Computational Study of Ni-Catalyzed C−H Functionalization: Factors That Control the Competition of Oxidative Addition and Radical Pathways

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ABSTRACT: The mechanisms of Ni-catalyzed C−H arylation, alkylation, and sulfonylation with N,N-bidentate directing groups are investigated using density functional theory (DFT) calculations. While the C−H cleavage occurs via the concerted metalation-deprotonation (CMD) mechanism in all types of reactions, the subsequent C−C and C−X bond formation steps may occur via either oxidative addition to form a Ni(IV) intermediate or radical pathways involving Ni(III) complexes generated from homolytic dissociation of disulfides/peroxides or halide-atom transfer from alkyl halides. DFT calculations revealed that radical mechanisms are preferred in reactions with sterically hindered coupling partners with relatively low bond dissociation energies (BDE) such as dicumyl peroxide, heptafluoroisopropyl iodide and diphenyl disulfide. In contrast, these radical processes are highly disfavored when generating unstable phenyl and primary alkyl radicals. In such cases, the reaction proceeds via an oxidative addition/reductive elimination mechanism involving a Ni(IV) intermediate. These theoretical insights into the substrate-controlled mechanisms in the C−H functionalizations were employed to investigate a number of experimental phenomena including substituent effects on reactivity, chemical and regioselectivity and the effects of oxidant in the intermolecular oxidative C−H/C−H coupling reactions.

1. INTRODUCTION

Transition metal-catalyzed C−H bond functionalization reactions are an efficient and versatile strategy for the construction of carbon−carbon and carbon−heteroatom bonds in organic synthesis.1,2 One of the grand challenges in the field of C−H functionalization is to develop new reactions employing earth-abundant first-row transition metal catalysts in place of precious metals such as palladium, iridium, and rhodium that are currently more commonly used.3 In this regard, there has been significant interest in the development of Ni-catalyzed C−H bond functionalization reactions.3 A powerful strategy to achieve site-selective C−H bond functionalization is to use N,N-bidentate directing groups discovered in the seminal work by Daugulis et al.4 In 2011, the Chatani group reported the first Ni-catalyzed chelation-assisted C−H functionalization utilizing the N,N-bidentate 8-aminoquinoline (AQ) directing group.5,6 Since then, extensive efforts have been devoted to extend this strategy to many different types of C(sp2)−H and C(sp3)−H bond functionalization reactions by the groups of Chatani,7 Shi,8 Ge,9 Zhang,10 Lu,11 and others12 (selected examples are shown in Scheme 1). Compared to the widely used Pd C−H functionalization catalysts, Ni-based catalysts are not only much more cost-effective, but can also potentially provide unique reactivities, such as one-electron processes involving open-shell Ni(I) or Ni(III) species.13−15 In addition, the notable differences between the electronic properties of Ni and Pd, such as the barriers of oxidative addition16 and the M−C bond strength,16,17 also offer opportunities to develop Ni-catalyzed C−C and C−X bond formation processes that are complementary to existing C−H functionalization reactions with Pd catalysts.

A thorough mechanistic understanding is desirable to guide the development of a more diverse set of Ni-catalyzed C−H bond functionalization reactions. However, the mechanisms of many of the previously reported processes are still not clear. Although it is generally accepted that the initial C−H metatation occurs via concerted-metalation deprotonation (CMD)18,19 to form a Ni(II) metallacycle A (Scheme 2), there are many mechanistic possibilities in the subsequent steps. For example, in the Ni-catalyzed C−H arylation and alkylation reactions with aryl or alkyl halides (R−X), the Ni(II) metallacycle may promote the R−X bond cleavage via two distinct pathways (Scheme 2): (i) oxidative addition of R−X to form a Ni(IV) intermediate B; and (ii) halogen atom transfer to homolytically cleave the R−X bond and form a Ni(III) intermediate C. The following C−C bond formation may occur via the reductive elimination from either the Ni(IV) intermediate B or the Ni(III) intermediate D. In addition, single electron transfer (SET) pathways that oxidize Ni(II) to...
Ni(III) species have also been proposed. Experimental mechanistic studies, including deuterium labeling experiments, kinetic isotope effects (KIE) studies, and trapping experiments with radical quenchers such as TEMPO, suggested that either the oxidative addition mechanism or a radical mechanism could be operative depending on the coupling partners and the reaction conditions. This mechanistic ambiguity is rather unique for Ni, as the corresponding C–H arylation and alkylation reactions with Pd catalysts often occur via the oxidative addition pathway. With Ni-catalysts, the initial C–H metalation is often reversible. This indicates the rate- and selectivity of the overall reaction may be affected by the mechanism in the subsequent R–X cleavage and C–C/X bond formation steps.

The objective of this computational study is to elucidate the underlying principles that determine the relative rates of the competing oxidative addition and radical pathways in Ni-catalyzed C–H functionalization reactions. We performed density functional theory (DFT) calculations to investigate the mechanisms of a broad range of C(sp²)–H and C(sp³)–H functionalizations with aryl halides, alky halides, disulfides, peroxides and the oxidative C–H/C–H coupling using heptafluoropropyl iodide (i-C₃F₇-I) as oxidant (Scheme 1). Through the investigations of the competing pathways in these different types of reactions, we aim to elucidate whether factors such as bond dissociation energies and steric properties of the coupling partners affect the mechanism of the functionalization and influence the reactivity and selectivity of the overall catalytic transformation.

2. COMPUTATIONAL METHODS

All calculations were performed using Gaussian 09. Geometry optimizations and vibrational frequency calculations were performed using the B3LYP functional in gas phase with the LANL2DZ effective core potential basis set for nickel and iodine, and the 6-31G(d) basis set for other atoms. The nature of all stationary points was confirmed by the number of imaginary frequencies. All minima have zero imaginary frequency and all transition states have only one imaginary frequency. Single-point energy calculations were carried out using the M06 functional and the SDD basis set for Ni and I, and 6-311+G(d,p) for other atoms. The SMD solvation model was used in the single-point energy calculations. Unless otherwise noted, the experimental solvents shown in Scheme 1 were used in the calculations: DMF in the calculations of the C(sp³)–H arylation (Scheme 1a), DMSO in the C(sp³)–H sulfenylation (Scheme 1b), and t-butylbenzene in the C(sp²)–H methylation with dicumylperoxide (Scheme 1c), etc. In the calculations of the base-promoted N–H/C–H metalation-deprotonation steps, explicit solvent molecules (DMF) were added to solvate the Na atoms in [Ni(NaCO₃)₂] and other compounds that contain Na. One or two explicit DMF molecules were added to each Na atom to make the Na four-coordinated. Outer-shell solvent molecules were treated using the implicit solvation model.
(SMD). This mixed cluster-continuum model is expected to provide a more realistic treatment of solvation effects of compounds with alkali metals.

3. RESULTS AND DISCUSSION


3.1.1. Mechanism of C−H Metalation. We first calculated the mechanism of the Ni-catalyzed C(sp^3)−H arylation reported by the Chatani group (Scheme 1a). This reaction is the first example of C(sp^3)−H functionalization employing Ni catalyst and an N_N-bidentate directing group. It is applicable to a wide variety of aryl iodides with different electronic properties with high levels of site-selectivity for primary C(sp^3)−H bond. However, the mechanism, and origin of site-selectivity and reactivity of different aryl iodides have not been investigated computationally. The reaction between model substrate 1 and phenyl iodide 2 to afford product 3 was used as the model reaction in the calculations (Scheme 3).

Scheme 3. Model Reaction Used in the Computational Study of the Mechanism of Ni-Catalyzed C(sp^3)−H Arylation

Under the experimental conditions (Ni(OTf)_2 precursor catalyst with 10 mol % 2-mesitylenecarboxylic acid (Mes-CO_2H) and 2 equiv Na_2CO_3), a number of anionic ligands (e.g., MesCO_2^−, OTf^−, HCO_3^−, and NaCO_3^−) can potentially bind to the Ni(II) catalyst and promote the C−H metation. These different mechanisms were considered computationally (see Supporting Information for details). Our calculations indicate that the most favorable C−H metation pathway involves Ni(NaCO_3)_2·4DMF as the active Ni(II) catalyst. Thus, Ni(NaCO_3)_2·4DMF was used as the active catalyst in the calculations.

The computed reaction energy profile for the Ni-promoted C−H metation step is shown in Figure 1a. After coordination of the quinoline directing group to the Ni catalyst, the base-assisted deprotonation of the amide N−H bond is fast with an activation barrier of 7.5 kcal/mol to form complex 4. The subsequent concerted C−H metation/deprotonation step with NaCO_3^− as the base (TS2) requires an activation free energy of 21.4 kcal/mol with respect to complex 4. The resulting C−H deprotonated metallacycle complex 5 is 1.4 kcal/mol less stable than 4. Ligand exchange with phenyl iodide replacing the NaHCO_3·2DMF in 5 to form 6 is endothermic.

The thermodynamics of this Ni(II)-mediated C−H metation process is fundamentally different from the corresponding CMD pathway with Pd(II) catalysts. Using the Pd(NaCO_3)_2·4DMF catalyst in place of Ni (Figure 1b), the C−H metation of 1 requires a comparable barrier (TS4, ΔG^‡ = 20.0 kcal/mol with respect to 7). However, the resulting C−H deprotonated pallacycle complexes 8 and 9 are both more stable than 7 while nickelacycle complexes 5 and 6 are less stable than the corresponding reactant complex 4. These results indicate the C−H metation is much less favorable thermodynamically.

![Figure 1](https://example.com/figure1.png)

Figure 1. Reaction energy profiles of C−H metation of 1 with (a) Ni(NaCO_3)_2·4DMF and (b) Pd(NaCO_3)_2·4DMF catalysts.
with Ni(II) catalysts than with Pd(II). The optimized transition state geometries indicate a later transition state in the metalation with the nickel catalyst (TS2) compared to that with palladium (TS4), which is consistent with the Hammond postulate.

The dramatic difference in the reaction energy of the C−H metalation is attributed to the difference in M−O and M−C bond energy between Pd and Ni. The forming Ni−C bond in 6 is weaker than the Pd−C bond in 9. Concurrently, the breaking Ni−O bond is stronger than Pd−O bond in the reactant complexes (4 and 7). Due to the endergonicity of the formation of nickelacycle, the Ni-mediated C−H metalation is more likely to be a reversible process, and thus the subsequent functionalization of the nickelacycle is rate-determining in many Ni-catalyzed C−H functionalization reactions (see later). This is consistent with previous experimental mechanistic studies by Chatani, Shi, and Zhang.

3.1.2. Mechanism of the Ph−I Bond Cleavage and the C−C Bond Formation Steps. After the formation of nickelacycle 6, several pathways are possible in the subsequent Ph−I bond cleavage and C−C bond formation steps (Scheme 2). The reaction energy profiles of the different mechanisms in these steps were computed and are shown in Figure 2a. Select transition states and intermediate structures are shown in Figure 2b. Starting from 6, the homolytic cleavage of the Ph−I bond via TS7 forms a Ni(III) complex 12 and a phenyl radical. This iodine atom transfer pathway requires an activation free energy of 29.6 kcal/mol with respect to 6 and is highly endergonic due to the generation of the unstable phenyl radical.

The oxidative addition/reductive elimination mechanism (in black) is the most preferred pathway for this reaction. The Ph−I oxidative addition transition state (TS5) requires a barrier of 13.8 kcal/mol from complex 6. This suggests the high-valent Ni(IV) intermediate 10 is kinetically accessible. Sanford et al. recently reported the synthesis and isolation of Ni(IV) complexes via oxidative addition with Ni(II). Our calculations suggest that the formation of the Ni(IV) intermediate 10 is facilitated by the strongly electron-donating 8-aminoquinoline directing group. Natural Population Analysis (NPA) charge analysis indicates that the directing group becomes less negatively charged in 10 and transfers 0.19 electron to the Ni during this oxidative addition process from 6 to 10 (Scheme 4). The Ni(IV) intermediate 10 then undergoes facile C−C reductive elimination through TS6 with a low activation free energy.
energy of 3.7 kcal/mol with respect to intermediate 10 to give 11.

Two alternative pathways from complex 10 were considered. Dissociation of the iodine atom to form a Ni(III) complex 13 (in red) is highly endergonic. This indicates the reductive elimination from this Ni(III) intermediate via TS8 is not likely to occur. In addition, the C−I reductive elimination from 10 via TS9 (in pink) requires an activation free energy that is 8.2 kcal/mol higher than the preferred C−C reductive elimination pathway (TS6). This explains why the C−I coupling product is not observed in experiment.

After formation of 11, the subsequent ligand exchange to form 15 and the protonation of the Ni−N bond (TS10) to regenerate the active Ni catalyst and to liberate the final product 3 are both facile (Figure 3).

3.1.3. Overall Catalytic Cycle and the Rate-Determining Step. In summary, the Ni-catalyzed C(sp³)−H arylation of 1 with Ph−I (2) initiates with N−H deprotonation to bind the N,N-bidentate directing group to the Ni, followed by C−H bond cleavage via the concerted metalation-deprotonation mechanism. The C−H cleavage requires a relatively low barrier and is reversible, in agreement with the deuterium labeling experiments from Chatani. The formation of the nickelacycle intermediate is much less thermodynamically favorable than the corresponding process with Pd(II) catalysts, due to the formation of the weaker Ni−C bond compared to the Pd−C bond (Figure 1). In the subsequent Ph−I bond cleavage and C−C bond formation steps, the most favorable mechanism is via oxidative addition of Ph−I to form a Ni(IV) intermediate, which undergoes rapid C−C reductive elimination to yield the C−H arylation product. The rate-determining step in the overall catalytic cycle is the oxidative addition to form the Ni(IV) intermediate. The oxidative addition mechanism is consistent with the experimental observation that addition of TEMPO did not shut down the reaction.

These theoretical insights about the mechanism and rate-determining step allowed us to carry out further computational investigation to explain the origins of reactivity and site-selectivity in the Ni-catalyzed C(sp³)−H arylation reactions (see below).

3.1.4. Reactivity of Aryl Halides. To investigate the origin of reactivity of aryl halides in the C−H arylation, the computed activation energies of the rate-determining oxidative addition step of various aryl halides in the reactions with benzamide 1 are summarized in Table 1. The more electron-rich p-MeO

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar−X</th>
<th>ΔG‡(OA) [ΔH‡(OA)]</th>
<th>Yield</th>
<th>G‡(OA) [H‡(OA)]</th>
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<tr>
<td>1</td>
<td>Ar-I</td>
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<td>not</td>
<td>24.3 [24.0]</td>
</tr>
<tr>
<td>2</td>
<td>Ar-MeO</td>
<td>−24.0 [−23.5]</td>
<td>83%</td>
<td>24.0 [23.5]</td>
</tr>
<tr>
<td>3</td>
<td>Ar-F</td>
<td>−24.3 [−23.6]</td>
<td>49%</td>
<td>24.3 [23.6]</td>
</tr>
<tr>
<td>4</td>
<td>Ar-Br</td>
<td>−31.3 [−31.0]</td>
<td>0%</td>
<td>31.3 [31.0]</td>
</tr>
<tr>
<td>5</td>
<td>Ar-I</td>
<td>−30.1 [−29.6]</td>
<td>0%</td>
<td>30.1 [29.6]</td>
</tr>
</tbody>
</table>

G‡(OA) and enthalpy [ΔH‡(OA)] of activation in the rate-determining oxidative addition step in the C−H arylation of 1. All energies are in kcal/mol with respect to the separate reactants. Experimental yield was determined in the reactions of the below structure in place of 1. The reactions were carried out at 140 °C for 24 h with Ni(OtO)2 catalyst. See ref 7a.
3.1.5. Origin of Site-Selectivity. The C(sp³)−H arylation reaction is highly selective for primary C−H bonds. In the reaction of 20, no secondary C(sp³)−H arylation product (22) was observed in experiment (Figure 4a). To investigate the origin of the site-selectivity, we performed calculations on the competing primary and secondary C(sp³)−H arylation pathways using 23 as the model substrate (Figure 4b). Select key transition state structures are shown in Figure 4c. Our calculations indicate that the C−H cleavage in both pathways are reversible, and thus, although the cleavage of the primary C−H bond occurs faster than the cleavage of the secondary C−H bond (ΔG‡ = 17.4 versus 20.4 kcal/mol), the site-selectivity of the product is determined in the subsequent oxidative addition and reductive elimination steps. Although the barriers of oxidative addition are similar in both pathways (TS12 and TS15), the highly unfavorable steric repulsions in the C−C reductive elimination with the secondary carbon (TS16) prohibit the formation of the secondary C(sp³)−H arylation product (29). This increased steric demand is evidenced by the elongated Ni−C bond (2.23 Å) in TS16. Taken together, these

Figure 4. Selectivity of primary (in black) versus secondary (in blue) C−H arylation. Only key transition states and intermediates are shown in the potential energy surfaces. All energies are with respect to the separate reactant (23) and catalyst [Ni(NaCO₃)₂·4DMF].
Figure 5. (a) Substrates used in the calculations of the C–H sulfenylation reaction. (b) Computed reaction energy profile of the C–S bond formation step in the C–H sulfenylation of 30. All energies are with respect to the nickelacycle 33.

Figure 6. (a) Substrates used in the calculations of the C–H methylation reaction with dicumyl peroxide (DCP). (b) Computed reaction energy profile of the C–C bond formation step in the reaction of the nickelacycle 41. All energies are with respect to the nickelacycle 41.
results indicate that the site-selectivity for primary C–H bond is controlled by the steric effects in the C–C bond forming reductive elimination step, rather than in the initial C–H bond metallaion step.11

3.2. Mechanism of the Ni(II)-Catalyzed C(sp²)−H Sulfenylation with Diphenyl Disulfide. Although the above calculations indicated that the Ni(II)/Ni(IV) mechanism is strongly favored in the Ni-catalyzed C–H arylation using aryl halides, radical pathways involving Ni(I) or Ni(III) species cannot be completely ruled out in other types of C–H functionalizations.8a,10a,11 We next investigated the mechanism of the Ni-catalyzed C(sp²)−H sulfenylation using diphenyl disulfide (PhS–SPh, 31) (Scheme 1b). Although the C–H metallaion step is expected to occur via a similar CMD mechanism as in the Ni-catalyzed C–H arylation reactions, in the subsequent reaction of the nickelacycle with the disulfide, both oxidative addition and homolytic S–S bond dissociation pathways have been proposed in previous experimental studies.8a,10a,11 The computed reaction energy profile of the reaction of nickelacycle complex 33 is shown in Figure 5. In the Ni(II)/Ni(IV) oxidative addition/reductive elimination pathway (shown in black), the rate-determining step is the oxidative addition (TS17) with a barrier of 17.1 kcal/mol with respect to 33. Interestingly, the homolytic S–S bond dissociation (TS19) to generate a PhS· radical and an open-shell Ni(III) sulfide complex 36 requires a comparable barrier of 18.7 kcal/mol with respect to 33. The activation energy difference between the oxidative addition and the homolytic S–S bond dissociation pathways is much smaller than in the C(sp³)−H arylation reaction. Although the C–S reductive elimination of 36 (TS20) to form the Ni(I) complex 37 requires a significantly higher barrier than the Ni(IV)/Ni(II) reductive elimination (TS18), the Ni(III) complex 36 may react with the free PhS· radical generated in the homolysis of disulfide to form the Ni(IV) intermediate 34, which then undergoes C–S reductive elimination via TS18 to form the C–S coupling product. Compared to the radical pathways with phenyl iodide (Figure 2), this homolysis dissociation pathway with diphenyl disulfide is much more favorable due to the lower BDE of the S–S bond in diphenyl disulfide compared to the C–I bond in phenyl iodide (see Supporting Information for calculated BDEs). These results indicate that the Ni(II)/Ni(IV) oxidative addition pathway and the open-shell Ni(II)/Ni(III) pathway may be competing in this reaction. Indeed, experimental mechanistic studies suggested that the oxidative addition and homolytic dissociation pathways may both be possible depending on the experimental conditions. Radical trapping experiments from Shi and Zhang suggested the oxidative addition mechanism8a,10a while mechanistic studies from Lu under different experimental conditions suggested formation of PhS· radical in the C–H sulfenylation in the presence of Ag2CO3.11

3.3. Mechanism of the Ni(II)-Catalyzed C(sp²)−H Methylation with Dicumyl Peroxide. We next investigated the mechanism of the Ni-catalyzed C(sp²)−H methylation using the sterically hindered dicumyl peroxide (DCP) (39) (Scheme 1c). The computed reaction energy profile of the reaction of nickelacycle complex 41 is shown in Figure 6. The Ni(II)/Ni(IV) oxidative addition has a barrier of $\Delta G_{\text{Ni,II}}^{\ddagger} = 25.6$ kcal/mol with respect to 41. Subsequent reductive elimination of the Ni(IV) intermediate 42 via TS22 gives the C–O coupling product (43), which was not observed in experiment. The homolytic O–O bond dissociation pathway (TS23) to generate the alkoxy radical (44) and an open-shell Ni(III) alkoxy complex (45) is much more favorable ($\Delta G_{\text{disoc}}^{\ddagger} = 11.6$ kcal/mol with respect to 41). Alkoxy radical 44 then undergoes facile fragmentation via TS24 to generate acetophenone 47 and a methyl radical, which rapidly combines with the Ni(III) complex 45 to form a Ni(IV) intermediate 46. Similar to the other Ni(IV) complexes in the reactions discussed above, 46 undergoes very facile reductive elimination via TS25 to form the methylated product, 48. Compared to the reactions with phenyl iodide (Figure 2) and diphenyl disulfide (Figure 5), the oxidative addition with phenyl iodide requires a much higher barrier because of the sterically congested transition state, TS21. Simultaneously, the homolytic dissociation pathway with DCP is facilitated due to the weaker O–O bond in DCP (the BDE of DCP and PhS–SPh are 32.9 and 40.3 kcal/mol, respectively). In summary, the unfavorable steric hindrance in the oxidative addition transition state TS21 and the tendency to form alkoxy radical 44 from cleavage of the weak DCP O–O bond promote the homolytic dissociation over the oxidative addition pathway in the C–H methylation reaction.

3.4. Substrate-Dependent Mechanisms in the Reactions with the C–H Metallated Nickelacycle Intermediate. The three different types of Ni-catalyzed C–H functionalization reactions discussed above clearly indicated the significant role of coupling partner on the mechanisms in the C–C and C–X bond formation steps. To reveal the factors that control the competing mechanisms and to develop a predictable model for the reactivity of different types of coupling partners, we calculated the activation energies of the oxidative addition/reductive elimination pathway and the homolytic dissociation pathway in the seven Ni-catalyzed C–H functionalization reactions shown in Scheme 1.

In the C–H/C–H oxidative coupling reaction (Scheme 1g), both i-C3F7−I and CF3C2H−I oxidants were used in the calculations. The computed activation free energies of the rate-determining steps in these two competing pathways are shown in Table 2. In all reactions studied, the reductive elimination from the Ni(IV) intermediate requires slightly lower barrier than the oxidative addition (TS-B).34 In the homolytic dissociation pathway, the X–Y bond cleavage to form the Ni(III) intermediate (TS-C) is rate-determining (see Supporting Information for the complete reaction energy profiles).

The additional examples in Table 2 further demonstrated that the mechanism of the reaction with the nickelacycle is strongly dependent on the coupling partner. Although the Ni(II)/(IV) oxidative addition pathway is generally favored in the C(sp³)−H and C(sp²)−H alkylation and arylation reactions (entries 1, 5, and 6), the homolytic dissociation mechanism has a comparable barrier in the sulfenylation reaction (entry 2) and the reaction with CF3C2H−I (entry 8). The homolytic dissociation pathway is strongly preferred in the reactions with DCP and i-C3F7−I (entries 3 and 7). A number of factors influence the competition of oxidative addition and homolytic dissociation pathways. First of all, sterically congested substrates, such as DCP and i-C3F7−I, require much higher barrier to oxidative addition, and thus these processes are generally disfavored. In addition, the oxidative addition barrier is affected by the strength of the cleaving bond, as evidenced by the higher barrier of activation in the reaction with Ph−Br than with Ph−I (see entries 1 and 4 in Table 1). Interestingly, the oxidative addition of Ph−I requires a lower barrier than the reaction of CF3C2H−I, although the Ph−I bond is stronger. The Ph−I bond oxidative addition is promoted by the orbital...
interactions between the π* of the Ph group and the filled d orbitals of the Ni center. These results indicate the reactivity of the oxidative addition pathway is controlled by a combination of steric effects, the strength of the cleaving bond, and substrate–metal orbital interactions.

In contrast, the reactivity of the homolytic dissociation pathway is mainly determined by the strength of the cleaving bond. The barriers of the homolytic dissociation pathway with coupling partners involving a weak bond, such as DCP, diphenyl disulfide, and i-C$_3$F$_7$·I, are more than 10 kcal/mol lower than those with phenyl iodide and n-butyl bromide. A good correlation between the activation free energy of the homolytic dissociation pathway and the BDE of the cleaving bond is observed (Figure 7). The only outlier is the reaction with i-C$_3$F$_7$·I, in which the C–I bond dissociation is further promoted by the steric bulk of the i-C$_3$F$_7$ group. These results indicate the strength of the cleaving bond is the most important factor that controls the reactivity of the homolytic dissociation pathway. Contributions from other factors, such as the strength of the forming Ni–X bond and the stability of the radical Y, are much less significant and do not correlate with the activation energies of the homolytic dissociation pathway (see Supporting Information for details).

In addition to the steric and electronic properties of the electrophiles, the strongly electron-donating N,N-bidentate directing group is also expected to affect the preference of the oxidative addition versus homolytic dissociation pathways. As shown in Scheme 4, the 8-aminoquinoline directing group stabilizes the Ni(IV) intermediate in the oxidative addition pathway. Thus, the nickelacycle compounds shown in Table 2 are expected to be more reactive in the oxidative addition than the reaction of other Ni(II) species with the same electrophile. For example, in previous studies of Ni-catalyzed cross-coupling reactions alkyl halides, a stepwise radical pathway had been generally proposed, while the present DFT calculations suggested the reactions of most alkyl halides with nickelacycles in Table 2 occur via the closed-shell oxidative addition pathway.

### 3.5. Effects of External Oxidants on the Mechanisms and Product Selectivity of Ni-Catalyzed C–H/C–H Oxidative Coupling

The substrate-dependent mechanisms can explain and potentially predict reactivity and selectivity in a broad range of Ni-catalyzed C–H functionalization reactions. We then explored whether these theoretical insights can be used to explain the chemoselectivity in the Ni-catalyzed oxidative C–H/C–H coupling of amide 49 and toluene (Scheme 1g). The choice of alkyl iodide oxidant is essential for this novel transformation (Figure 8). In the reaction of other Ni(II) species with the same electrophile, the strongly electron-donating N,N-bidentate directing group is also expected to affect the preference of the oxidative addition versus homolytic dissociation pathways. As shown in Scheme 4, the 8-aminoquinoline directing group stabilizes the Ni(IV) intermediate in the oxidative addition pathway. Thus, the nickelacycle compounds shown in Table 2 are expected to be more reactive in the oxidative addition than the reaction of other Ni(II) species with the same electrophile. For example, in previous studies of Ni-catalyzed cross-coupling reactions alkyl halides, a stepwise radical pathway had been generally proposed, while the present DFT calculations suggested the reactions of most alkyl halides with nickelacycles in Table 2 occur via the closed-shell oxidative addition pathway.

### Table 2. Activation Free Energies in the (a) Oxidative Addition ($\Delta G^\ddagger_{\text{OA}}$) and (b) Homolytic Dissociation ($\Delta G^\ddagger_{\text{dissoc}}$) Pathways in Reactions of Nickelacycles with Different Coupling Partners

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction</th>
<th>$\Delta G^\ddagger_{\text{OA}}$ (a)</th>
<th>$\Delta G^\ddagger_{\text{dissoc}}$ (b)</th>
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<td>12.9</td>
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<td>21.9</td>
<td>22.7</td>
</tr>
</tbody>
</table>

*The activation free energy of the oxidative addition pathway. bThe activation free energy of the homolytic dissociation pathway. All energies are in kcal/mol and with respect to the complex A′.*

![Figure 7. Correlation of the activation free energy of homolytic dissociation pathway ($\Delta G^\ddagger_{\text{dissoc}}$) with the bond dissociation energy (BDE) of the cleaving bond.](image)

The correlation indicates the strength of the cleaving bond is the most important factor that controls the reactivity of the homolytic dissociation pathway. Contributions from other factors, such as the strength of the forming Ni–X bond and the stability of the radical Y, are much less significant and do not correlate with the activation energies of the homolytic dissociation pathway (see Supporting Information for details).

In addition to the steric and electronic properties of the electrophiles, the strongly electron-donating N,N-bidentate directing group is also expected to affect the preference of the oxidative addition versus homolytic dissociation pathways. As shown in Scheme 4, the 8-aminoquinoline directing group stabilizes the Ni(IV) intermediate in the oxidative addition pathway. Thus, the nickelacycle compounds shown in Table 2 are expected to be more reactive in the oxidative addition than the reaction of other Ni(II) species with the same electrophile. For example, in previous studies of Ni-catalyzed cross-coupling reactions alkyl halides, a stepwise radical pathway had been generally proposed, while the present DFT calculations suggested the reactions of most alkyl halides with nickelacycles in Table 2 occur via the closed-shell oxidative addition pathway.
I. While the iodine atom transfer pathway forms the oxidative C–H/C–H coupling product 54, the competing oxidative addition pathway promotes the coupling with the alkyl iodide oxidant to form the alkylation side product 56 (see Supporting Information for detailed reaction energy profile for this side-reaction pathway). These results indicate it is critical to use a sterically hindered oxidant, such as i-C3F7−I, to prevent the formation of the alkylation side product formed via the oxidative addition pathway.

4. CONCLUSION

The reaction mechanisms of Ni-catalyzed C(sp3)−H and C(sp2)−H arylation, alkylation, sulfonylation, and oxidative C–H/C–H coupling of benzamides containing N,N-bidentate directing groups were investigated using DFT calculations. The C–H bond cleavage to form the nickelacycle intermediate occurs via the concerted metalation-deprotonation (CMD) mechanism. The formation of the metalacycle is thermodynamically much less favorable than the corresponding C–H metatation process with Pd(II) catalyst. Due to this difference, the C–H metatation step with Ni catalyst is often reversible and the subsequent functionalization of the nickelacycle is more likely to be rate- and selectivity-determining compared to Pd-catalyzed C–H functionalization reactions.

The subsequent functionalization step of the nickelacycle intermediate with the coupling partner (X−Y) involves an X−Y bond cleavage and a C−C or C−X bond formation step. The exact mechanisms in these steps are dependent upon the nature of the coupling partner. The X−Y bond homolytic dissociation to form a Ni(III) complex and a radical species is favored if the bond dissociation energy of X−Y is relatively low or the substrate is too sterically congested for the alternative oxidative addition pathway (e.g., DCP and i-C3F7−I). In contrast, substrates featuring a relatively strong and less hindered X−Y bond (e.g., most aryl halides and alkyl halides) prefer the oxidative addition/reductive elimination pathway via a Ni(IV) intermediate. These theoretical insights into the substrate-dependent mechanisms in the functionalization of the nickelacycle intermediate were applied to predict the effects of substituents and oxidants on the reactivity, chemo- and site-selectivity in various types of C–H functionalization reactions. We expect the mechanistic insights revealed by the computations in the current study will guide the development of new catalyst systems for C–H functionalization reactions.
of a more diverse set of Ni-catalyzed C–H bond functionalization reactions utilizing N,N-bidentate directing groups.

**ASSOCIATED CONTENT**

1. Supporting Information
   The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b03548.

   Computational details, computed energy profiles of reaction pathways, Cartesian coordinates of optimized geometries (PDF)

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Notes

The authors declare no competing financial interest.

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**REFERENCES**


(4) For reviews on selected catalyzed C–H functionalization, see: (a) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. Nature 2014, 509, 299.


(28) Another two possible pathways involving open-shell Ni species are considered computationally. The dissociative single electron transfer (DSET) from the Ni(II) metallocycle with Ph−I to form a Ni(III) radical cation, phenyl radical and iodide anion, and the iodine atom transfer from Ph−I to a Ni(I) complex 14 to form Ni(II) iodide 11 and a phenyl radical are both highly endergonic (62.0 and 34.9 kcal/mol, respectively with respect to 1 and the catalyst resting state Ni(NaCO3)4-DMF) and thus can be ruled out (see the Supporting Information for details).


(30) In the arylation of the sterically more demanding secondary C(sp2)−H bond, reductive elimination becomes rate-determining (see later).

(31) (a) Similarly, in Pd-catalyzed C−H bond functionalization reactions, functionalization is preferred at primary sp3 C−H bonds. (b) Neufeldt, S. B.; Sanford, M. S. Acc. Chem. Res. 2012, 45, 936. (c) See ref 4c. (d) He, J.; Wasi, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. Chem. Rev. 2016, DOI: 10.1021/acs.chemrev.6b00632.


(33) β-Methyl elimination from 45 via a concerted four-membered transition state requires an activation free energy of 37.9 kcal/mol with respect to 45 and thus can be ruled out.

(34) Reductive elimination may become rate-determining with increased steric demand about the forming C−C and C−X bond. For example, the reductive elimination with a secondary sp3 carbon in the C−H arylation of 23 (Figure 4) requires 5.0 kcal/mol higher activation energy than the oxidative addition. In addition, experimental mechanistic studies suggested reductive elimination is rate-determining in the Ni-catalyzed C(sp2)−H arylation (see ref 7d).


(36) In contrast, there is no clear correlation between the activation energy of the oxidative addition pathway and the R−X or RX−RX BDEs (see Supporting Information for details). This further confirmed the reactivity of the oxidative addition is controlled by a combination of factors, and is more sensitive to steric effects than the strength of the cleaving bond.

(37) An excellent correlation (R2 = 0.993) between ΔG‡iso and BDE was obtained after removing the reaction with i-C3F7-I from the plot shown in Figure 7. The steric repulsion with the i-C3F7 group destabilizes the four-coordinated nickelacycle complex A, and thus reduces the barrier of the homolytic dissociation pathway.

(38) Nickelacycle S3 was used as the model substrate in the calculations because experimentally, a Cl substitution at the 5 position of the quinolone directing group leads to greater yield. See ref 7e.