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Mild and efficient synthesis of indoles and isoquinolones *via* a nickel-catalyzed Larock-type heteroannulation reaction

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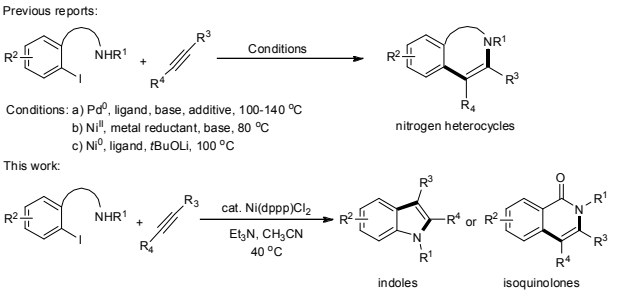
A simple and efficient approach for the preparation of substituted indoles and isoquinolones *via* a nickel-catalyzed Larock-type heteroannulation reaction is reported. This transformation employed air-stable and inexpensive $Ni(dppp)Cl_2$ as a precatalyst and Et_3N as a mild base. Moreover, the reaction occur efficiently under mild conditions, and a wide range of substituted indoles and isoquinolones bearing various functional groups are obtained in moderate to excellent yields.

Introduction

Nitrogen heterocycles, especially indoles and isoquinolones, are ubiquitous structural motifs present in many natural products, medicinally relevant compounds, and functional materials.[1,2] Because of the importance of these structures in medicinal chemistry and drug discovery the development of new and efficient synthetic methods for their preparation continues to be a very active field of research in organic chemistry.[3] Pioneering work by Larock demonstrated an efficient method for the preparation of substituted indoles *via* a palladium-catalyzed heteroannulation reaction of *ortho*-haloaniline derivatives with alkynes.[4] From then on, this methodology became an efficient synthetic platform for the preparation of substituted indoles. The development of approaches to couple *ortho*-haloaniline derivatives with alkynes has been studied extensively in the past decades, and recent progress has greatly expanded the scope of palladium-catalyzed heteroannulation reaction.[5] Apart from indoles, this kind of Larock-type heteroannulation reaction was also successfully applied to the construction of other nitrogen heterocycles (Scheme 1, a).[6] Nevertheless, in these processes, the use of expensive palladium catalyst is not cost-efficient for industrial use. Moreover, these approaches usually required specialized ancillary ligands, high temperatures, and/or an excess of the alkyne. In this regard, the development of a new strategy to produce nitrogen heterocycles using inexpensive metal catalytic systems and mild reaction conditions is still attractive.

Recently, tremendous interest has been attracted to develop cross-coupling reactions catalyzed by non-precious metals that



Scheme 1 Preparation of substituted nitrogen heterocycles *via* a transition-metal-catalyzed Larock-type heteroannulation reaction.

are typically catalyzed by precious metal catalysts.[7] In particular, the utilization of nickel catalysts in cross-coupling reactions has received considerable attention, because nickel is cheaper and significantly more abundant than its precious metal counterparts (e.g., palladium).[8] Notably, some studies on the preparation of substituted indoles and isoquinolones *via* a nickel-catalyzed Larock-type heteroannulation reaction have been reported. In 2010, Cheng and co-workers developed a nickel-catalyzed heteroannulation reaction of *ortho*-iodobenamides with alkynes to produce substituted isoquinolones (Scheme 1, b).[9] In 2011, Matsubara and co-workers described a similar protocol to construct substituted indoles (Scheme 1, c).[10] However, the former approach requires elevated temperatures and stoichiometric metal reductant (Zn), and the latter approach suffers from harsh reaction conditions and the use of strong base (*t*BuOLi) and air/moisture-sensitive Ni(0) catalyst.

With these limitations in mind, we sought to develop a general, mild, and practical approach for the synthesis of these useful nitrogen heterocycles. Along this line, we recently developed a simple and cost-efficient nickel catalytic system that can efficiently catalyze the formation of isoquinolines starting from 2-haloaldimines and alkynes under very mild

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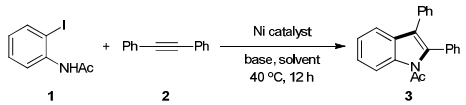
conditions.[11] This nickel catalytic system uses air-stable and inexpensive Ni(II) salt as a catalyst and Et_3N as a mild base. Encouraged by this work, we questioned whether indoles and isoquinolones can be obtained by a nickel-catalyzed Larock-type heteroannulation reaction using a simple Ni(II)/Et_3N system. Herein, we report a general and efficient nickel-catalyzed Larock-type heteroannulation reaction to prepare substituted indoles and isoquinolones under mild conditions (Scheme 1). The new Larock-type heteroannulation variant can be accomplished in moderate to excellent yields with a broad substrate scope. The reaction employs inexpensive and air/mosture-stable Ni(II) catalysts that are advantageous over Ni(0). Importantly, this protocol operates efficiently without the need for stoichiometric metal reductants and additional ligands.

Results and discussion

Our studies started with the indolization reaction of *N*-(2-iodophenyl)acetamide **1** and 1,2-diphenylethyne **2** in the presence of Ni(dppp)Cl_2 as a precatalyst and Et_3N as a base in CH_3CN at room temperature for 12 h. Fortunately, we found that the indole **3** was obtained in 75% yield (Table 1, entry 1). Upon slightly elevating reaction temperature, the yield of **3** could reach to 91% (Table 1, entry 2). Investigations were continued by screening different bases, including Cs_2CO_3, Na_2CO_3, K_2CO_3, DBU, 2,6-lutidine, DABCO, and *i*PrNEt, and we found that this transformation could work in the presence of Et_3N, DABCO or *i*PrNEt, and Et_3N performed best (Table 1, entries 3-9). With Et_3N as a base, several nickel sources were then examined. Some nickel complexes with phosphine ligands, such as Ni(dppe)Cl_2, Ni(dppf)Cl_2, and Ni(PPh_3)Cl_2, delivered **3** in 20-86% yields (Table 1, entries 10-12). However, the reaction did not occur in the absence of a ligand (Table 1, entry 13). Other solvents were also surveyed but consistently led to lower conversion (Table 1, entries 14-20). No **3** was observed when the reaction was carried out in the absence of a nickel catalyst, thus confirming the catalytic effect of nickel salt (Table 1, entry 21).

Table 1 Optimization of the reaction conditions[a]



1 2 3

Entry	Catalyst	Base	Solvent	Yield[b] (%)
1[c]	Ni(dppp)Cl_2	Et_3N	CH_3CN	75
2	Ni(dppp)Cl_2	Et_3N	CH_3CN	91
3	Ni(dppp)Cl_2	Cs_2CO_3	CH_3CN	0
4	Ni(dppp)Cl_2	Na_2CO_3	CH_3CN	trace
5	Ni(dppp)Cl_2	K_2CO_3	CH_3CN	0
6	Ni(dppp)Cl_2	DBU	CH_3CN	0
7	Ni(dppp)Cl_2	2,6-lutidine	CH_3CN	0
8	Ni(dppp)Cl_2	DABCO	CH_3CN	52
9	Ni(dppp)Cl_2	*i*PrNEt	CH_3CN	64
10	Ni(dppe)Cl_2	Et_3N	CH_3CN	20
11	Ni(dppf)Cl_2	Et_3N	CH_3CN	86
12	Ni(PPh_3)Cl_2	Et_3N	CH_3CN	30
13[d]	NiX_2	Et_3N	CH_3CN	0
14	Ni(dppp)Cl_2	Et_3N	THF	37
15	Ni(dppp)Cl_2	Et_3N	DCE	10
16	Ni(dppp)Cl_2	Et_3N	DMSO	10
17	Ni(dppp)Cl_2	Et_3N	DMF	13
18	Ni(dppp)Cl_2	Et_3N	EtOAc	trace
19	Ni(dppp)Cl_2	Et_3N	MeOH	trace
20	Ni(dppp)Cl_2	Et_3N	toluene	trace
21	none	Et_3N	CH_3CN	0

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), catalyst (10 mol%), and base (0.4 mmol) in solvent (2.0 mL) at 40 °C under N_2 for 12 h [b] Isolated yields. [c] The reaction was conducted at room temperature. [d] Using $NiCl_2$, $Ni(acac)_2$, $Ni(NO_3)_2$•$6H_2O$, $Ni(OTf)_2$, or $Ni(OAc)_2$•$4H_2O$ as a precatalyst. dppp = 1,3-bis(diphenylphosphino)propane, dppe = 1,2-bis(diphenylphosphino)ethane, dppf = 1,1'-bis(diphenylphosphino)ferrocene, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DABCO = 1,4-diazabicyclo[2.2.2]octane.

With optimized experimental conditions established, the scope of this indolization reaction was next explored. As showed in Table 2, various electron-donating and electron-withdrawing substituents at the 4- or 5-positions of the *ortho*-iodoacetanilide electrophile were well tolerated (**4**-**14**). Substitution at the 3-position of the aromatic ring resulted in moderate yield, probably for steric reasons (**15**). Moreover, naphthalene-derived substrate could also participate in the reaction to deliver the desired product **16**. Unfortunately, 2-iodo-*N*-methylaniline failed to afford the desired product. We then investigated the scope of alkyne coupling partners (Table 2). Symmetrical diaryl-substituted alkynes bearing electron-donating or electron-withdrawing substituents consistently afforded the desired indoles **17**-**21** in moderate to excellent yields. A thiophene-derived internal alkyne also produced the targeted product **22** in good yield. Besides diaryl-substituted alkynes, symmetrical dialkyl-substituted alkynes could also participate in our nickel-catalyzed Larock-type

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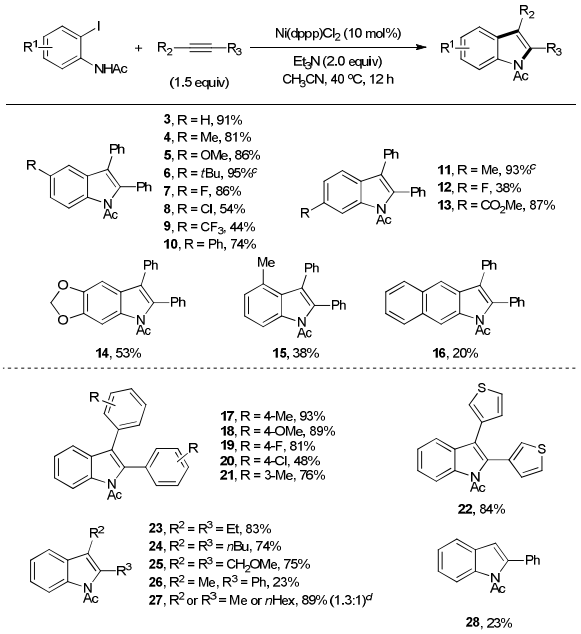
Table 2 Scope of the nickel-catalyzed Larock-type heteroannulation reaction of *ortho*-iodoacetanilides with alkynes[a,b]

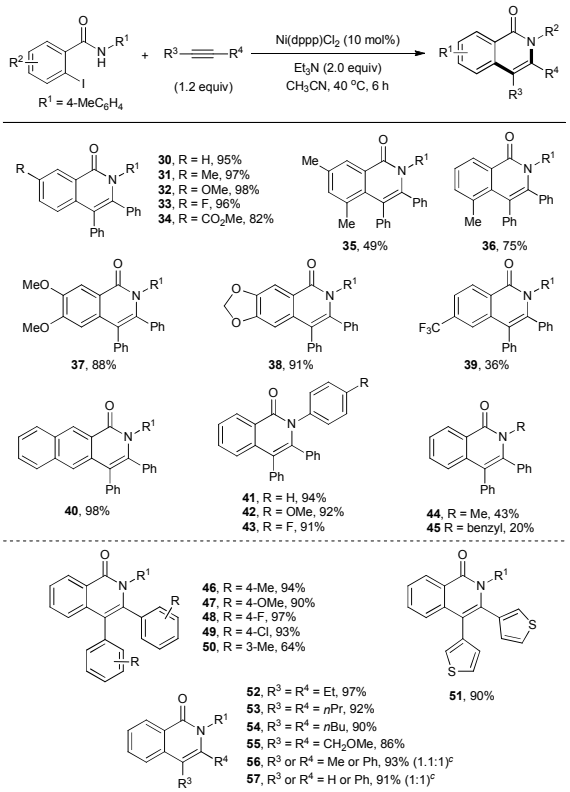


[a] Reactions were conducted on a 0.2 mmol scale following the reaction conditions given in Table 1. [b] Isolated yields. [c] The reaction was conducted in the presence of $Ni(dppe)Cl_2$ (15 mol%) for 24 h. [d] Ratio of regioisomers.

heteroannulation reaction to afford the corresponding products in good yields (**23**-**25**). In addition, we investigated unsymmetrical alkynes and found that prop-1-yn-1-ylbenzene and phenylacetylene reacted under optimized conditions with complete regioselectivity to **26** and **28**. The reaction conducted with unsymmetrical dialkyl-substituted alkyne provided the indole product **27** as a 1.3:1 regioisomeric mixture. The low yields for **12**, **15**, **16**, **26**, and **28** were due to the incomplete conversions of substrates.

To further probe the applicability of this protocol, we turned out attention to the synthesis of isoquinolones. To our delight, under the same reaction conditions, the reaction of 2-iodo-*N*-(*p*-tolyl)benzamide **29** with 1,2-diphenylethyne **2** afforded the desired isoquinolone **30** in 95% yield. Intriguingly, the yield of **30** was not affected when the reaction was conducted with a slight excess (1.2 equiv) of 1,2-diphenylethyne for 6 h. Under this reaction condition, we examined the scope of this transformation (Table 3). *Ortho*-iodobenzamides carrying various substituents are suitable substrates, leading to the corresponding isoquinolones **31**-**39** in good to excellent yields regardless of their electronic and steric properties. Naphthalene-derived substrate coupled readily with 1,2-diphenylethyne to give the isoquinolone **40**. Moreover, the phenyl protecting groups bearing electron-donating and electron-withdrawing substituents did not hamper the

Table 3 Scope of the nickel-catalyzed Larock-type heteroannulation reaction of *ortho*-iodobenzamides with alkynes[a,b]



[a] Reactions were conducted on a 0.2 mmol scale. [b] Isolated yields. [c] Ratio of regioisomers.

reactivity (**41**-**43**). However, substrates with a methyl or benzyl protecting group reacted sluggishly to give the products in low yields (**44** and **45**). Next, we examined the scope of alkyne coupling partners (Table 3). Various symmetrical diaryl-substituted alkynes and symmetrical dialkyl-substituted alkynes with different functional groups underwent this facile cyclization to deliver the corresponding isoquinolones in good to excellent yields (**46**-**55**). For unsymmetrical alkynes, we found that prop-1-yn-1-ylbenzene and phenylacetylene afforded the products as a 1:1 regioisomeric mixture (**56** and **57**). Compared to Cheng's protocol,[9] the advantages of the current method include: (1) simple and mild reaction conditions; (2) broad substrate scope; (3) a stoichiometric amount of metal reductant is not required. These advantages make this method very practical.

To show the practical usefulness of this method, the nickel-catalyzed Larock-type heteroannulation reaction has been performed on a gram scale. As shown in Scheme 2, the indole **3** and isoquinolone **29** were prepared in 82% yield (1.27g) and 90% yield (1.39 g), respectively.

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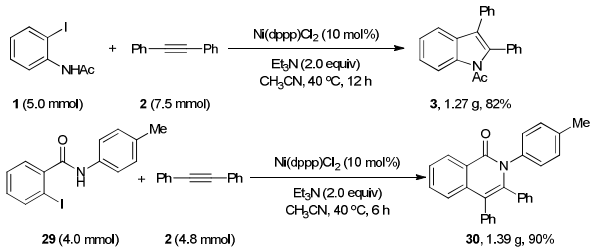
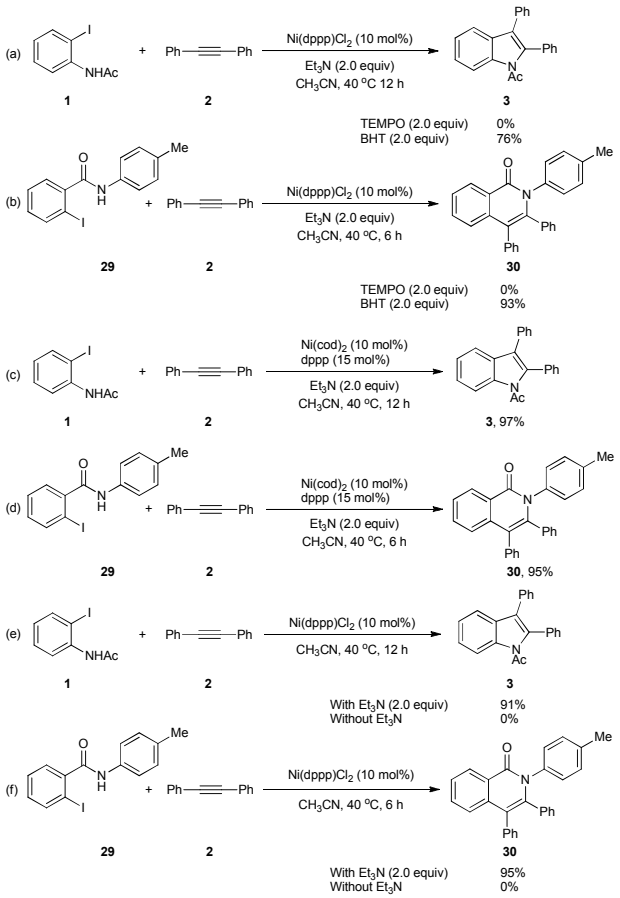


Scheme 2 Gram-scale reactions.

To gain further insight into the reaction mechanism, some control experiments were conducted. When TEMPO was added as a radical scavenger, the desired transformations were completely inhibited. However, when BHT was added into the reactions, the targeted products were formed in good yields, which is different from the result of TEMPO (Scheme 3a and 3b). We hypothesized that TEMPO on one hand acts as a radial scavenger, and on the other hand it might interact with Ni(II) to stop these reactions. To probe whether these reactions occur through a radical pathway, we performed radical clock experiments and radical trapping experiments, and found that no ring-opening products or radical adducts were formed (for details see the Supporting Information). These experimental results indicated that aryl radicals are not likely involved in these reactions. Next, these reactions were conducted in the presence of a catalytic amount of $Ni(cod)_2$ (cod = 1,5-cyclooctadiene) and dppp, and the desired products **3** and **30** were obtained in excellent yields, thus indicating that Ni(0) may be the active catalyst in the current reactions (Scheme 3c and 3d). Furthermore, we found that the reactions did not take place in the absence of Et_3N, thus suggesting that Et_3N is key for the heteroannulation reaction to occur (Scheme 5e and 5f). According to these experimental observations and previous reports,[4,5,9] we proposed a plausible reaction mechanism. The active Ni(0) catalyst is first formed by an *in situ* reduction of Ni(II) with the help of Et_3N,[11,12] followed by oxidative addition into the corresponding C-I bond to form aryl-Ni(II)I species. Subsequent deprotonation of the amide hydrogen by Et_3N gives the five-membered ring nickelacycle intermediate. Finally, coordinative insertion of alkyne, followed by reductive elimination delivers the product. This process allows the regeneration of the active Ni(0) catalyst.[13]



Scheme 3 Mechanistic studies.

Conclusions

In summary, we have presented a simple and mild nickel-catalyzed Larock-type heteroannulation reaction, in which the air-stable and inexpensive $Ni(dppp)Cl_2$ was used as a precatalyst and Et_3N as a mild base. Notably, neither stoichiometric metal reductant nor additional ligand is required in this process. This protocol provides an efficient methodology to access a wide range of substituted indoles and isoquinolones in moderate to excellent yields. These reactions are easy to carry out and amenable to gram-scale synthesis. Further studies on the mechanism and the synthetic applications are currently ongoing.

Experimental

General information

All manipulations were conducted with a standard *Schlenk* tube under a nitrogen atmosphere. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. *Ortho*-iodoacetanilides were prepared according to a reported method.[5c] *Ortho*-iodobenzamides were prepared according to a reported method.[9] Flash column chromatography was carried out on

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silica gel (200-300 mesh). Thin layer chromatography (TLC) was performed using silica gel 60 F_{254} plates. ^{1}H NMR spectra were recorded on a *Bruker AV-300* spectrometer at room temperature. Chemical shifts (in ppm) were referenced to tetramethylsilane (δ = 0 ppm) in $CDCl_3$ as an internal standard. ^{13}C NMR spectra were obtained by the same NMR spectrometer and were calibrated with $CDCl_3$ (δ = 77.00 ppm). Data for ^{1}H NMR are reported as follows: chemical shifts (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, br s = broad singlet), coupling constant (Hz) and integration. Data for ^{13}C NMR are reported in terms of chemical shift and multiplicity where appropriate. Mass spectra were performed on an *Aglient 6530 Q-TOF* for HRMS. The yields were determined on a *METTLER TOLEDO ME 104* balance (accuracy: 0.1 mg). Melting points (Mp) were determined on a SGW X-4B and are uncorrected.

General procedure for the synthesis of indoles *via* a nickel-catalyzed Larock-type heteroannulation reaction of *ortho*-iodoacetanilides with alkynes (GP1)

Ortho-iodoacetanilide (0.2 mmol, 1.0 equiv), alkyne (0.3 mmol, 1.5 equiv), Ni(dppp)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 40 °C 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 isoquinolones *via* a nickel-catalyzed Larock-type heteroannulation reaction of *ortho*-iodobenzamides with alkynes (GP2)

Ortho-iodobenzamide (0.20 mmol, 1.0 equiv), alkyne (0.24 mmol, 1.2 equiv), Ni(dppp)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 40 °C for 6 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.

Characterisation data for representative products

1-(2,3-Diphenyl-1*H*-indol-1-yl)ethanone (3)

White solid (56.7 mg, 91%). Mp: 130-132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.4 Hz, 1H), 7.56 (dd, *J* = 7.8, 0.6 Hz, 1H), 7.43-7.20 (m, 12H), 1.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 136.7, 134.9, 133.0, 132.9, 130.7, 130.0, 129.2, 128.6, 128.6, 128.2, 126.9, 125.5, 123.4, 123.3, 119.5, 116.2, 27.9; HRMS (ESI) calculated for $C_{22}H_{18}NO$ $[M+H]^+$ m/z 312.1383, found 312.1382.

3,4-Diphenyl-2-(*p*-tolyl)isoquinolin-1(2*H*)-one (30)

White solid (73.7 mg, 95%). Mp: 216-218 °C; ^{1}H NMR (300 MHz, CDCl3) δ 8.57 (d, *J* = 7.5 Hz, 1H), 7.58-7.47 (m, 2H), 7.26-7.12 (m, 6H), 6.99 (s, 4H), 6.89 (s, 5H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 162.7, 141.2, 137.6, 137.2, 136.8, 136.4, 134.9, 132.4, 131.6, 131.0, 129.2, 129.1, 128.2, 127.9, 127.1, 127.0, 126.8, 126.7, 125.5, 118.6, 21.0; HRMS (ESI) calculated for $C_{28}H_{22}NO$ $[M+H]^+$ m/z 388.1696, found 388.1704.

Acknowledgements

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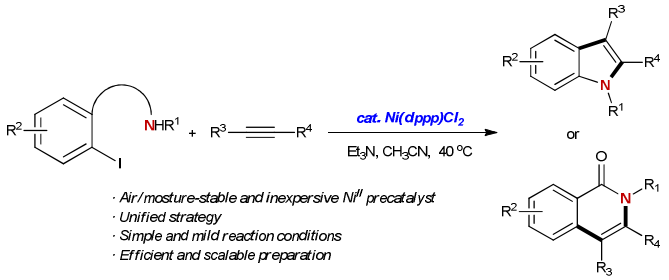
Mild and efficient synthesis of indoles and isoquinolones *via* a nickel-catalyzed Larock-type heteroannulation reaction



A simple and mild approach for the preparation of substituted indoles and isoquinolones *via* nickel-catalyzed Larock-type heteroannulation reaction is reported.