

# Mechanistic insights into the nickel-catalyzed addition of amides with strained alkenes

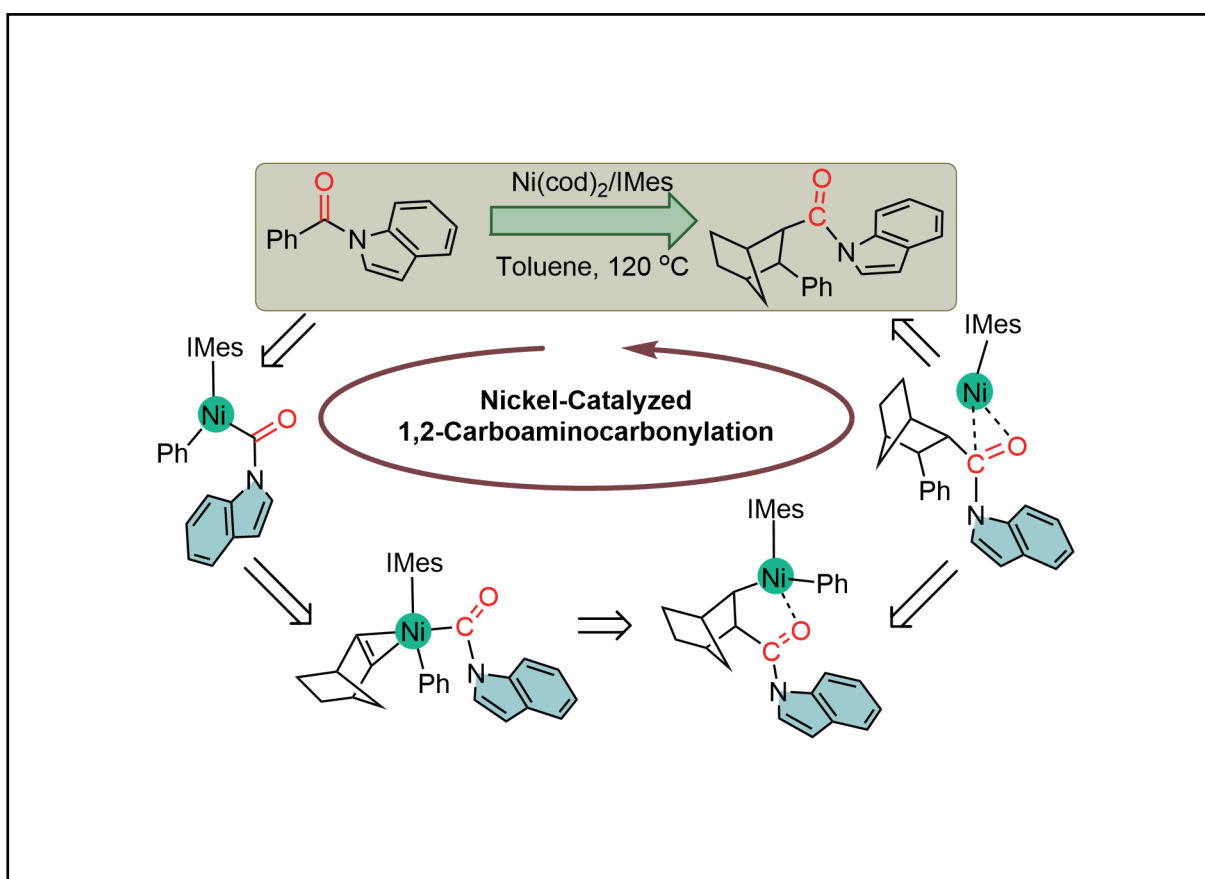
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## Graphical abstract



*Mechanistic pathway of Ni-catalyzed amide addition to strained alkenes.*

## Public summary

- DFT calculations revealed that the nickel-catalyzed addition of amides to strained alkenes proceeds via C(acyl)–N bond oxidative addition, Ni–C(acyl) insertion, and reductive elimination.
- The Ni–C(acyl) insertion was identified as the rate-determining step with an energy barrier of 25.8 kcal/mol, which is kinetically more favorable than Ni–C(aryl) insertion.
- Substitution of IMes ligand with  $\text{PCy}_3$  significantly increases the energy barrier for alkene insertion, consistent with experimentally observed low yields, highlighting the critical importance of ligand selection.

# Mechanistic insights into the nickel-catalyzed addition of amides with strained alkenes

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Supporting Information

**Abstract:** Recent advancements have introduced a nickel-catalyzed method in which the C(aryl)–C(acyl) bond of aryl amides is activated and added to alkenes to achieve difunctionalized species. While this scenario holds significant promise for application, the underlying mechanism remains unclear, particularly with respect to the site of oxidative addition and the possible occurrence of carbonyl elimination-reinsertion. Herein, we utilize density functional theory (DFT) calculations to investigate the mechanistic pathway of nickel-catalyzed addition between aryl amides and strained alkenes. Our computational analysis demonstrates that the reaction proceeds through oxidative addition of the C(Ar)–C(acyl) bond, alkene coordination, Ni–C(acyl) insertion and reductive elimination. Alternative pathways involving oxidative addition of the C(acyl)–N bond and carbonyl elimination-reinsertion are energetically unfavorable. Although oxidative insertion into the C(acyl)–N bond faces a lower energy barrier than does the C(aryl)–C(acyl) bond, the subsequent alkene insertion step becomes kinetically unfavorable. The rate-determining step is Ni–C(acyl) insertion, which is more favorable than Ni–C(aryl) insertion. Additionally, both the choice of ligands and the indole amide substrates are critical: substituting with PCy<sub>3</sub> ligands or using aryl ester substrates results in challenging energy barriers. These insights provide a comprehensive understanding of the reaction mechanism and offer strategic guidance for the development and optimization of amide-involved difunctionalizations of alkenes.

**Keywords:** DFT; amide addition; C–C bond activation; nickel catalysis; strained alkenes

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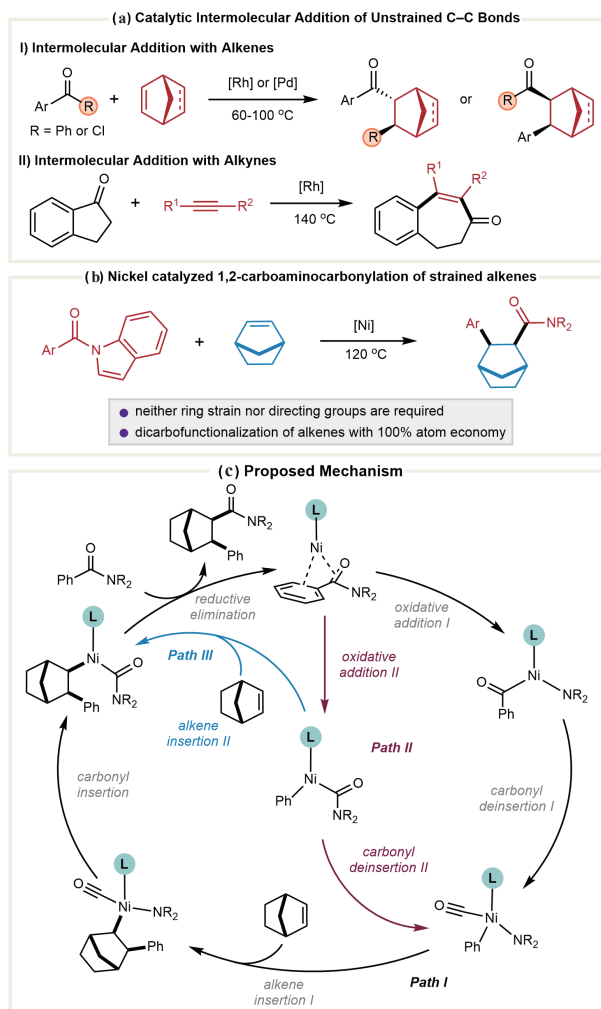
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## 1 Introduction

The cleavage of C–C bonds and their subsequent addition to alkenes for the difunctionalization of unsaturated hydrocarbons has garnered increasing attention in recent years<sup>[1–4]</sup>. This is due mainly to the high atom economy that the scheme provides. However, the development of such methodologies is challenging, largely because of the inherent inertness of C–C bonds<sup>[5–7]</sup>. Fortunately, rapid advancements in transition metal catalysis have provided efficient solutions across various domains of synthetic organic chemistry<sup>[8,9]</sup>. Early work by Douglas and colleagues<sup>[10]</sup> demonstrated that rhodium catalysts could facilitate the acylation and arylation of alkene substrates in the presence of directing groups on diaryl ketones, resulting in difunctionalized products. To eliminate the necessity for directing groups, the Morandi group<sup>[11]</sup> reported a palladium-catalyzed strategy in which the C(aryl)–C(acyl) bond is cleaved and subsequently added to derivatives of limonene, yielding aryl-acyl chloride adducts. Similarly, the Tobisu group<sup>[12]</sup> reported an addition reaction between limonene and aryl amide derivatives, resulting in C(aryl)–C(acyl) bond activation without the directing groups. To explain these mechanisms, a plausible pathway was proposed by Tobisu et al. and is illustrated as **Path I** (Scheme 1C). According to this mechanism, the nickel catalyst

initially undergoes oxidative addition into the C(acyl)–N bond of the amide, followed by carbonyl deinsertion to form a four-coordinate Ni(II) intermediate. The alkene is subsequently coordinated and inserted into the Ni–C(aryl) site, followed by the insertion of the carbonyl group into the Ni–C(alkyl) site. Finally, reductive elimination occurs to produce the target product. One of the most intriguing questions arising from the proposed mechanism is whether the oxidative addition of the amide substrate is strictly confined to the C(acyl)–N bond. Additionally, the necessity of the carbonyl deinsertion-reinsertion step warrants further investigation.

In this study, we employ density functional theory (DFT) calculations to conduct an in-depth exploration of the reaction mechanism. Beyond the previously proposed **Path I**, we introduce and evaluate alternative pathways, namely, **Path II** and **Path III**. Our computational results indicate that **Path III** (oxidative addition **II**, alkene insertion **II** and reductive elimination) is the most favorable pathway. For the oxidative addition step, although the nickel catalyst has a lower energy barrier when inserted into the C(acyl)–N bond (**Path I**) than when inserted into the C(aryl)–C(acyl) bond in **Path II**, the subsequent alkene insertion step is kinetically disfavored, regardless of whether carbonyl deinsertion occurs. This kinetic bottleneck renders the C(acyl)–N oxidative addition reversible; thus, the reaction reverses to favor the C(aryl)–C(acyl)

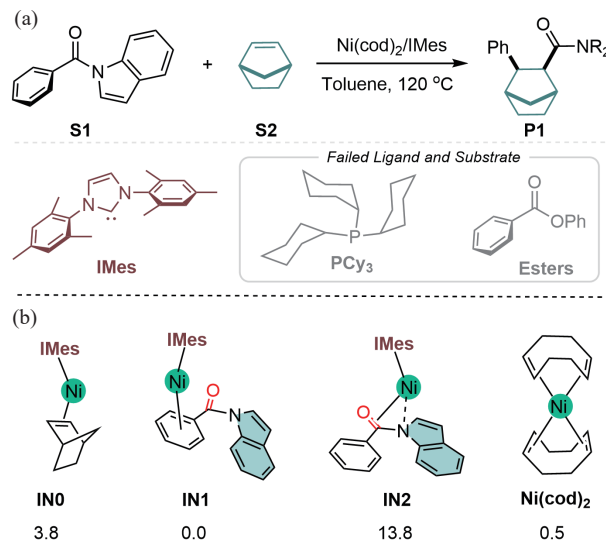


**Scheme 1.** The addition reaction with alkenes or alkynes and the proposed mechanism.

bond insertion pathway, despite the higher energy barrier. After oxidative addition, executing carbonyl deinsertion makes both concerted and stepwise alkene insertions challenging. In contrast, bypassing carbonyl deinsertion allows the intermediate formed after oxidative addition into the C(acyl)–N bond to readily undergo alkene coordination, Ni–C bond insertion, and reductive elimination, ultimately leading to the desired product. Furthermore, our analysis of the Ni–C bond insertion step reveals that insertion into the Ni–C(acyl) bond is kinetically more favorable than insertion into the Ni–C(aryl) bond.

## 2 Results and discussion

**Model reaction.** Building upon the experimental findings of Tobisu and colleagues<sup>[12]</sup>, we investigated the nickel-catalyzed addition of limonene (**S2**) with phenylindole amide under the catalysis of Ni(cod)<sub>2</sub> in the presence of an N-heterocyclic carbene ligand (IMes), utilizing toluene as the solvent (Fig. 1a). Starting from Ni(0), multiple species can coordinate with the Ni(0) center to increase its stability, including the alkene, amide, and initial 1,5-cyclooctadiene (cod) ligands (Fig. 1b). For the amide substrates, the



**Fig. 1.** Model reaction and coordination of Ni(0) species ( $\Delta G$  in kcal/mol).

presence of multiple unsaturated bonds provides several potential coordination sites, such as the aryl group (**IN1**), the carbonyl group (**IN2**), and the indole moiety. Structural optimizations indicate a preference for the **IN2** configuration. Among all possible sites, **IN1** has the lowest energy, being 0.5 kcal/mol greater than that of Ni(cod)<sub>2</sub>. For clarity, the Ni(0) intermediate **IN1** is set as the energy reference point.

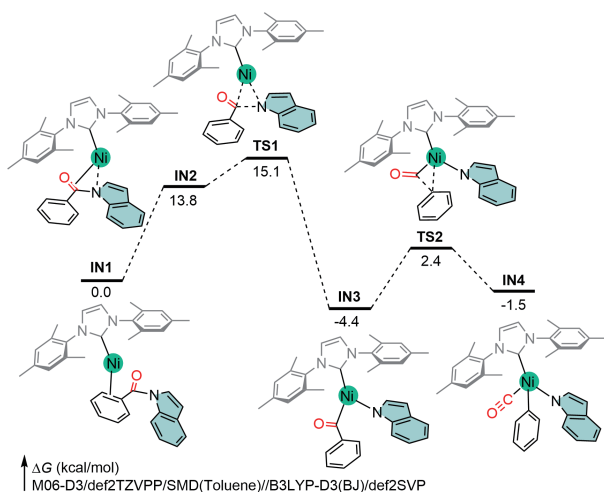
**Oxidative addition and carbonyl deinsertion.** From **IN1**, we considered pathways involving oxidative addition at either the C(acyl)–N bond or the C(aryl)–C(acyl) bond (Figs. 2 and 3). The computational results reveal that the energy barrier for oxidative addition at the C(acyl)–N bond is significantly lower (15.1 kcal/mol for **TS1** vs. 17.1 kcal/mol for **TS3**), indicating that the formation of **IN3** is both thermodynamically and kinetically favorable. Compared with **IN5**, the carbonyl deinsertion from **IN3** subsequently has a much lower energy barrier (2.4 kcal/mol for **TS2** vs. 21.5 kcal/mol for **TS4**). Both steps ultimately lead to the formation of nearly identical four-coordinate Ni(II) complexes (**IN4** or **IN6**).

**Alkene insertion and reductive elimination.** At this stage, the data seemingly favor oxidative addition at the C(acyl)–N bond. This was our initial assumption until we delved into the subsequent alkene insertion steps. Excluding the possibility of alkene insertion at the nitrogen site, intermediate **IN4** (or **IN6**) is capable of progressing to yield the target product, whereas **IN3** cannot. Consequently, we conducted a detailed examination of the steps following **IN4**, as illustrated in Fig. 4. Extending to the left is the concerted insertion pathway, wherein the alkene does not coordinate with Ni but instead directly links the carbonyl and aryl groups, proceeding through a five-membered transition state **TS10** to form the inserted intermediate **IN8**. Extending to the right is the stepwise insertion pathway, where the alkene approaches the Ni center and inserts into either the Ni–C(acyl) site (**TS7**) or the Ni–C(aryl) site (**TS5**). These pathways subsequently undergo C(alkyl)–C(aryl) elimination (**TS8**) or C(alkyl)–C(acyl) elimination (**TS6**), culminating in the same Ni(II) intermediate **IN8**, which can undergo reductive elimination at the C(acyl)–N site to yield the target product. Overall,

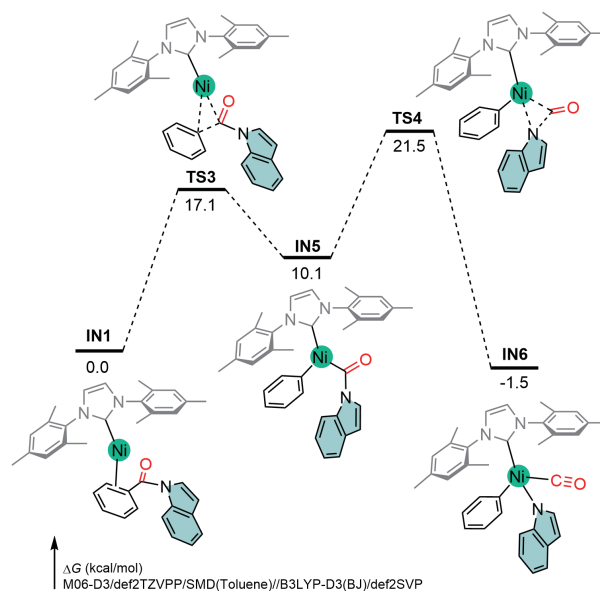
the pathway involving Ni–C(aryl) insertion followed by C(alkyl)–C(acyl) elimination results in the lowest energy barrier, yet it remains at 39.6 kcal/mol, which is prohibitively high under experimental conditions. We also examined the possibility of high-spin states, and the corresponding energy data are displayed in parentheses in Fig. 4. However, with the exception of IN9, all high-spin species have unfavorable energies relative to low-spin species. This suggests the implausibility of the pathway and the need to explore additional mechanistic avenues.

**Path III: without carbonyl deinsertion.** We subsequently considered the transformations involving the intermediate IN5. In the absence of carbonyl deinsertion, the alkene can directly be coordinated to the nickel atom to form the intermediate IN11 (Fig. 5). Similarly, two Ni–C sites could promote the insertion of alkenes, with corresponding transition

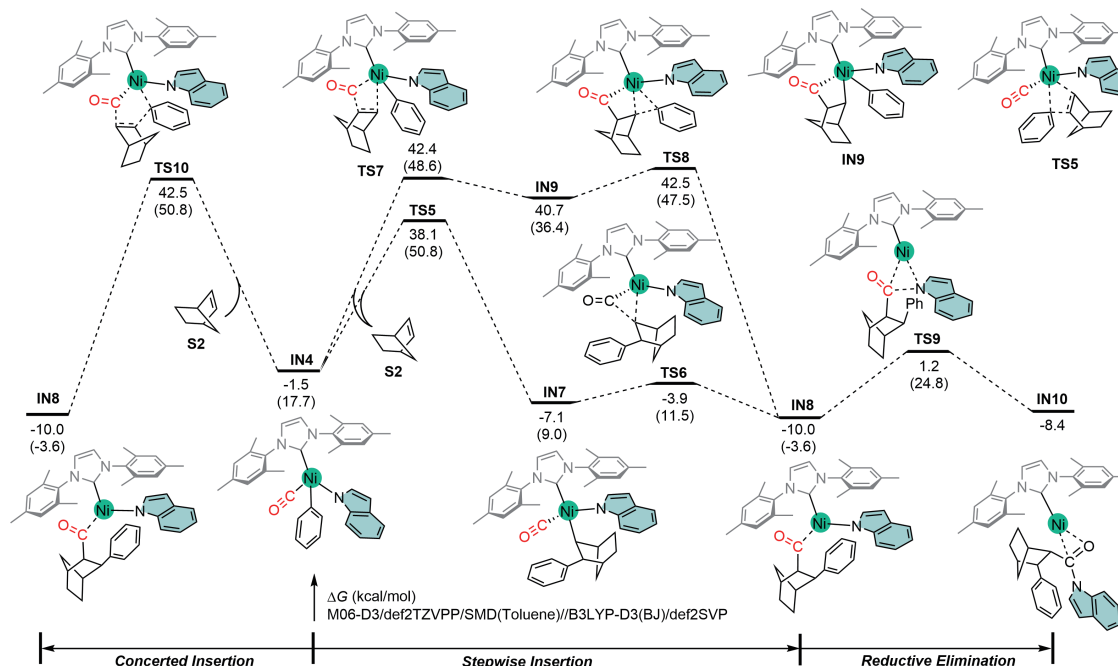
states TS11 and TS12. Upon insertion of the alkene, these intermediates undergo reductive elimination to form the intermediate IN10. Finally, the corresponding product P1 is substituted by coordination to the substrate S1, and the catalytic cycle is achieved. Our calculations indicate that alkene insertion into the Ni–C(acyl) site presents a lower energy barrier (21.4 kcal/mol for TS11 vs. 22.5 kcal/mol for TS12). Although the subsequent reductive elimination barrier is greater (20.5 kcal/mol for TS14 vs. 12.6 kcal/mol for TS13), it remains below that of TS12. This suggests that the formation of IN10 predominantly proceeds via the Ni–C(acyl) insertion and C(alkyl)–C(aryl) elimination pathways. The computational



**Fig. 2.** Gibbs free energy profiles of the oxidative addition of C(acyl)–N bonds and carbonyl deinsertion.



**Fig. 3.** Gibbs free energy profiles of the oxidative addition of C(aryl)–C(acyl) bonds and carbonyl deinsertion.



**Fig. 4.** Gibbs free energy profiles of alkene insertion and reductive elimination (Path I). The energy data for high-spin species are shown in parentheses.

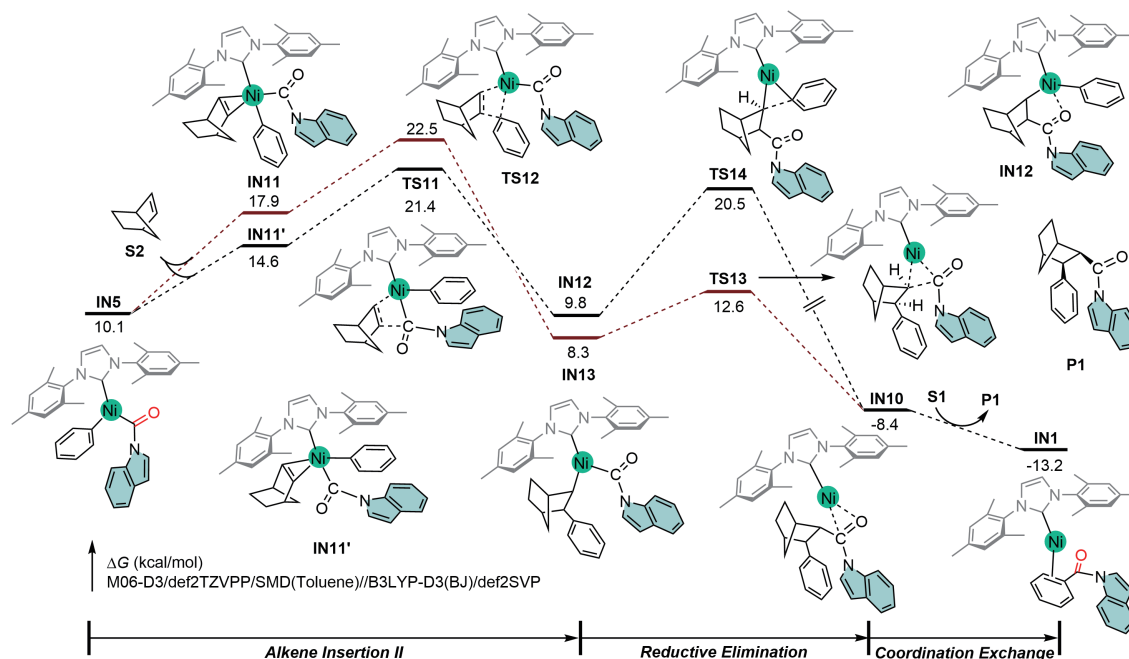


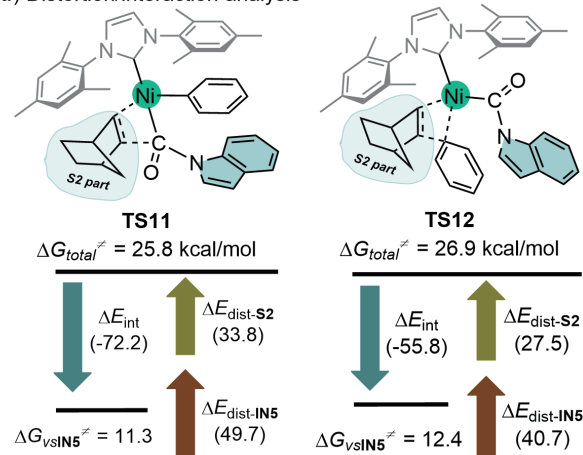
Fig. 5. Gibbs free energy profiles of alkene insertion and reductive elimination (Path III).

results collectively elucidate the mechanistic pathway for the nickel-catalyzed addition of amides to constrained alkenes, and the overall conclusions are in some agreement with those of previous reports<sup>[13]</sup>. These results highlight the preference for C(acyl)–N bond oxidative addition and Ni–C(acyl) insertion steps, providing crucial insights for the rational design and optimization of two-carbon functionalization reactions involving amides and alkenes.

**Site-selective analysis of insertions.** To gain deeper insight into the observed alkene insertion, we conducted distortion/interaction energy analysis<sup>[14]</sup> to investigate the differences in energy barriers associated with alkene insertion pathways, as depicted in Fig. 6a. The transition state structures were divided into two fragments: The IN5 part represents the precursor of alkene insertion, and the S2 part corresponds to the alkene fragment. Our calculations indicate that TS11 faces more distortion energy to reach the transition state. However, TS11 has a more favorable interaction energy, which is sufficient to reverse the detrimental effects of distortion. We demonstrated the relevant bond parameters and performed independent gradient model Hirshfeld (IGMH)<sup>[15]</sup> analysis, as illustrated in Fig. 6b. In TS11, the S2 part is significantly closer to the IN5 part and has a higher bond order. The results confirm our initial assumption, demonstrating a significant interaction between the alkene and the Ni–C bond.

**Path III with the PCy<sub>3</sub> ligand.** Furthermore, we explored the reaction behavior under different ligand environments to elucidate the discrepancies observed when using IMes. Experimentally, employing PCy<sub>3</sub> as the ligand resulted in a markedly reduced yield of only 2%<sup>[12]</sup>. To simulate this scenario, we substituted the original IMes ligand with PCy<sub>3</sub> in the key pathway and obtained the results presented in Fig. 7. Computational findings reveal that, in the presence of PCy<sub>3</sub>, the site selectivity for both oxidative addition and alkene insertion remains consistent with that of the IMes–Ni catalytic system. Similarly, the carbonyl deinsertion pathway

(a) Distortion/interaction analysis



(b) IGMH and bond order analysis

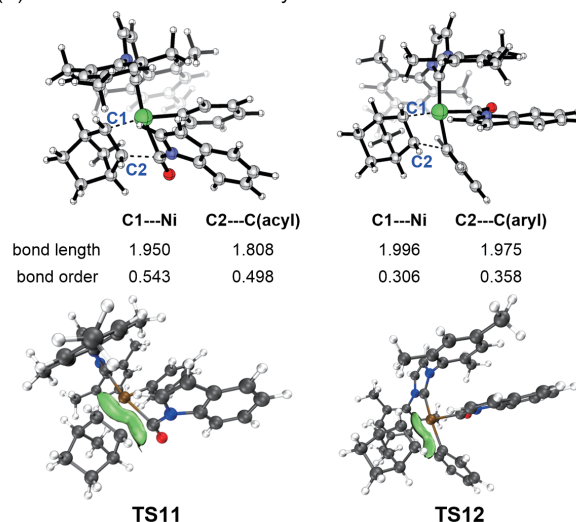


Fig. 6. Analysis of the transition states of alkene insertion II (TS11 vs TS12).

remains energetically unfavorable (to **IN4-Cy**). Regarding the rate-determining step of alkene insertion, the total energy barrier was calculated to be 31.8 kcal/mol (the higher insertion energy barrier makes the generation of **IN3-Cy** via **TS1-Cy** feasible, and therefore, **IN3-Cy** is regarded as the energy minimum in the mechanistic process). This relatively high energy barrier correlates well with the experimentally observed low yield.

**Energetic barriers of unreactive substrates.** In addition to investigating ligand changes, we also investigated other nonreactive substrates via computational analysis to understand the factors that contribute to the lack of reactivity. The focus was on the intermediate **IN3** series formed during the oxidative addition step (probably the most stable species prior to the rate-determining step) and on the transition state associated with alkene insertion (the rate-determining transition state). As shown in Fig. 8, we considered additional

amide substrates (**S1A** and **S1C**) and ester substrates (**S1B**). When the C–N oxidative addition intermediate was used as the reference point, the energies of the alkene insertion transition states were generally high, ranging from 29.5 to 45.5 kcal/mol (**TS11** series and **TS12** series). These high barriers suggest that the substrates are unlikely to form the target products under the experimental conditions. This conclusion was confirmed by experimental observations<sup>[12]</sup>, where no product formation was detected (yields of 0% were reported for all substrates **S1A–S1C**).

In addition, Tobisu et al. reported that the use of strained compounds is essential and that unstrained alkenes, including simple terminal alkenes and cycloalkenes, fail to participate in the reaction under these conditions. This sparked our interest in understanding the factors leading to this outcome. Therefore, we investigated the key alkene insertion and reductive elimination steps using cyclopentene (**S3**) as the

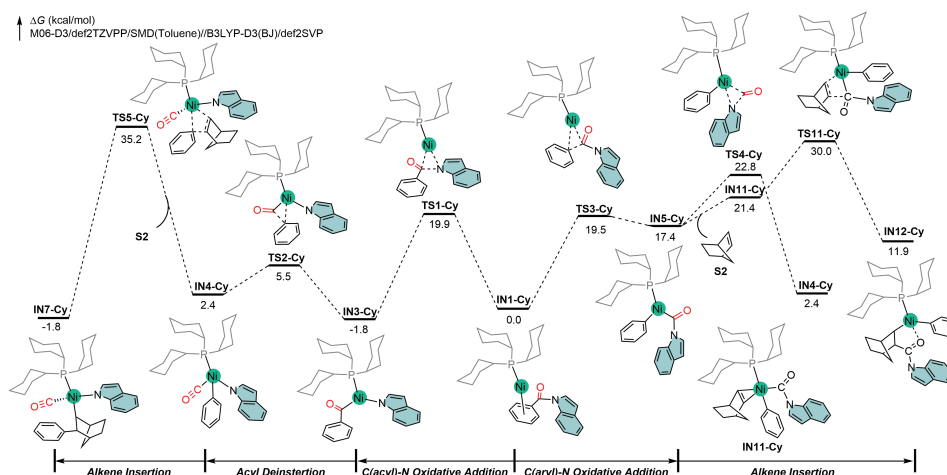


Fig. 7. Gibbs free energy profiles of Path III with the  $\text{PCy}_3$  ligand.

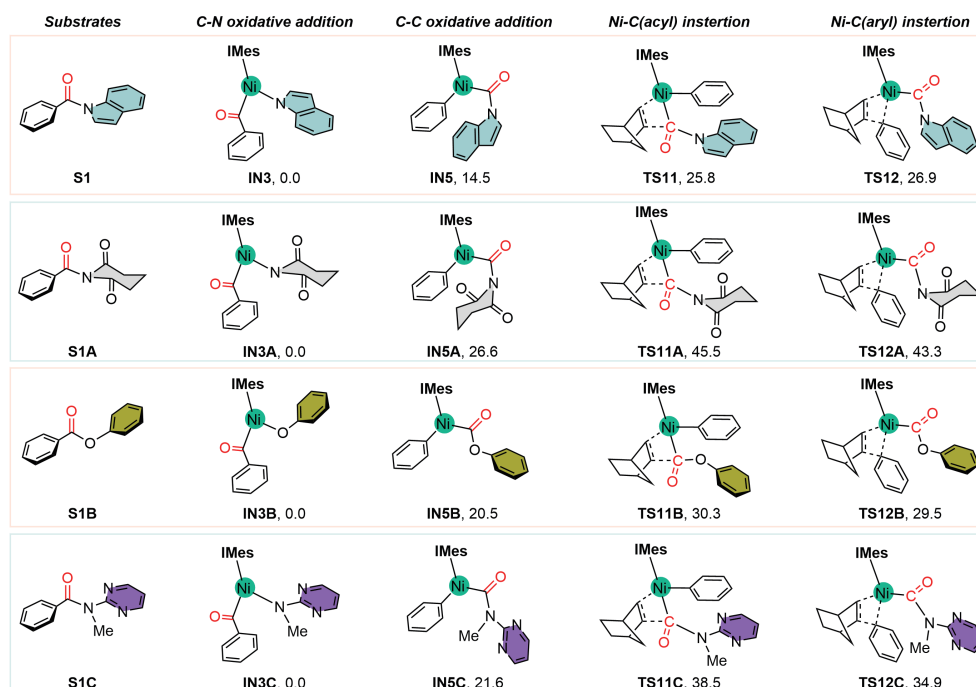


Fig. 8. The critical species energies in the reaction pathways for different substrate scenarios ( $\Delta G$  in kcal/mol).

substrate (Fig. 9). The results indicated that when **S3** undergoes insertion, the energy barrier is significantly greater than that for **S2** insertion, despite insertion into the Ni–C(aryl) bond being more favorable for **S3**. Subsequent distortion/interaction energy analysis revealed that, compared with **S2** insertion, **S3** insertion into the Ni–C(aryl) bond (**TS12'**) was less favorable interaction energy, whereas **S3** insertion into the Ni–C(Acyl) bond (**TS11'**) resulted in unfavorable distortion energy (particularly deformation of the alkene substrate). Since **TS12'** was determined to be the more favorable transition state in this case, our comprehensive analysis suggests that the experimental results can be attributed to unstrained alkenes providing less interaction energy during insertion (compared with strained alkenes).

These comprehensive computational studies not only reveal the preferred mechanistic pathway for nickel-catalyzed amide addition reactions with strained alkenes but also provide valuable insights into the limitations imposed by different ligands and substrates. Understanding the interplay between ligand effects and substrate reactivity is crucial for the rational design and optimization of more efficient catalytic systems for difunctionalization reactions.

### 3 Conclusions

In summary, the mechanistic pathways of the nickel-catalyzed addition of aryl amides to strained alkenes have

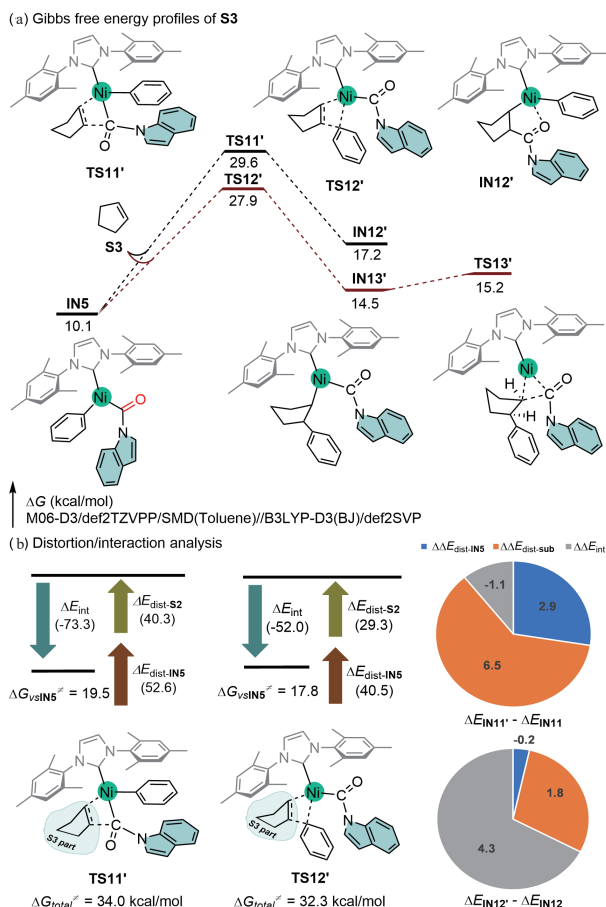
been elucidated through DFT calculations. The study revealed that the reaction predominantly involves an oxidative addition of the C(acyl)–N bond, Ni–C(acyl) insertion and a reductive elimination pathway (Path III), rather than the previously proposed carbonyl deinsertion-reinsertion steps. This finding underscores the critical role of Ni–C(acyl) insertion as the rate-determining step and highlights the influence of bonding interactions in facilitating favorable alkene insertion. The overall reaction energy barrier was determined to be 25.8 kcal/mol relative to the lowest energy state **IN3** along the entire pathway. Furthermore, the study revealed that ligand substitution from IMes to PCy<sub>3</sub> resulted in a significant increase in the energy barrier for alkene insertion, which is consistent with the low experimental yields. This finding highlights the importance of ligand selection in improving catalytic efficiency. In addition, various amide and ester substrates were computationally analyzed and found to lose reactivity due to the increased energy barrier for alkene insertion. The results presented here contribute to a deeper understanding of C–C bond activation in nickel catalysis and provide strategic guidelines for the development of more efficient catalytic systems for difunctionalization reactions in synthetic organic chemistry.

### Computational methods

Unless otherwise stated, the following are the default calculations in this study: the DFT calculations were performed via the Gaussian 16, C.01 program<sup>[16]</sup>. The geometry optimization calculations were performed at 298 K via the B3LYP<sup>[17–19]</sup> functional with the Grimme D3 empirical dispersion of BJ damping and the def2-SVP<sup>[20,21]</sup> basis set for all the atoms. Frequency analysis was performed at the same level as the optimization to confirm that the optimized structure was a local minimum (no imaginary frequencies) or transition state (with only one imaginary frequency) and to obtain the thermal corrections to the Gibbs free energy. On the basis of the optimized structure, single-point energy calculations were carried out at the M06/def2-TZVPP<sup>[22,23]</sup> level with the Grimme D3 empirical dispersion of zero-damping as well as the solvation model SMD<sup>[24]</sup> (toluene) to accommodate the solvent effect. The intrinsic reaction coordinate (IRC)<sup>[25,26]</sup> calculations were employed to ensure that the transition states connected the correct reactants and products. The energy is given in kcal/mol. The structures are drawn with CYLview 1.0b<sup>[27]</sup>. Distortion/interaction analysis was employed via the protocol provided by Houk et al<sup>[14]</sup>. The noncovalent interactions between the fragments were analyzed via an independent gradient model based on the Hirshfeld partition (IGMH) method<sup>[15]</sup> via Multiwfn<sup>[28,29]</sup> and VMD<sup>[30]</sup> software. Mayer bond order is also obtained through Multiwfn software.

### Supporting information

The supporting information for this article can be found online at <https://doi.org/10.52396/JUSTC-2025-0034>. The supporting information includes details of the coordinates and energy information for the intermediates and transition states.



**Fig. 9.** Gibbs free energy profiles of **S3** and the related distortion/interaction analysis.

## Acknowledgements

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## Conflict of interest

The authors declare that they have no conflict of interest.

## Biography

**Deguang Liu** is currently a postdoctoral researcher at the University of Science and Technology of China, under the supervision of Prof. Yao Fu. He received his Ph.D. degree from the University of Science and Technology of China in 2023. His research mainly focuses on structure–activity relationships by means of density functional theory (DFT) calculations.

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