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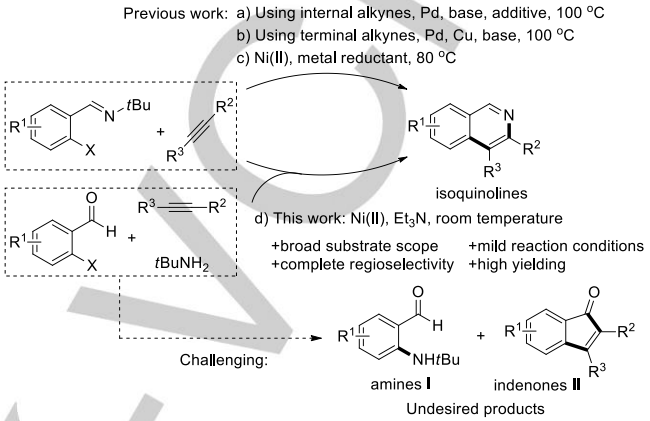
Highly Regioselective Isoquinoline Synthesis via Nickel-Catalyzed Iminoannulation of Alkynes at Room Temperature

Jian-Guo Sun, Xiao-Yu Zhang, Hua Yang, Ping Li, and Bo Zhang*[a]

Abstract: A simple and cost-efficient nickel catalytic system for the annulation of 2-haloaldimines with alkynes to synthesize 3,4-disubstituted and 3-substituted isoquinolines at room temperature has been developed. The air-stable and inexpensive Ni(dppe)Cl_2 was employed as a precatalyst, and Et_3N was found to be an essential additive for obtaining high yields. By using this nickel catalytic system one-pot three-component direct synthesis of isoquinolines starting with simple 2-halobenzaldehydes, *tert*-butyl amine, and alkynes were also achieved. These reactions occur in moderate to excellent yields with complete regioselectivity. Moreover, these reactions feature a broad substrate scope, easy scalability, operational simplicity, and excellent practicality.

Introduction

Heterocyclic compounds, especially nitrogen heterocycles, are among the most important structural classes of chemical substances in the pharmaceutical, agrochemical, and chemical industries.[1] Among them, isoquinolines are very common structural motifs that are frequently found in numerous natural products, bioactive molecules, and functional materials.[2] Wide applications trigger continued interest in the preparative chemistry of isoquinolines.[3] Traditional methods for the preparation of isoquinolines rely on the Bischler-Napieralski reaction, the Pomeranz-Fritsch reaction, and the Pictet-Spengler reaction.[4] Nevertheless, the harsh acidic conditions, high temperatures, as well as tedious reaction procedures and poor regioselectivity during ring closure remain impediments of these approaches. Since the pioneering work of Larock and co-workers in 1998,[5] a palladium-catalyzed annulation reaction of 2-halobenzaldimines with internal alkynes has become a powerful and efficient synthetic tool for the construction of 3,4-disubstituted isoquinolines (Scheme 1a).[6] Later, a palladium- and copper-catalyzed coupling and annulation reaction of 2-halobenzaldimines with terminal alkynes has been developed to prepare 3-substituted isoquinolines (Scheme 1b).[7] Despite significant advances, these procedures are associated with one or more limitations such as the use of an expensive palladium catalyst, the need for specialized ancillary ligands, high temperatures, superfluous usage of alkynes, and so on. Therefore, seeking new and efficient synthetic methods that employ inexpensive metal catalytic systems and mild reaction conditions for a facile access to diverse isoquinolines is highly warranted.



Scheme 1. Synthesis of substituted isoquinolines via transition-metal-catalyzed iminoannulation of alkynes.

In recent years, considerable attention has been paid to develop cross-coupling reactions that were facilitated by nickel catalysis.[8] In comparison to palladium, nickel is much less expensive and significantly more abundant. In light of these advantages offered by nickel, a variety of elegant nickel-catalyzed cross-coupling reactions have been established to form C-C[9] and C-heteroatom bonds.[10] It was however surprising to note that investigations on building the isoquinoline moiety *via* a nickel-catalyzed Larock-type annulation reaction is very rare. In 2005, Cheng and co-workers reported a nickel-catalyzed cyclization of 2-iodobenzaldimines with alkynes to synthesize substituted isoquinolines (Scheme 1c).[11,12] However, this method require high temperatures and the use of a stoichiometric metal reducing agent (Zn), thus limiting the further application of such a method.

On the other hand, most of these reported transition-metal-catalyzed methods suffer from the use of 2-halobenzaldimine substrates.[5-7a-c,11] Examples of direct construction of isoquinolines starting with simple 2-halobenzaldehydes, *tert*-butyl amine, and alkynes have rare precedents,[7d] although it can provide a straightforward and step-economical route to isoquinolines. This approach presents two main challenges that need to be addressed: 1) amination of 2-halobenzaldehydes with *tert*-butyl amine might occur when a transition-metal catalyst was employed;[13] 2) 2-halobenzaldehydes undergo the annulation reaction easily with alkynes to produce indenones **II**.[6c,14] These issues and challenges mentioned above reinforce the need for the development of a general, cost-efficient, and practical catalytic system to realize the construction of important isoquinolines.

Herein, we present a simple and cost-efficient nickel catalytic system that can efficiently catalyze the formation of substituted isoquinolines from 2-haloaldimines and alkynes. This nickel

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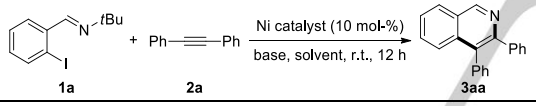
catalytic system employs air-stable and inexpensive Ni(dppe)Cl_2 as a precatalyst and Et_3N as a mild base. Moreover, we also showed that this nickel catalytic system is capable of achieving direct preparation of isoquinolines starting with readily available 2-halobenzaldehydes, *tert*-butyl amine, and alkynes in one step. These reactions proceed at room temperature with complete regioselectivity, and a variety of substituted isoquinolines can be readily obtained in high yields (Scheme 1d).

Results and Discussion

We began our investigations by finding mild catalytic conditions for the annulation of 2-iodobenzaldimine **1a** and 1,2-diphenylethyne **2a**. We first surveyed various Ni(II) salts as precatalysts in the presence of Cs_2CO_3 as base in CH_3CN at room temperature for 12 h. Unfortunately, the isoquinoline **3aa** was not formed in the presence of $NiCl_2$, Ni(acac)$_2$, $Ni(NO_3)_2{\cdot}6H_2O$, Ni(OTf)$_2$, or $Ni(OAc)_2{\cdot}4H_2O$ (Table 1, entry 1). As for other nickel-catalyzed coupling reactions,[8-10] we anticipated that ligands would play a key role for success. Thus, the influence of ligands on this annulation reaction was next examined. Reactions conducted in the presence of some nickel complexes with phosphine ligands, including Ni(dppe)Cl_2, Ni(dppp)Cl_2, Ni(dppf)Cl_2, and Ni(PPh_3)Cl_2 did not afford **3aa**. Exemplary, the result obtained with Ni(dppe)Cl_2 is depicted in Table 1 (entry 2; for full list of results, see the Supporting Information). Intriguingly, upon switching to Na_2CO_3 as base, **3aa** was obtained in 44% yield (Table 1, entry 3). Encouraged by this result, we surveyed a range of bases. Some bases, such as KO*t*Bu, DBU, 2,6-lutidine, and DABCO were shown to be ineffective for this transformation (Table 1, entries 4-7). *i*PrNEt resulted in a low yield due to the incomplete conversion of **1a** (Table 1, entry 8). Surprisingly, the greatest improvement came from Et_3N, which gave **3aa** in 91% yield (Table 1, entry 9). With Et_3N as base, other nickel(II) sources, such as Ni(dppf)Cl_2, Ni(dppp)Cl_2, and Ni(PPh_3)Cl_2, provided poorer results (Table 1, entries 10-12). The annulation reaction did not proceed in the absence of ligand (Table 1, entry 13). Solvent screening showed that CH_3CN was optimal (Table 1, entries 14-20). Notably, decreasing the Ni(dppe)Cl_2 loading to 5 mol-% still provided **3aa** in good yield (Table 1, entry 21). However, no product was observed in the absence of the nickel catalyst (Table 1, entries 22 and 23).

Table 1. Optimization of reaction conditions.[a]

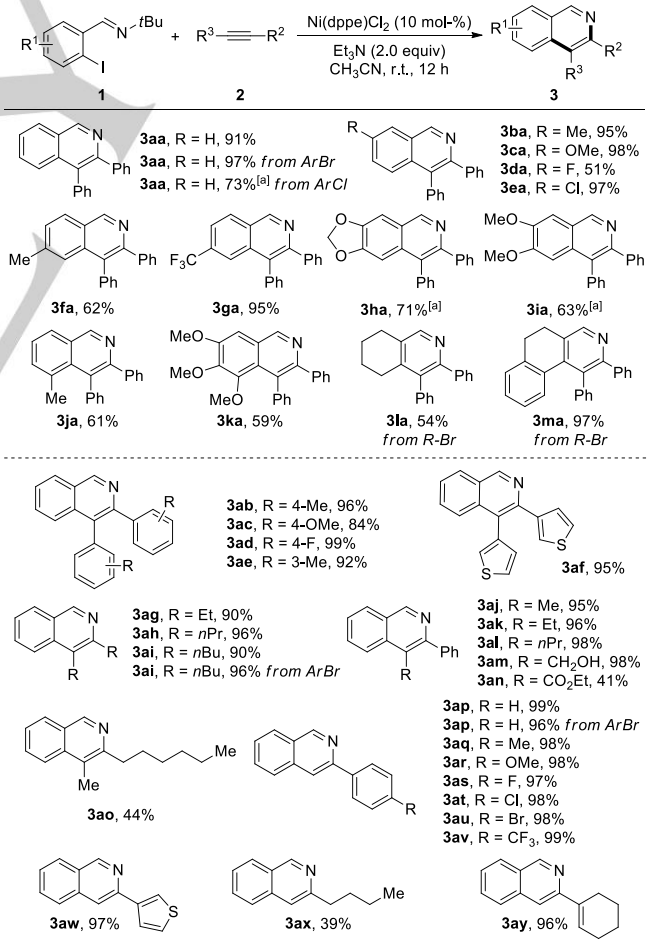


1a 2a 3aa

Entry	Catalyst	Base	Solvent	Yield[b] [%]
1[c]	NiX_2	Cs_2CO_3	CH_3CN	0
2	Ni(dppe)Cl_2	Cs_2CO_3	CH_3CN	0
3	Ni(dppe)Cl_2	Na_2CO_3	CH_3CN	44
4	Ni(dppe)Cl_2	KO*t*Bu	CH_3CN	0
5	Ni(dppe)Cl_2	DBU	CH_3CN	0
6	Ni(dppe)Cl_2	2,6-lutidine	CH_3CN	0
7	Ni(dppe)Cl_2	DABCO	CH_3CN	0
8	Ni(dppe)Cl_2	*i*PrNEt	CH_3CN	20
9	Ni(dppe)Cl_2	Et_3N	CH_3CN	91
10	Ni(dppf)Cl_2	Et_3N	CH_3CN	10
11	Ni(dppp)Cl_2	Et_3N	CH_3CN	44
12	Ni(PPh_3)Cl_2	Et_3N	CH_3CN	trace
13[c]	NiX_2	Et_3N	CH_3CN	0
14	Ni(dppe)Cl_2	Et_3N	THF	trace
15	Ni(dppe)Cl_2	Et_3N	DCE	trace
16	Ni(dppe)Cl_2	Et_3N	DMSO	trace
17	Ni(dppe)Cl_2	Et_3N	DMF	trace
18	Ni(dppe)Cl_2	Et_3N	MeOH	trace
19	Ni(dppe)Cl_2	Et_3N	EtOAc	0
20	Ni(dppe)Cl_2	Et_3N	toluene	0
21[d]	Ni(dppe)Cl_2	Et_3N	CH_3CN	84
22	dppe	Et_3N	CH_3CN	0
23	none	Et_3N	CH_3CN	0

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (10 mol-%), and base (0.4 mmol) in solvent (2.0 mL) at r.t. under N_2 for 12 h. [b] Isolated yields. [c] Using $NiCl_2$, Ni(acac)$_2$, $Ni(NO_3)_2{\cdot}6H_2O$, Ni(OTf)$_2$, or $Ni(OAc)_2{\cdot}4H_2O$ as a precatalyst. [d] Using 5 mol-% of Ni(dppe)Cl_2. dppe = 1,2-bis(diphenylphosphino)ethane, dppf = 1,1'-bis(diphenylphosphino)ferrocene, dppp = 1,3-bis(diphenylphosphino)propane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DABCO = 1,4-diazabicyclo[2.2.2]octane.

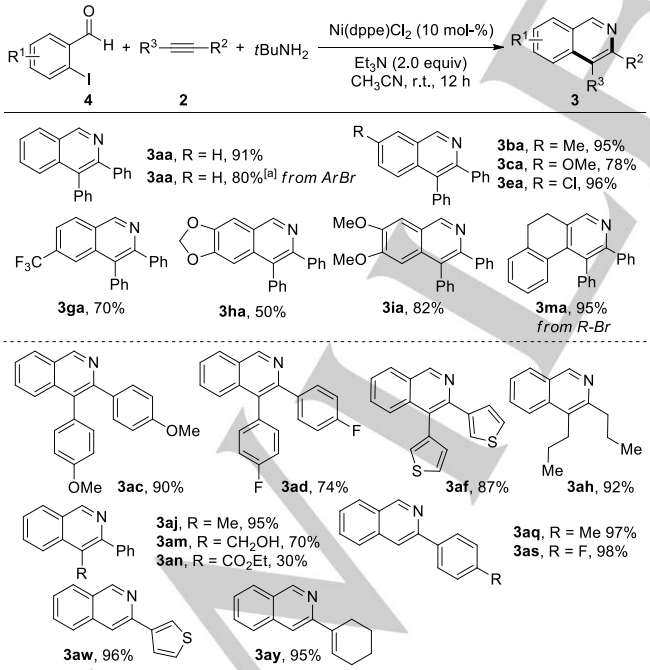
With the optimal conditions established, we then explored the scope of this nickel-catalyzed annulation reaction. As shown in Scheme 2, the reaction tolerates various electron-donating and electron-withdrawing substituents at the 4- or 5-positions of 2-iodobenzaldimines, and the corresponding products **3ba**-**ia** were obtained in moderate to excellent yields. Substrates with *ortho* substituents also gave good yields (see **3ja** and **3ka**). Besides 2-



Scheme 2. Scope of the nickel-catalyzed annulation reaction of 2-haloaldimines with alkynes. Reaction conditions: see entry 9, Table 1. Yields of isolated products are given. [a] The reaction was conducted for 24 h.

iodobenzaldimines, the corresponding bromo species exhibited excellent reactivity. Moreover, the corresponding chloro species reacted smoothly with **2a** to form **3aa** in 73% yield, albeit a much longer reaction time for 24 h. It is noteworthy that the current methodology can be applied to the construction of pyridine derivatives. For example, aldimines **1l** and **1m** were successfully converted to the desired products **3la** and **3ma** in moderate to excellent yields.

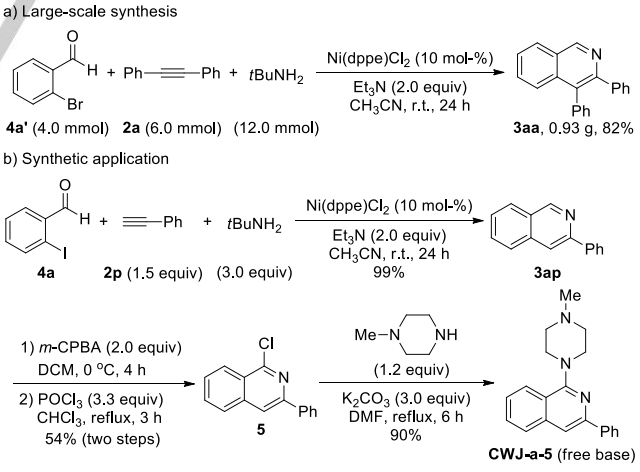
Next, the scope of alkyne coupling partners was investigated (Scheme 2). Symmetrical diaryl-substituted alkynes bearing electron-donating or electron-withdrawing substituents were readily converted in high yields to the corresponding products **3ab**-**ae**. An internal alkyne with a heterocycle such as thiophene afforded the product **3af** in 95% yield. Moreover, symmetrical dialkyl-substituted alkynes are also compatible with this protocol, leading to the products **3ag**-**ai** in excellent yields. To investigate the regioselectivity of this reaction, we studied unsymmetrical alkynes. The regiochemistry of these products was determined by comparing their NMR spectral data with those reported or by NOE experiments (see the Supporting Information). Unsymmetrical phenyl-substituted alkynes **2j**-**n** reacted under optimized conditions with complete regioselectivity to **3aj**-**an** in up to 98% yield. The phenyl group in these products is placed at the C3 position of the isoquinoline products. For unsymmetrical dialkyl-substituted alkyne **1o**, only product **3ao** with the larger substituent attached to the carbon adjacent to the nitrogen atom was obtained. Intriguingly, the insertion of terminal alkynes occurs regioselectivity with the substituents (e.g., aryl, heteoaryl, alkyl, and alkenyl group) being installed at the C3 position of the products (see **3ap**-**ay**). The low yields for **3ao** and **3ax** were due to the incomplete conversions of substrates.



Scheme 3. Scope of the nickel-catalyzed one-pot three-component assembly of isoquinolines. Reaction conditions: **4** (0.2 mmol), **2** (0.3 mmol), *t*BuNH$_2$ (0.6 mmol), Ni(dppe)Cl$_2$ (10 mol-%), and Et$_3$N (0.4 mmol) in CH$_3$CN (2.0 mL) at r.t. under N$_2$ for 12 h. Yields of isolated products are given. [a] The reaction was conducted for 24 h.

From a practical viewpoint, one-pot three-component direct synthesis of isoquinolines starting with readily available 2-halobenzaldehydes, *tert*-butyl amine, and alkynes is highly desirable. Next, we turned out attention to three-component assembly of isoquinolines (Scheme 3). Gratifyingly, under this nickel catalytic system, both 2-iodobenzaldehyde and 2-bromobenzaldehyde reacted readily with *tert*-butyl amine and 1,2-diphenylethyne **2a** to give the targeted product **3aa** in high yields. However, when 2-chlorobenzaldehyde was used as substrate, only traces of **3aa** were obtained. 2-Iodobenzaldehydes carrying different substituents consistently provided the expected products in good to excellent yields regardless of their electronic properties (see **3ba**-**ia**). Furthermore, three-component assembly of pyridine derivative is also proved to be viable (see **3ma**). Both internal alkynes and terminal alkynes underwent this transformation smoothly to give the desired products **3ac**-**ay** in moderate to excellent yields. For unsymmetrical alkynes, products are all formed as the exclusive regioisomers (see **3aj**-**ay**). In all cases, byproducts **I** and **II** were not observed.

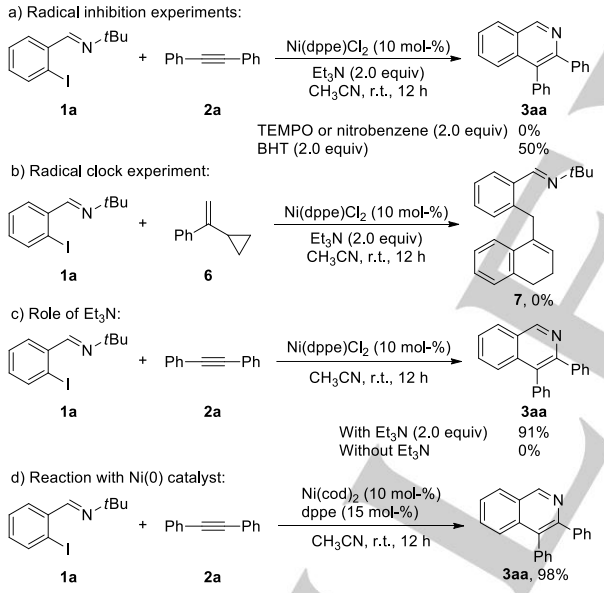
To show the practical usefulness of this method, we carried out a preparative scale reaction of **4a'** with **2a** and *tert*-butyl amine to produce **3aa** in 82% yield (Scheme 4a). Moreover, the utility of the current methodology is further demonstrated by applying it toward the total synthesis of CWJ-a-5 (free base), which was the representative compound identified as a topoisomerase 1 inhibitor.[15] In the key step, 3-phenylisoquinoline **3ap** could be easily prepared in 99% yield from commercially available 2-iodobenzaldehyde **4a**, ethynylbenzene **2p**, and *tert*-butyl amine, which was converted to 1-chloro-3-phenylisoquinoline **5** by *N*-oxidation and sequential chlorination. Amination of **5** with 1-methylpiperazine delivered CWJ-a-5 (free base) in total yield of 48% (Scheme 4b).



Scheme 4. Large-scale synthesis and synthetic application.

Several experiments were conducted to shed light on the mechanism of this transformation. We found that the reaction was completely inhibited by the addition of TEMPO (radical scavenger) or nitrobenzene (electron acceptor). The addition of BHT resulted in a sharp decrease in the yield (Scheme 5a). These observations indicate that single electron transfer processes might come into play. Next, we conducted a radical

clock experiment. Starting with olefin **6** containing a radical clock cyclopropane moiety, no ring-opening product **7** was obtained (Scheme 5b). Meanwhile, radical trapping experiment with 1,1-diphenylethylene as the radical trapper on **1a** did not give radical adduct (for details see the Supporting Information). These results imply that aryl radicals are not likely involved in the current reaction. Moreover, we found that this reaction did not work in the absence of Et_3N, thus indicating that Et_3N is key for a successful outcome (Scheme 5c). When the reaction was initiated with a catalytic amount of $Ni(cod)_2$ (cod = 1,5-cyclooctadiene) and dppe, **3aa** was obtained in 98% yield, thus suggesting that Ni(0) may be the active catalyst in the current transformation (Scheme 5d). Based on these experimental observations and previous reports,[6,11] we believe that the reaction is triggered by an *in situ* reduction of Ni(II) to the active Ni(0) catalyst with the aid of Et_3N[16] upon SET processes, followed by oxidative addition into the corresponding C-X bond. Subsequently, coordinative insertion of alkyne, followed by reductive elimination would produce the corresponding *tert*-butylcarbolinium salt with concomitant regeneration of the active Ni(0) catalyst. Finally, the *tert*-butyl group on the *tert*-butylcarbolinium salt was removed by the attack of halide ion generated during the reaction process to give the expected product.



Scheme 5. Mechanistic studies.

Conclusions

In summary, we have described a highly efficient, simple, and mild nickel-catalyzed annulation reaction of 2-haloaldimines with alkynes to prepare 3,4-disubstituted and 3-substituted isoquinolines in high yields. The air-stable and inexpensive $Ni(dppe)Cl_2$ was employed as a precatalyst, and we discovered that Et_3N play an important role for obtaining high yields. Importantly, we also showed that this simple but robust nickel catalytic system is capable of achieving three-component assembly of isoquinolines in a single step starting with readily available starting materials. These reactions are characterized by a broad substrate scope, good functional group tolerance, easy scalability, operational simplicity, and complete regioselectivity. We expect that this simple and cost-efficient nickel catalytic system will provide a practical, operationally simple, and user-friendly tool for the construction of various important nitrogen heterocycles.

Experimental Section

General procedure for the synthesis of isoquinolines via nickel-catalyzed annulation reaction of 2-haloaldimines with alkynes: 2-Haloaldimine **1** (0.2 mmol, 1.0 equiv), alkyne **2** (0.3 mmol, 1.5 equiv), $Ni(dppe)Cl_2$ (0.02 mmol, 0.1 equiv), and Et_3N (0.4 mmol, 2.0 equiv) were placed in a dry 10 mL Schlenk tube under a nitrogen atmosphere. Dry CH_3CN (2.0 mL) was added with a syringe and the reaction mixture was stirred at room temperature for 12 h monitored with TLC. After completion of the reaction, it was transferred to a round-bottomed flask after dilution with CH_2Cl_2. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel to afford the product.

General procedure for the synthesis of isoquinolines via nickel-catalyzed one-pot three-component reaction of 2-halobenzaldehydes, alkynes, and *tert*-butyl amine: 2-Halobenzaldehyde **4** (0.2 mmol, 1.0 equiv), alkyne **2** (0.3 mmol, 1.5 equiv), $tBuNH_2$ (0.6 mmol, 3.0 equiv), $Ni(dppe)Cl_2$ (0.02 mmol, 0.1 equiv), and Et_3N (0.4 mmol, 2.0 equiv) were placed in a dry 10 mL Schlenk tube under a nitrogen atmosphere. Dry CH_3CN (2.0 mL) was added with a syringe and the reaction mixture was stirred at room temperature for 12 h monitored with TLC. After completion of the reaction, it was transferred to a round-bottomed flask after dilution with CH_2Cl_2. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel to afford the product.

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Keywords: alkynes • isoquinolines • annulation • nickel • regioselectivity

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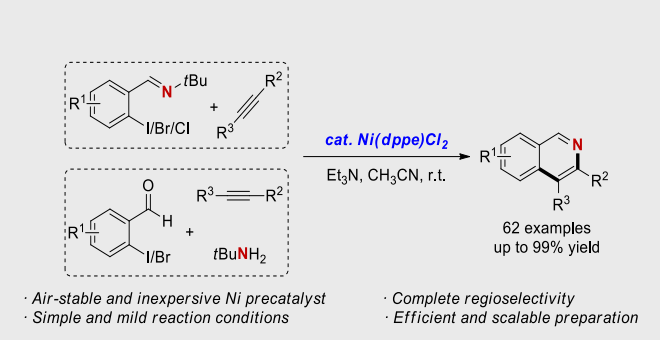

Nickel Catalysis

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Highly Regioselective Isoquinoline Synthesis via Nickel-Catalyzed Iminoannulation of Alkynes at Room Temperature

The air-stable and inexpensive Ni(dppe)Cl_2 along with Et_3N efficiently catalyzes the iminoannulation of alkynes at room temperature, allowing for the preparation of important 3,4-disubstituted and 3-substituted isoquinolines in high yields with complete regioselectivity. These annulation reactions feature a broad substrate scope, easy scalability, operational simplicity, and excellent practicality.