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Nickel Catalysis Enables Hetero [2+2+1] Cycloaddition between Yne-Isothiocyanates and Isonitriles with Low Catalyst Loading

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Abstract: Nickel(II) can be used to catalyze the hetero [2+2+1] cycloaddition of 2-alkynylaryl isothiocyanates and isonitriles in 2-methyltetrahydrofuran (2-MeTHF) to give a wide array of thieno[2,3-*b*]indoles in excellent yields. The reaction is featured by employing as little as 0.3 mol% nickel(II) acetylacetonate [Ni(acac)$_2$] under air conditions in the absence of any additives (additional reducing agents and external ligands). This is the first successful example to apply nickel(II) directly in hetero [2+2+1] cycloadditions.

Keywords: 2-alkynylaryl isothiocyanates; hetero [2+2+1] cycloaddition; isonitriles; nickel catalyst

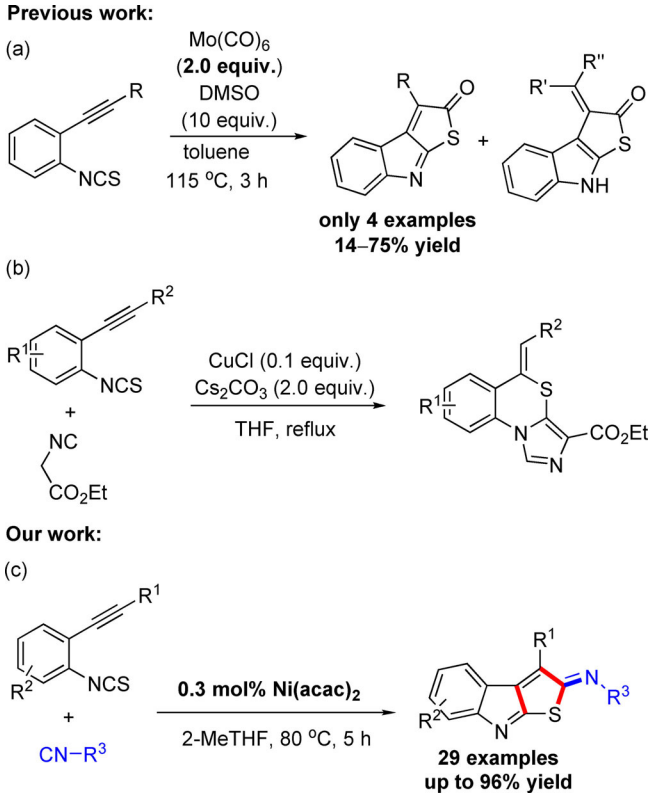
Introduction

Thienodolin, a new plant growth-regulating substance containing a thieno[2,3-*b*]indole skeleton, was isolated from the fermentation broth of a streptomycete strain identified as *Streptomyces albogriseolus* MJ286-76F6, which has been reported as the basis for both growth promoting and inhibiting activities in rice seedlings.[1] Some thieno[2,3-*b*]indole derivatives are known as electron transfer agents which can reduce the residual potential and improve sensitivity of electrophotographic photoreceptors.[2] So construction of the thieno[2,3-*b*]indole motif still remains an important task.

The hetero [2+2+1] cycloaddition process has also become one of the most powerful methodologies for the construction of bicyclic frameworks.[3] Mukai[4] and Saito[5] reported a $Co_2(CO)_8$-catalyzed and a Rh(I)-catalyzed hetero [2+2+1] cycloaddition of yne-carbodiimides leading to pyrrolo[2,3-*b*]indol-2-ones, respectively. Tu and co-workers[6] achieved a Co(acac)$_2$-catalyzed double insertion of two identical isonitriles into 2-ethynylanilines to obtain functionalized pyrrolo[2,3-*b*]indoles. Very recently, Zhang and co-workers[7] reported a synthesis of pyrrolo[2,3-*b*]indoles through self-relay Rh(I)-catalyzed cyclization of alkyne-azides with two isonitriles *via* tandem nitrene transformation.

Alkynyl isothiocyanates have been used to synthesize various fused ring compounds containing nitrogen and sulfur heteroatoms.[8] For example, Saito and co-workers[8e] reported an $Mo(CO)_6$-catalyzed [2+2+1] cycloaddition of yne-isothiocyanates for the synthesis of thieno[2,3-*b*]indol-2-ones, in which only 4 examples were disclosed and used 2 equiv. of $Mo(CO)_6$ (Scheme 1a). Cai and co-workers[8f] developed a copper(I)-catalyzed tandem reaction of yne-isothiocyanates with ethyl 2-isocyanoacetate to obtain 5*H*-benzo[*d*]imidazo[5,1-*b*][1,3]thiazines (Scheme 1b).

Owing to their low cost and unique properties, nickel-catalyzed carbon-carbon and carbon-heteroatom bond-forming reactions have become powerful tools in organic syntheses.[9] The most common Ni(0) source for catalysis is Ni(cod)$_2$, however, it is expensive and must be used under rigorously air-free conditions. The inexpensive nickel catalysts such as Ni(II) compounds have been preferable to Ni(cod)$_2$ because they are readily available, cheaper, and convenient to manipulate.[10] Isonitriles[11] have long proved to be irreplaceable building blocks in modern organic chemistry. Based on our ongoing research interest and preceding work of others on the utility of isonitriles as synthons,[12] herein, we report a Ni(II)-catalyzed hetero [2+2+1] cycloaddition of yne-isothiocyanates with isonitriles to form thieno[2,3-*b*]indoles without any additive or ligand (Scheme 1c).



Scheme 1. The reactions of yne-isothiocyanates.

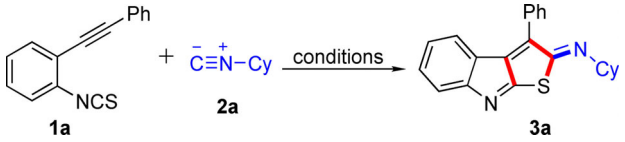
Results and Discussion

We commenced with an optimization of the reaction conditions by conducting the model reaction of 2-alkynylphenyl isothiocyanate **1a** with cyclohexyl isonitrile **2a**, and the results are summarized in Table 1.

Initially, without any catalyst, the model reaction did not occur in toluene at room temperature or at 80 °C after 48 h (Table 1, entries 1 and 2). Gratifyingly, when 10 mol% $Ni(acac)_2$ was used in the reaction, the reaction was accomplished within 5 min, and the yield of **3a** reached up to 95% (entry 3). Then other inexpensive inorganic nickel salts such as $Ni(ClO_4)_2$, $Ni(OAc)_2$, and $NiCl_2$ were also examined. Unfortunately, they did not work as well as $Ni(acac)_2$ (entries 4–6). Next, the same amount of $Ni(cod)_2$ was tested, and the yield of **3a** reached 95% within just 3 min (entry 7). Considering the air-instability and uneasy handling of expensive $Ni(cod)_2$, $Ni(acac)_2$ was selected as the catalyst to screen other reaction conditions. When the amount of $Ni(acac)_2$ was reduced to 1 mol%, a 96% yield was afforded even though the reaction time was prolonged to 4 h (entry 8). Subsequently, other solvents such as H_2O, EtOH, CH_3CN, DCE, THF, and 2-MeTHF were screened (entries 9–14). More gratifyingly, the yield of **3a** still reached 93% within 5 min in THF and 2-MeTHF, which might be due to the fact that $Ni(acac)_2$ could dissolve well in these two solvents and the free coordination sites could be occupied by the solvents.[13] Inspired by this result, the lower amount of $Ni(acac)_2$ was investigated in 2-MeTHF,[14] it was found that the reaction time was prolonged but the yield of **3a** was not reduced when the amount of $Ni(acac)_2$ was decreased (entries 15 and 16). However, when 0.1 mol% $Ni(acac)_2$ was used, the yield declined to 80% (entry 17). Finally, the reaction temperature was tested in 2-MeTHF, but use of a lower temperature prolonged the reaction time and reduced the yield of **3a** (entry 18). Taking temperature, reaction time and amount of nickel catalyst into consideration, 0.3 mol% of $Ni(acac)_2$ as the catalyst in 2-MeTHF at 80 °C for 5 h (entry 16) were selected as the best reaction conditions.

Successively, the reactions of various 2-alkynylaryl isothiocyanates **1** with isonitriles **2** were performed under the optimal conditions for exploring the substrate scope and limitations (Table 2).

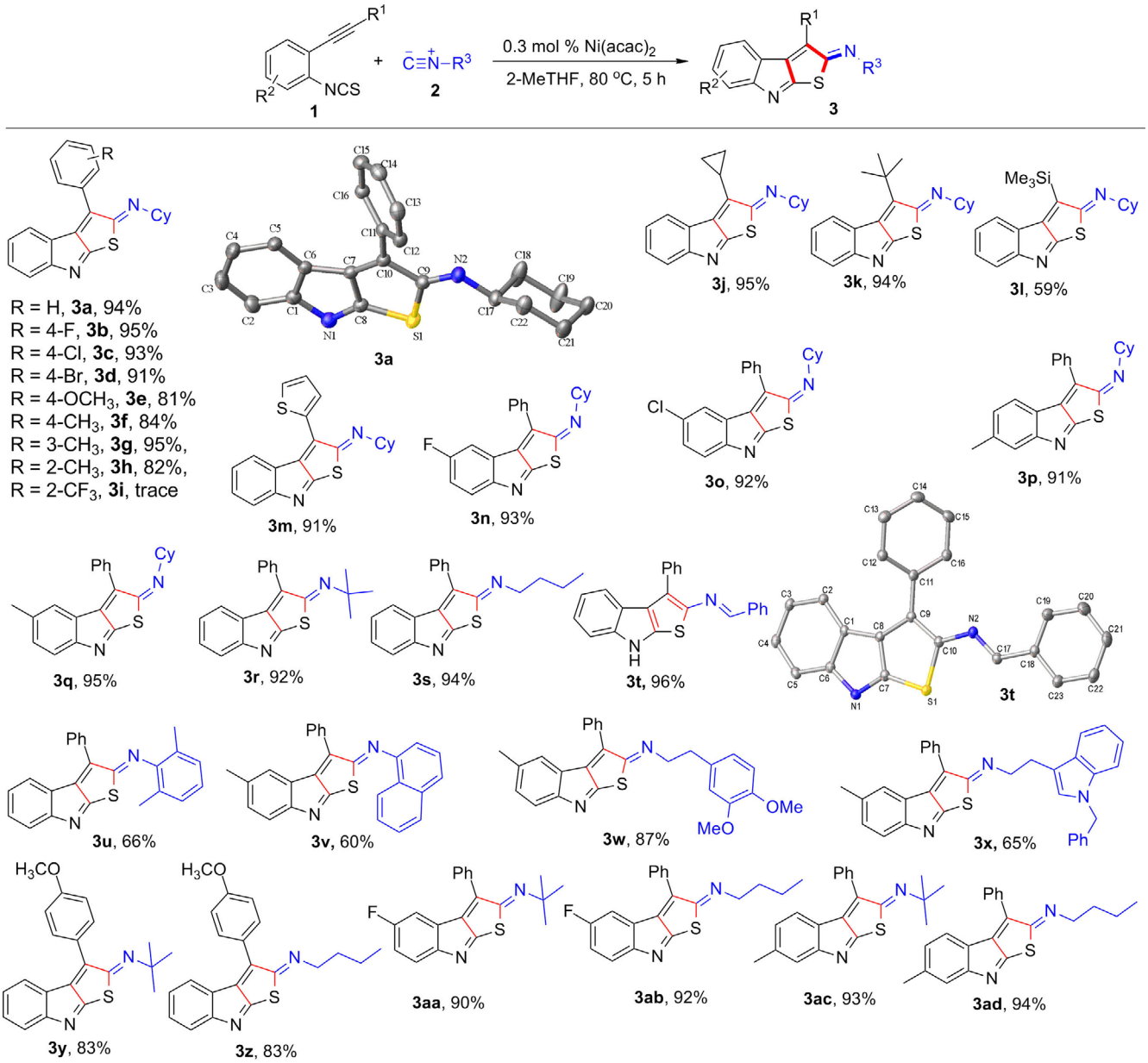
Table 1. Optimization of the reaction conditions.[a]



Entry	Ni (mol%)	Solvent	*T* [°C]	Time [h]	Yield [%][b]
1	none	toluene	r.t.	48	NR
2	none	toluene	80	48	NR
3	$Ni(acac)_2$ (10)	toluene	80	5 min	95
4	$Ni(ClO_4)_2$ (10)	toluene	80	24	trace
5	$Ni(OAc)_2{\cdot}4H_2O$ (10)	toluene	80	1.5	85
6	$NiCl_2{\cdot}6H_2O$ (10)	toluene	80	2	48
7	$Ni(cod)_2$ (10)	toluene	80	3 min	95
8	$Ni(acac)_2$ (1.0)	toluene	80	4	96
9	$Ni(acac)_2$ (1.0)	H_2O	80	5	71
10	$Ni(acac)_2$ (1.0)	EtOH	80	1.5	75
11	$Ni(acac)_2$ (1.0)	CH_3CN	80	1.5	82
12	$Ni(acac)_2$ (1.0)	DCE	80	0.5	80
13	$Ni(acac)_2$ (1.0)	THF	80	5 min	93
14	$Ni(acac)_2$ (1.0)	2-MeTHF	80	5 min	93
15	$Ni(acac)_2$ (0.5)	2-MeTHF	80	2.5	93[c]
16	$Ni(acac)_2$ (0.3)	2-MeTHF	80	5	94[d]
17	$Ni(acac)_2$ (0.1)	2-MeTHF	80	17	80[e]
18	$Ni(acac)_2$ (0.3)	2-MeTHF	50	8	82

[a] *Reaction conditions:* **1a** (0.3 mmol), **2a** (0.36 mmol), solvent (1 mL).
[b] Isolated yield.
[c] The reaction was performed on a 1 mmol scale in 2-MeTHF (3 mL).
[d] The reaction was performed on a 2 mmol scale in 2-MeTHF (6 mL).
[e] The reaction was performed on a 4 mmol scale in 2-MeTHF (12 mL).

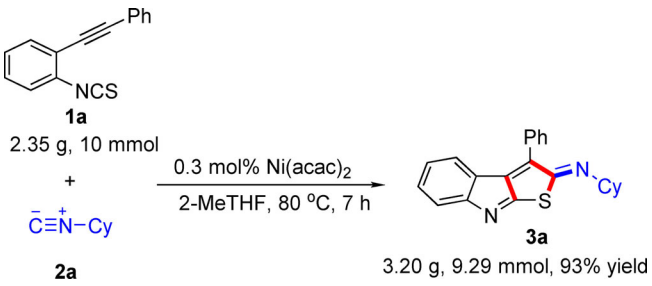
Table 2. Scope of the substrates.[a]



[a] *Reaction conditions:* **1** (1 mmol), **2** (1.2 mmol), 2-MeTHF (3 mL). Isolated yields.

As shown in Table 2, for substrates **1**, a wide variety of 2-alkynylphenyl isothiocyanates (**1a–1q**) were perfectly tolerated, giving the desired products (**3a–3q**) in excellent yields of 81–95% except for **1i** and **1l**. Due to the special property of the trifluoromethylgroup, **1i** only gave a trace of product **3i** that cannot be identified by spectroscopy. Additionally, **1l** containing an alkyne with a trimethylsilyl group gave a relatively low 59% yield (**3l**), which might be due to steric hindrance. For substrates **2**, various aliphatic isonitriles such as cyclohexyl, *tert*-butyl, *n*-butyl and 2-dimethoxyphenylethyl (**3w**) provided excellent yields, but indolylethyl isonitrile gave only a 65% yield (**3x**). Furthermore, aromatic isonitriles such as 1,3-dimethylphenyl (**3u**) and 1-naphthyl (**3v**) afforded relatively low 66% and 60% yields, respectively. Notably, benzyl isonitrile gave a isomerized product (**3t**) in a yield of 96%. Unfortunately, however, some active isonitriles[8f] such as ethyl isocyanoacetate and *p*-toluenesulfonyl isonitrile gave complex mixtures.

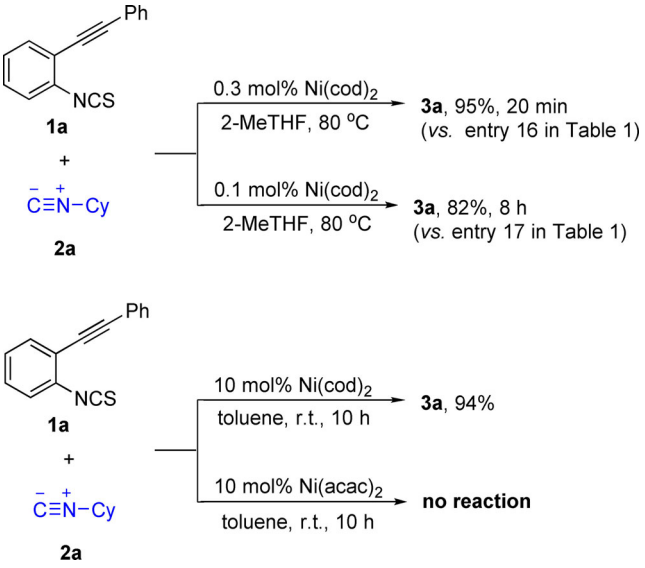
In order to demonstrate the synthetic utility of this method, the model reaction was performed on a 10 mmol scale under the standard conditions, and the desired product **3a** was provided in 93% yield after 7 h (Scheme 2).



Scheme 2. Gram-scale experiment.

To better understand the present catalytic reaction, three control experiments were investigated (Scheme 3). For ensuring the catalyst to fully exert its catalytic activity, 1 mol% $Ni(acac)_2$ was used in 2-MeTHF at 80 °C. When 1,2-diphenylethyne **4** and phenyl isothiocyanate **5** were separately employed to react with **2a**, both reactions did not occur even though the reaction time was prolonged to 5 h (Scheme 3a and b). Next, a three-component reaction of **4**, **5** with **2a** was also performed under the same conditions, similarly, no reaction took place (Scheme 3c). These results suggest that the present transformation results from a synergistic effect of Ni coordination with the alkyne bond and the isothiocyanate group followed by an isonitrile insertion.

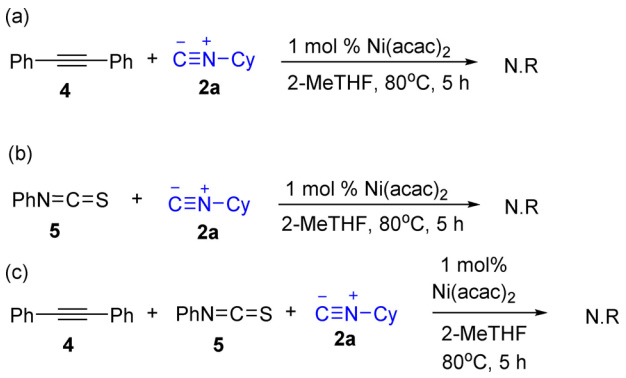
Notably, both $Ni(acac)_2$ and $Ni(cod)_2$ could catalyze this reaction efficiently under the tested conditions. To elucidate key mechanistic features of this Ni-catalyzed hetero [2+2+1] cycloaddition, two comparative experiments using the model reaction were conducted in 2-MeTHF with 0.3 mol% and 0.1 mol% $Ni(cod)_2$ as the catalyst, respectively (the reaction was performed on the vacuum line) (Scheme 4, *top*). The results showed that the two reaction times were 20 min and 8 h, respectively, which were all significantly faster than those with the counterpart $Ni(acac)_2$. Additionally, the other two comparative experiments were also investigated on the model reaction at room temperature with 10 mol% $Ni(cod)_2$ and $Ni(acac)_2$ in toluene for 10 h, respectively, it was found that Ni(II) had no



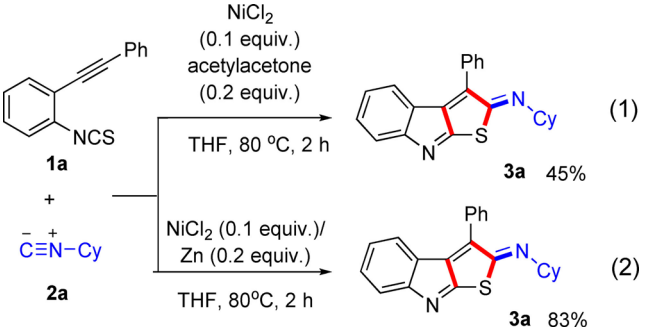
Scheme 4. Comparative experiments with Ni(0) and Ni(II) catalysis.

catalytic activity for this reaction at room temperature (Scheme 4, *bottom*). Apparently, the key active species of the catalyst in this reaction is Ni(0). This observed result was accordance with the findings of Ranu, who reported that the acetylacetone moiety in $Ni(acac)_2$ catalyst is responsible for the reduction of Ni(II) to Ni(0).[15]

In order to verify the reducing effect of the acetylacetone moiety, another two control experiments with the model reaction using $NiCl_2$ (0.1 equiv.) as Ni(II) source were conducted in THF at 80 °C for 2 h (Scheme 5). It was found that free acetylacetone (0.2 equiv.) did not play the role of a reducing agent [Scheme 5, Eq. (1)], only giving a 45% yield, the same as $NiCl_2$ alone; while the addition of zinc powder (0.2 equiv.) increased the yield of **3a** to 83% [Scheme 5, Eq. (2)]. These results indicated that the reduction of Ni(II) to Ni(0) might be the result of a synergistic action of several substances in the reaction system in a specific chemical environment.



Scheme 3. Control experiments.

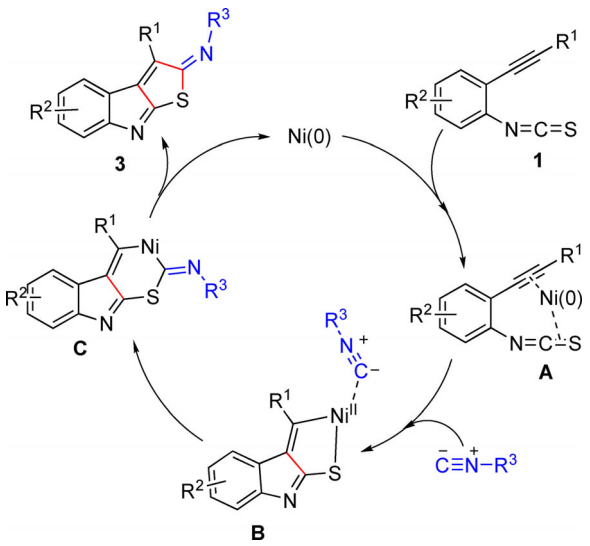


Scheme 5. Control experiments.

On the other hand, in order to check for *in situ* generated Ni(0), two XPS experiments was attempted, (i) the model reaction system with 0.5 equiv. of $Ni(acac)_2$ as catalyst at 80 °C for 1 min; (ii) only adding cyclohexyl isonitrile (**2a**) without substrate **1a** at 80 °C for 30 min to verify if isonitriles can reduce Ni(II) to Ni(0). Unfortunately, in the two cases, we did not trap an Ni(0) signal but only observed an Ni(II) peak.[15b] This might be due to the fact that the trace of *in situ* generated Ni(0) from Ni(II) is too reactive to immediately take part in the catalytic reaction or be oxidized by air during XPS and TEM tests.

Although it is not yet clear what plays the reduction role in the catalytic reaction, based on the above experimental results, a plausible reaction scenario to account for the formation of **3** is proposed (Scheme 6). Firstly, the existing donor–acceptor interactions between the alkyne and the C=S bond of the 2-alkynylaryl isothiocyanate **1** with empty *d* orbitals of Ni(0) exist in the π-complex **A** are predicted to play a key role.[16] The subsequent oxidative coupling of the alkyne with N=C=S bonds and the coordination of isonitriles **2** deliver a fused bicyclic nickel(II) complex **B**. Next, a migratory insertion of isonitriles **2** to the Ni–S bond provide the intermediate **C**. Finally, a reductive elimination of nickel from **C** gives the desired products **3**.

In conclusion, we have demonstrated a low-cost and air-stable nickel(II)-catalyzed hetero [2+2+1] cycloaddition of yne-isothiocyanates and isonitriles for the synthesis of thieno[2,3-*b*]indoles in excellent yields. The protocol can be performed by employing as little as 0.3 mol% $Ni(acac)_2$ catalyst in 2-MeTHF. Most distinctively, $Ni(acac)_2$ could exhibit excellent performance in this hetero [2+2+1] cycloaddition without needing additional reducing agents[17] and external ligands. This newly developed method provides a convenient, efficient, and less expensive alternative for the synthesis of thieno[2,3-*b*]indoles on a large scale.



Scheme 6. Plausible mechanism.

Experimental Section

General Procedure for the Synthesis of Thieno[2,3-*b*]indoles 3

The mixture of 2-alkynylaryl isothiocyanate **1** (1.0 mmol), isonitrile **2** (1.2 mmol), $Ni(acac)_2$ (0.3 mol%), and 2-MeTHF (3 mL) was stirred at 80 °C in a 25-mL round-bottom flask for the indicated time until complete consumption of starting materials as monitored by TLC. After the reaction was finished, the mixture was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 20:1) to afford the desired product **3** as a red solid or an oil.

CCDC 1038976 (**3a**) and CCDC 1514722 (**3t**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

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