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Nickel-catalyzed oxidative C–H/N–H annulation of *N*-heteroaromatic compounds with alkynes†

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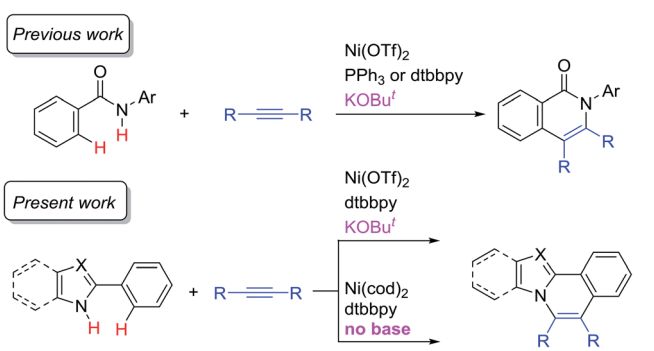
The reaction of N-heteroaromatic compounds, such as 2-aryl-pyrrole, benzimidazole, imidazole, indole, and pyrazole derivatives, with alkynes in the presence of a catalytic amount of a nickel complex results in C–H/N–H oxidative annulation. The reaction shows a high functional group compatibility. While both Ni(0) and Ni(II) complexes show a high catalytic activity, Ni(0) is proposed as a key catalytic species in the main catalytic cycle. In the case of the Ni(II) system, the presence of a catalytic amount of a strong base, such as KOBu^t, is required for the reaction to proceed. In sharp contrast, a base is not required in the case of the Ni(0) system. The proposed mechanism is supported by DFT studies.

Introduction

Transition-metal catalyzed C–H functionalization reactions have experienced notable progress over the past two decades.[1] At the early stage of the development of such reactions, noble metals, such as Pd, Rh, Ir, and Ru, were frequently used as catalysts and these metals continue to be the catalysts of choice in various C–H functionalization reactions. However, the use of first row transition metals,[2] such as Fe,[3] Co,[4] Ni,[5] and Cu,[6] has attracted a great deal of interest because they are earth-abundant and therefore less expensive than noble metals. If these elements could be used in such transformations, it would permit the scope of C–H functionalization reactions to be greatly expanded. Among these metals, nickel catalysts are of particular interest. Although a pioneering example of cyclometalation with the cleavage of an *ortho* C–H bond was achieved by the reaction of azobenzene with a nickel complex,[7] Ni-catalyzed C–H functionalization reactions have generally remained undeveloped. One of the reasons for this is the absence of a general and reliable catalytic system for Ni-catalyzed C–H functionalization. In fact, Ni-catalyzed C–H functionalization reactions were limited to specific substrates that contain an acidic C–H bond, such as pentafluorobenzene, pyridine derivatives, and azoles.[5a] However, since our initial report in 2013 on the use of an 8-aminoquinoline directing group[8] in Ni(II)-catalyzed C–H alkylation with alkyl halides,[9a] a combination of Ni(II) catalysts and *N*,*N*′-bidentate directing groups has now emerged as a powerful methodology for use in Ni-catalyzed C–H functionalization reactions.[5b,c] Since then, the Ni(II) catalyst/8-aminoquinoline directing system has been extensively used for the development of Ni-catalyzed C–H functionalizations.[5b,c,9,10]

In a previous study, we reported on the Ni-catalyzed oxidative annulation of C–H bonds in aromatic amides with alkynes, leading to the production of 1(2*H*)-isoquinolinones (Scheme 1).[11] In this reaction, a specific *N*,*N*′-bidentate directing group is not required for the reaction to proceed, in contrast to our study in 2011.[12] A key to the success of the reaction is the use of a catalytic amount of KOBu^t. We wish to report herein that this newly developed system is also applicable to the oxidative annulation of C–H bonds in various 2-aryl-*N*-heteroaromatic compounds (Scheme 1). A theoretical study was also conducted in connection with these experimental findings. The DFT studies indicated that the reaction proceeds *via* two reaction paths. One mechanism is initiated by Ni(II) and KOBu^t, and the other, the main catalytic cycle, is initiated by Ni(0). Although the Ni(II) system requires a base, the Ni(0) system proceeds even in the absence of KOBu^t. Nitrogen-containing polyaromatic scaffolds are widely found in natural products, pharmaceutical agents, and π-conjugated functional materials.[13] A similar transformation was previously reported using noble metal



Scheme 1 Ni-catalyzed oxidative C–H/N–H annulation of N-heteroaromatic compounds with alkynes.

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complexes, such as $[Cp^*RhCl_2]_2$ and $[RuCl_2(p\text{-cymene})]_2$.[14] The present reaction is the first example of the use of a nickel catalyst in oxidative C–H/N–H annulation reactions with alkynes.

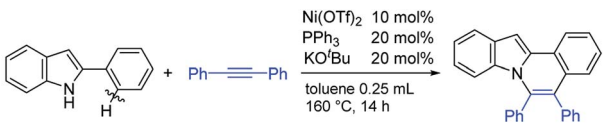
Results and discussion

The reaction of 2-phenylindole (**1a**) with diphenylacetylene was carried out under the same reaction conditions as were used in the reaction of aromatic amides.[11a] Unexpectedly, no reaction took place (entry 1 in Table 1). However, the use of 4,4-di-*tert*-butyl-2,2-dipyridyl (dtbbpy) as a ligand in place of PPh_3 gave the expected product, 5,6-diphenylindolo[2,1-*a*]isoquinoline (**2a**) (entry 2). Increasing the reaction temperature to 180 °C slightly improved the product yield (entry 3). Conducting the reaction in the absence of a solvent resulted in a further improvement in the product yield (entry 4). Finally, the reaction conditions shown in entry 5 were used as standard reaction conditions. Curiously, $Ni(cod)_2$ also showed catalytic activity (entry 6). This result will be discussed below in relation to the reaction mechanism.

The scope of this oxidative annulation reaction with respect to 2-arylindole derivatives was also investigated (Table 2). A variety of functional groups, including methoxy, fluoride, trifluoromethyl, and even formyl groups, were tolerated in the reaction. In the reaction of 3-trifluoromethylphenylindole (**2g**), the less hindered C–H bond was selectively activated. In all cases, the yields of the expected product determined by ^1H NMR were good to high. However, a small amount of an unidentified product was produced as a contaminant. To remove this contaminant from the expected products, the product was purified by Gel Permeation Chromatography (GPC), which reduced the product yield.

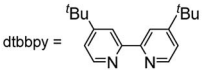
To expand the present protocol, the reaction of 2-phenylbenzimidazole (**3a**) with diphenylacetylene was examined under the same reaction conditions as were used in the reaction of 2-phenylindole (Table 3). As expected, the corresponding product, 5,6-diphenylbenzo[4,5]imidazo[2,1-*a*]isoquinoline (**4a**), was formed in nearly quantitative yield (entry 1). A screening of various nickel salts indicated that other Ni(II) complexes also showed catalytic activity (entries 2–5). Curiously, $Ni(cod)_2$ again showed a high catalytic activity (entry 6). We then decided to optimize the reaction conditions using $Ni(OAc)_2$ because $Ni(OTf)_2$ is prepared from $Ni(OAc)_2$ and trifluoromethanesulfonic acid in CH_3CN,[9a] and is sensitive to moisture and air. The use of a longer reaction time resulted in an increased product yield (entry 7). In the absence of $KOBu^t$,

Table 1 Ni-catalyzed reaction of 2-phenylindole (**1a**) with diphenylacetylene



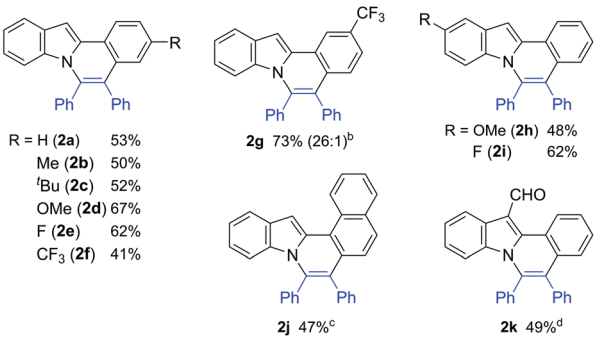
1a 0.25 mmol 1.25 mmol **2a**

Entry	Deviation for the standard conditions	NMR yields 2a	1a[b]
1	–	Trace	76%
2	dtbbpy	19%	n.d.
3	dtbbpy, 180 °C	30%	61%
4	dtbbpy, no solvent, 180 °C	51%	n.d.
5	dtbbpy, no solvent, 180 °C, 36 h	85% (53%)[a]	n.d.
6	$Ni(cod)_2$, dtbbpy, no solvent, 180 °C, 36 h	57%	n.d.



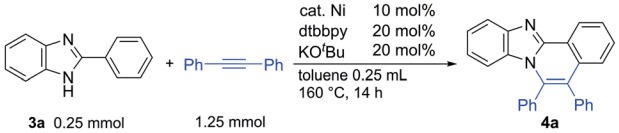
[a] Isolated by GPC. [b] n.d. = not determined.

Table 2 Scope of 2-arylindoles[a]



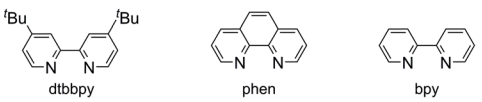
[a] Reaction conditions: 2-arylindole (0.25 mmol), diphenylacetylene (1.25 mmol), $Ni(OTf)_2$ (0.025 mmol), dtbbpy (0.05 mmol), and $KOBu^t$ (0.05 mmol) at 180 °C for 36 h. Isolated by GPC. [b] The number in parentheses refers to the regioselectivity. [c] The reaction was carried out for 60 h. [d] Ligand (50 mol%) and toluene (0.25 mL).

Table 3 Ni-catalyzed reaction of 2-phenylimidazole (**3a**) with diphenylacetylene



3a 0.25 mmol 1.25 mmol **4a**

Entry	Catalyst	Notes	NMR yields 4a	3a
1	$Ni(OTf)_2$		~100% (88%)[a]	0%
2	$Ni(OAc)_2$		56%	0%
3	$Ni(acac)_2$		33%	42%
4	$NiCl_2$		34%	39%
5	$NiCp_2$		28%	54%
6	$Ni(cod)_2$		72%	0%
7	$Ni(OAc)_2$	20 h	89%	0%
8	$Ni(OAc)_2$	20 h, w/o KO^tBu	6%	65%
9	$Ni(OAc)_2$	20 h, toluene 0.5 mL	97%	0%
10	$Ni(OAc)_2$	20 h, toluene 0.5 mL, 140 °C	51%	46%
11	$Ni(OAc)_2$	20 h, phen, toluene 0.5 mL	87%	0%
12	$Ni(OAc)_2$	20 h, bpy, toluene 0.5 mL	46%	26%



[a] Isolated yield.

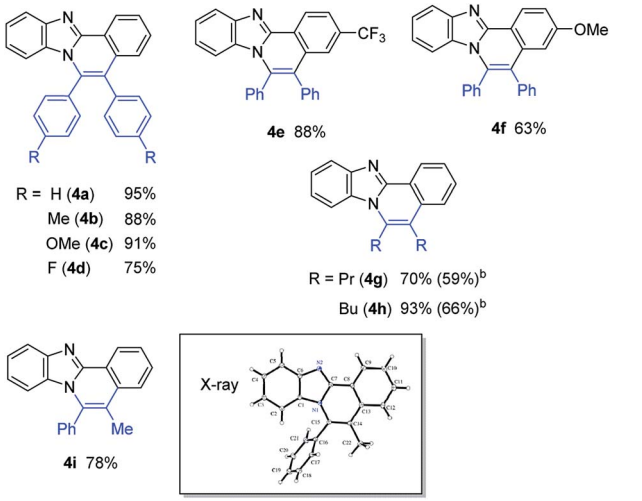
the product yield was dramatically decreased (entry 8). The use of phenanthroline (phen) also gave **4a** in high yield (entry 11), but the use of the bipyridine (bpy) ligand did not lead to optimal yields (entry 12). Finally, we determined that the reaction conditions shown in entry 9 are standard reaction conditions for the reaction of 2-phenylimidazole with alkynes.

With the optimized reaction conditions in hand, we examined the scope of 2-arylimidazoles **3** and alkynes (Table 4). Not only diarylalkynes, but also aliphatic alkynes were applicable to the reaction. The reaction of **3** with aliphatic internal alkynes gave the corresponding benzo[4,5]imidazo[2,1-*a*]isoquinoline derivatives **4g** and **4h** in high yields. The reaction of **3** with phenylpropyne gave the corresponding product **4i** in a regioselective manner, the structure of which was confirmed by X-ray crystallographic analysis.

The reaction of 2-phenylimidazole (**5**), 3,5-diphenylpyrazole (**7**), and 2-phenylpyrrole (**9**) also gave the corresponding nitrogen-containing polyaromatic compounds, **6**, **8**, and **10**, respectively (Table 5).

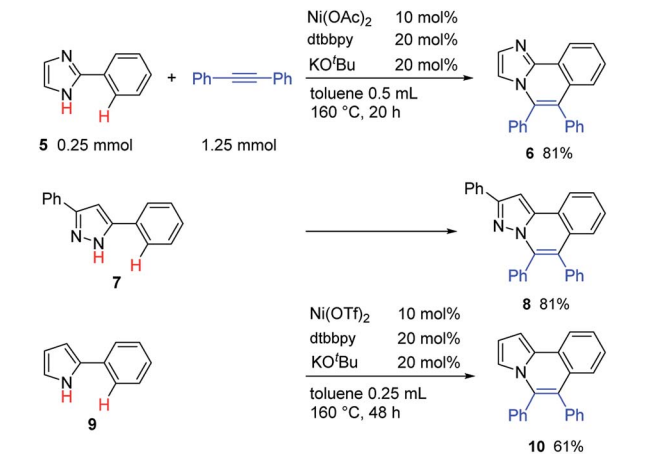
To gain insights into the reaction mechanism, the reaction was carried out in the presence of two equivalents of TEMPO. However, TEMPO did not inhibit the reaction, indicating that a radical path is not involved in the catalytic system (Scheme 2). As shown in Tables 1 and 3, the catalytic activity of $Ni(cod)_2$ was comparable to that of Ni(II) complexes in the presence of $KOBu^t$. Curiously, it was found that the reaction proceeds in a highly efficient manner, even in the absence of $KOBu^t$. The reaction of **3a** without $KOBu^t$ gave **4a** in a quantitative yield. Indole **1a** also gave **2a**. Thus, the use of $KOBu^t$ is crucial for the reaction to proceed when Ni(II) complexes are used as a catalyst. In sharp contrast, $KOBu^t$ is not required when Ni(0) is used as a catalyst. The reaction of **3a** with diphenylacetylene in the presence of $Ni(cod)_2$/dtbbpy gave **4a** in 85% NMR yield, along with a 55%

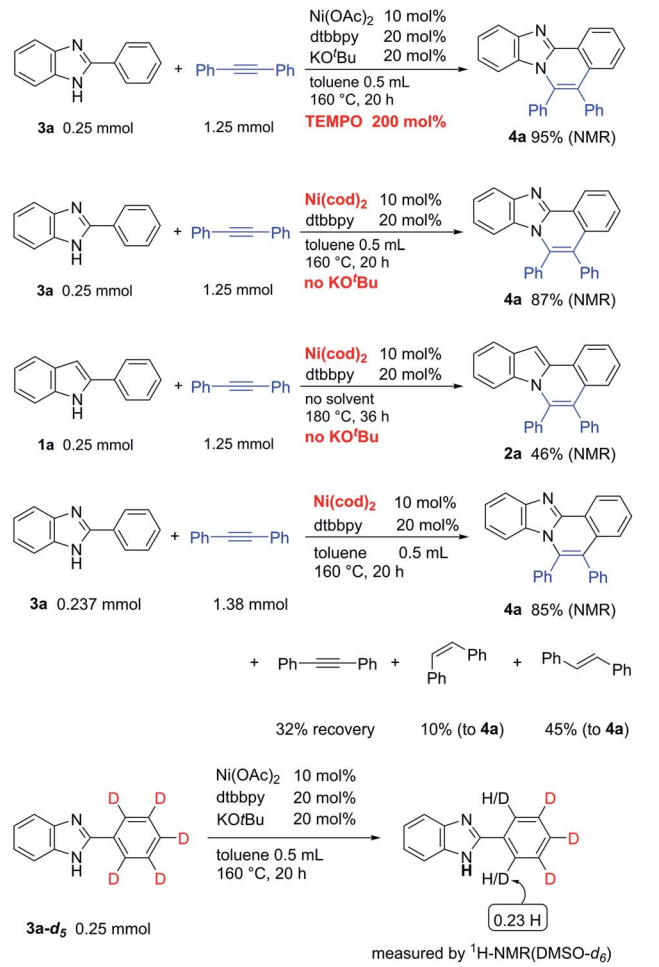
Table 4 Ni-catalyzed reaction of 2-arylimidazoles (**3**) with alkynes[a]



[a] Reaction conditions: 2-arylimidazole (0.25 mmol), alkyne (1.25 mmol), $Ni(OAc)_2$ (0.025 mmol), dtbbpy (0.05 mmol), and $KOBu^t$ (0.05 mmol) in toluene (0.5 mL) at 160 °C for 20 h. [b] The number in parentheses refers to the isolated yield by HPLC.

Table 5 Other *N*-heteroaromatic compounds

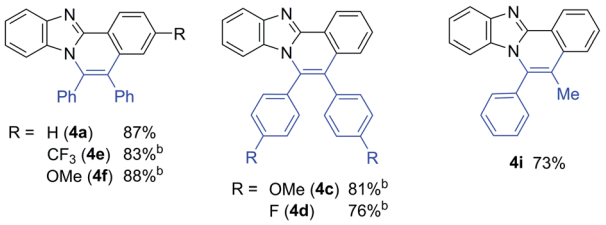




Scheme 2 Mechanistic experiments.

yield of stilbene relative to **4a**. In the absence of **3a**, no evidence was found for the formation of stilbene. These results indicate that diphenylacetylene functions as a hydrogen acceptor as well as a two-component coupling partner. A deuterium-labelling experiment in the absence of an alkyne was also carried out. H/D exchange took place only at the *ortho*-position.

Table 6 Ni(0)/no base catalytic system[a]



[a] Reaction conditions: 2-arylimidazole (0.25 mmol), alkyne (1.25 mmol), $Ni(cod)_2$ (0.025 mmol), and dtbbpy (0.05 mmol) in toluene (0.5 mL) at 160 °C for 20 h. [b] 0.125 Mmol scale.

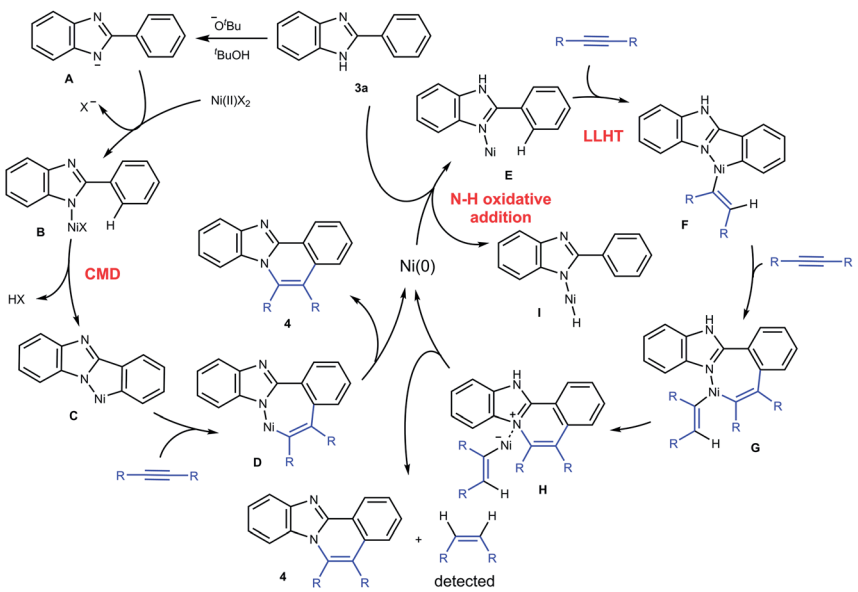
Some examples of the use of other substrates in the $Ni(cod)_2$/no base system are summarized in Table 6.

Based on these results, a mechanism for the C–H/N–H oxidative annulation is proposed, as shown in Scheme 3. The mechanism involves two paths and is initiated by the Ni(II) complex (left scheme). An NH proton is abstracted from **3a** by $KOBu^t$ to generate the anion **A**, which reacts with Ni(II) to give the complex **B**. The cleavage of the *ortho* C–H bond followed by the insertion of an alkyne into a C–Ni bond in **C** gives complex **D**. A reductive elimination from **D** then gives **4a** and Ni(0). However, Ni(0) cannot be re-oxidized to Ni(II) to complete a catalytic cycle under the reaction conditions employed. Instead, Ni(0) initiates another catalytic cycle (right scheme). The coordination of a $N(sp^2)$ atom in **3a** to Ni(0) gives complex **E**, which involves a ligand-to-ligand hydrogen transfer (LLHT) mechanism,[15,16] in which the *ortho* hydrogen atom is directly transferred to the alkyne carbon. The successive insertion of an alkyne into C–Ni bonds gives the complex **G**. Reductive elimination followed by deprotonation affords **4a** with the regeneration of Ni(0) and the concomitant formation of an alkene. In fact, the formation of alkenes was detected by GC (Scheme 2).

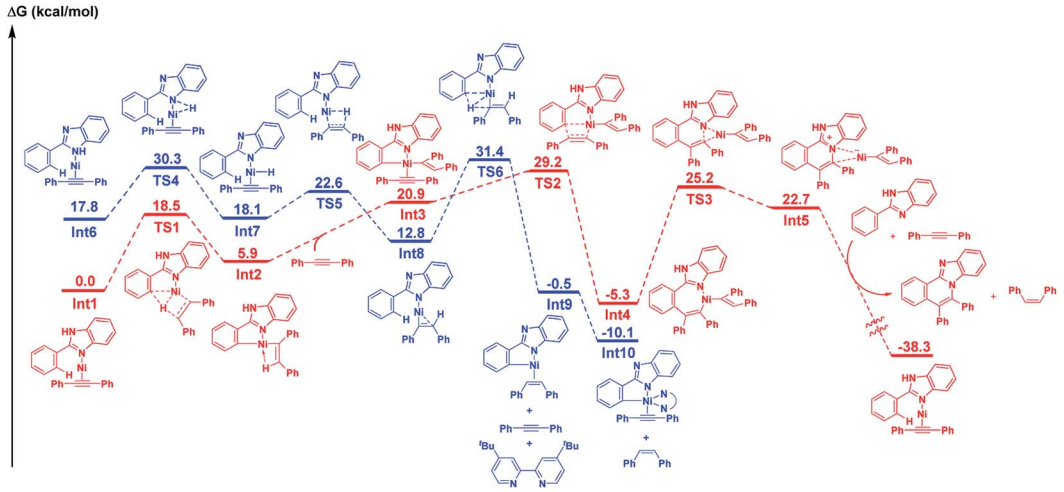
An alternative mechanism involves the oxidative addition of a N–H bond in **3a** to Ni(0), leading to the generation of complex **I**. The possibility of this alternative mechanism being operative will be discussed below in conjunction with DFT studies.

DFT studies were conducted in an attempt to obtain a better understanding of the mechanism for this reaction. The resulting DFT studies are essentially supportive of the mechanism that is proposed above. As shown by the mechanistic details in Scheme 3, the presence of $KOBu^t$ is crucial for the success of the initial reaction path (left scheme in Scheme 3), which is catalyzed by Ni(II), but it is not required for the main catalytic cycle in which Ni(0) functions as a catalyst (right scheme in Scheme 3). Therefore, we focused on the main reaction path that is initiated by Ni(0) under neutral conditions (red line in Scheme 4).[17] The LLHT mechanism for the main catalytic cycle that proceeds *via* **TS1** has a low energy barrier (18.5 kcal mol^{-1}). After coordination with a second alkyne molecule, the insertion of the alkyne into a Ni–C bond through **TS2** proceeds smoothly, with an activation energy of 8.3 kcal mol^{-1}. A final reductive elimination through **TS3** from the relatively stable seven-membered metallacycle **Int4** requires a large amount of energy to produce **Int5**, which is comprised of an ammonium cation and nickel anion pair. This step is followed by a proton shift to afford the product and the *cis*-alkene with the regeneration of **Int1**. While a detailed mechanism for the proton shift is not given here, the large amount of energy released during the course of the catalytic cycle is assumed to be the driving force for the reaction.

We also investigated the case where the main catalytic cycle is initiated by the oxidative addition of an N–H bond (complex **I** in Scheme 3 and the blue line in Scheme 4), because the presence of an $N(sp^2)$ atom in the substrate is not essential for the reaction to proceed, as in 2-phenylindole or pyrrole. The coordination of an $N(sp^2)$ atom to nickel, as in **Int6**, was found to be energetically unfavorable, compared with the coordination of



Scheme 3 Proposed mechanism.



Scheme 4 Comparison of the LLHT path (red line) and the N–H oxidative addition path (blue line) in the main catalytic cycle calculated at the B3PW91/6-311+G(2d,p)-SDD(Ni)/PCM//B3LYP/6-31+G(d)-Lanl2dz(Ni) level of theory.

an N(sp^2) atom. While a LLHT path from the N–H bond of 2-phenylimidazole to an alkyne could not be located, the oxidative addition of the N–H bond in **Int6** through **TS4**, followed by the insertion of the alkyne into a Ni–H bond is a feasible step. The σ-bond metathesis through **TS6** proceeds with an activation energy of 18.6 kcal mol^{-1} to give a five membered metallacycle **Int9**. The highest Gibbs free energy for this step is the transition state of the σ-bond metathesis step (31.4 kcal mol^{-1}), which is slightly higher than that for the LLHT mechanism (29.2 kcal mol^{-1}). These results indicate that, while the reaction of 2-phenylimidazole proceeds through a LLHT mechanism, it is possible that the reaction of 2-phenylindole could proceed *via* the N–H oxidative addition-σ-bond metathesis sequence.

Conclusions

We report on the development of a new catalytic system for oxidative C–H/N–H annulation with alkynes which is promoted by a Ni(II)/$KOBu^t$ or Ni(0) system. Using this system it is possible to use N-heteroaromatic compounds, such as 2-aryl-pyrrole, benzimidazole, imidazole, indole, and pyrazole, in Ni-catalyzed oxidative C–H/N–H annulation reactions with alkynes, leading to the production of highly conjugated compounds. While noble metal complexes, such as $[Cp^*RhCl_2]_2$ and $[RuCl_2(p\text{-cymene})]_2$, were used in the past in a similar transformation, the present reaction is the first example of the oxidative C–H/N–H annulation with alkynes in which a nickel catalyst is used. DFT studies indicate that the reaction involves two reaction paths. One mechanism is initiated by Ni(II) and the other by Ni(0), the latter being the main catalytic cycle. Although the Ni(II) system requires a base, the Ni(0) system proceeds, even in the absence of $KOBu^t$. C–H activation in the first step proceeds through a CMD mechanism and C–H activation in the main catalytic cycle proceeds through a LLHT mechanism.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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