formation of **8** is not kinetically feasible at rt (Figure 1). It is plausible that the increased barrier for forming **8** stems in part from the terminal alkene being less electron-rich than an internal alkene. As a result, the LLHT,<sup>5b</sup> which is essentially a metal-assisted deprotonation, becomes more difficult. Treatment of  $\text{C}_6\text{F}_5\text{H}$  with **7** returned only starting material at rt, and no evidence for the formation of **8** was obtained by  $^{19}\text{F}$  NMR analysis of the reaction mixture. Thus, both computation and experiment suggested that **7** does not activate  $\text{C}_6\text{F}_5\text{H}$  at rt.

To assess the relative effects that **3** and **8** have on catalysis, we investigated the mechanism for functionalizing 4-octyne (Figure 1). C–H activation from **11** follows a similar LLHT path, yielding vinyl species **12**. This transformation has a barrier of 7.3 kcal/mol and is exothermic by 10.1 kcal/mol. The reaction barriers for the formation of both **3** and **12** are sufficiently low that they are accessible at rt, providing two operative and divergent pathways. As mentioned, it is likely that the barrier of step **9t** is kinetically infeasible at rt; thus, if COD is present, off-cycle activity becomes operative, whereas 1,5-hexadiene-based systems do not allow entry into off-cycle activity at rt. The inability of **7** to directly react with  $\text{C}_6\text{F}_5\text{H}$  at rt suggests that formation of **8** does not compete with productive catalysis. Therefore, the difference in catalytic activity between **7** and **4** originates from the high barrier for forming off-cycle intermediate **8** compared with the facile formation of intermediate **3**, which is unproductive. As a result, high temperatures are required for the catalyst to re-enter the productive catalytic pathway (Scheme 2). With COD-free catalysts such as **7**, off-cycle activity involving  $\pi$ -allyl formation is minimized, allowing efficient catalysis at rt.

The greater activity of **7** compared to  $\text{Ni}(\text{COD})_2/\text{IMes}$  resulted in a substantial increase in efficiency for several classes of substrates. Table 1 shows comparisons in C–H functionalization reactivity of hexadiene and COD-based systems. Couplings of fluorobenzenes or fluoropyridines with alkynes were efficient with catalyst **7** at rt, whereas conversions with  $\text{Ni}(\text{COD})_2/\text{IMes}$  were inefficient (entries 1, 2). The alkenylation of benzoxazole was also accelerated, with quantitative yields being obtained after 1 h with **7** (entry 3),

## Scheme 2. Competing Pathways for Reactivity

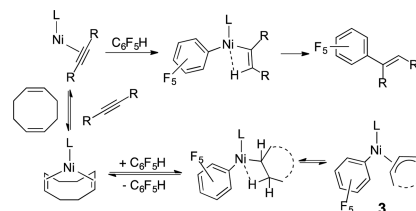


Table 1. Pre-catalyst Comparison

entry	substrate	product	time (h)	proc. A % yield	proc. B % yield
1			3	93 <sup>a</sup>	8 <sup>a</sup>
2			3	91 <sup>a</sup>	24 <sup>a</sup>
3			0.5	>99 <sup>a</sup>	8 <sup>a</sup>
4			8	75 <sup>b</sup>	32 <sup>b</sup>
5			24	51 <sup>b</sup>	3 <sup>b</sup>
6 <sup>c</sup>			1	91 <sup>a</sup>	40 <sup>a</sup>
7 <sup>c,f</sup>			16	NR	NR
8 <sup>c,d,f</sup>	<b>14</b>	<b>15</b>	16	<5 <sup>b</sup>	<5 <sup>b</sup>
9 <sup>c,e,f</sup>	<b>14</b>	<b>15</b>	1	81 <sup>b</sup>	72 <sup>b</sup>

Procedure A: 5 mol% **7**. Procedure B: 10 mol%  $\text{Ni}(\text{COD})_2$  and IMes, pre-stirred 10 min. Entries 1–6 were carried out at 0.1 M and 7–9 at 0.67 M in toluene. <sup>a</sup>Isolated yields. <sup>b</sup>NMR yields using  $\text{CH}_2\text{Br}_2$  as an internal standard. <sup>c</sup>20 mol%  $\text{AlMe}_3$ . <sup>d</sup> $T = 60^\circ\text{C}$ . <sup>e</sup> $T = 100^\circ\text{C}$ . <sup>f</sup>In all cases endo:exo >20:1.

whereas the  $\text{Ni}(\text{COD})_2$  system was much less active. For functionalizing substrates with higher  $\text{pK}_a$  values, such as benzofuran and benzothiophene, catalyst **7** produced 75 and 51% yield (entries 4, 5), respectively.  $\text{Ni}(\text{COD})_2/\text{IMes}$  provided lower yields under the same conditions. Substrates that require activation by Lewis acid co-catalysts, such as 1,3-dimethyluracil, are also more efficiently transformed using catalyst **7**. In this instance, the reaction was high yielding, with 20 mol%  $\text{AlMe}_3$  after 1 h at rt (entry 6). Intramolecular directed C–H functionalization was also investigated using 2-pyrindones, where cyclization yields hydroarylation of a tethered olefin. These examples (entries 7–9) required  $\text{AlMe}_3$  as co-catalyst (20 mol%) and elevated temperatures. Consistent with studies from Cramer, the regioselectivity favored the endo



product, with ratios of >20:1 (endo:exo) in all cases.<sup>15</sup> At 100 °C, **7** produced 81% yield, and Ni(COD)<sub>2</sub>/IMes formed 78% yield (entry 9). In this intramolecular case, the effects of COD were less pronounced, and **7** displayed reactivity similar to that of Ni(COD)<sub>2</sub>/IMes.

From these results, a number of predictions can be made regarding expectations for the benefits of using catalyst **7**. During intramolecular C–H functionalization, little benefit is expected since proximity of the tethered substrate alkene to the catalyst during the C–H bond activation likely leads to a rapid insertion of the alkene rather than COD, thus avoiding formation of deactivating  $\pi$ -allyl complexes. Regarding substrates with less acidic C–H bonds where higher temperatures are needed for C–H activation, it is likely that activation of the C–H bond itself limits reaction efficiency, and rate accelerations through avoiding COD will be diminished. However, with substrates where the pK<sub>a</sub> of the C–H bond is sufficiently low,  $\pi$ -allyl complexes will have a significant inhibitory effect on catalysis, and significant benefits from the use of catalyst **7** will be realized.

In summary, this work highlights that COD, despite being widely utilized as an attractive Ni(0) precursor, can have a significant inhibitory role in C–H functionalization processes. The origin of the effect derives from the facile generation of off-cycle  $\pi$ -allyl complexes by migration of the activated H to COD. Mechanistic insight from our computational reaction discovery approach<sup>10,11</sup> suggested that Ni(0) precursors involving 1,5-hexadiene would avoid formation of these off-cycle intermediates. This enabled C–H functionalization at room temperature using Ni(0) through careful choice of catalyst precursor. This work highlights the often-overlooked role of ancillary ligands in diminishing the efficiency of catalytic processes.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

Experimental and computational details. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04548.

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### Notes

The authors declare no competing financial interest.

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