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Nickel-Catalyzed Mizoroki–Heck/Amination Cascade Reactions of *o*-Dihaloarenes with Allylamines: Synthesis of Indoles

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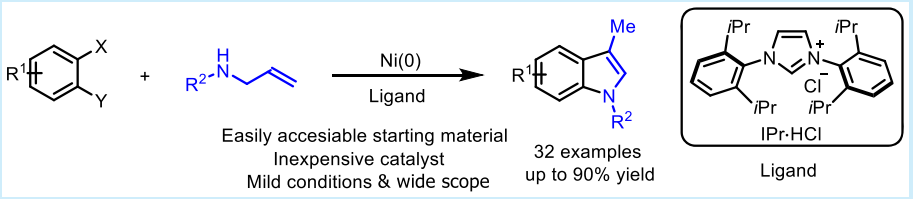

ABSTRACT: An efficient Mizoroki–Heck/amination cascade reaction of *o*-dihaloarenes with allylamines has been developed using nickel and IPr carbene ligand as catalyst. This protocol enables the synthesis of a broad range of substituted indoles by a cascade process, from readily available starting materials. Mechanistic studies suggest that the Mizoroki–Heck reaction occurred first under IPr-nickel catalysis.

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Mizoroki–Heck and amination reactions represent one of the most powerful and versatile tools in modern synthetic chemistry.[1] Traditionally, most of the Mizoroki–Heck and amination processes have focused on palladium complexes as catalysts.[2] However, a major limitation of palladium-catalyzed Mizoroki–Heck and amination reactions is the low reactivity of aryl chlorides.[3] Compared to bromides, iodides, and triflates, the use of aryl chlorides would be more appealing due to the low cost and the wide chemical diversity.[4] Additionally, both the palladium metal and the ligands used for the Mizoroki–Heck and amination reactions are costly. Therefore, considerable research effort has been paid recently to explore cheaper and more available metals and ligands as catalysts.

Cascade reactions have been widely used for the rapid construction of complex molecular architectures from simple building blocks.[5] In particular, palladium-catalyzed cascade processes for the synthesis of nitrogen-containing heterocycles have undergone rapid development in recent years.[6] For instance, in 2007, Barluenga et al. reported a palladium-catalyzed cascade reaction of *o*-dihaloarenes with imines to afford diverse indoles (Scheme 1a).[7] Subsquently, the group of Ackermann disclosed a palladium-catalyzed cascade reaction of *o*-dihaloarenes with anilines to access valuable annulated heterocycles (Scheme 1b).[8] Moreover, an amination/Mizoroki–Heck sequence of *o*-dihaloarenes with allylamines for the construction of indole skeleton with palladium as catalyst was developed by Jørgensen and co-workers (Scheme 1c). However, with 1,2-dichlorobenzene substrate, the palladium catalytic system was not effective.[9a]

In contrast to palladium catalysts, the major advantages of nickel-based catalysts are their much lower cost and increased reactivity toward readily available unactivated aryl chlorides.[3,10] Recent studies have demonstrated that the respective utility of nickel-catalyzed Mizoroki–Heck and amination reactions in the activation of aryl halides and pseudohalides.[11] However, the direct application of nickel catalysts in the Mizoroki–Heck/amination cascade reactions has never been reported to date. Our laboratory has recently developed an intramolecular Mizoroki–Heck reaction of imines with nickel and DPEphos ligand as catalyst.[12] In continuation of our studies, we envisioned a Mizoroki–Heck/amination cascade reaction would provide straightforward synthesis of indoles, common motifs in natural products and pharmaceuticals.[13] The initial Mizoroki–Heck reaction would form the corresponding intermediate **A**, which could be cyclized by intramolecular amination giving the final diversely substituted indoles (Scheme 1d).

We initially examined the Mizoroki–Heck/amination cascade reaction of 1,2-dichlorobenzene **1a** with *N*-allylaniline **2a** through the use of the combination of $Ni(cod)_2$ (cod = 1,5-cyclooctadiene) and nitrogen-containing bidentate ligands in toluene at 80 °C for 14 h (Table 1).

Trace amounts of the desired product **3a** was obtained when the nitrogen-containing bidentate and phosphine ligands were used (entries 1–5). To our delight, the use of $Ni(cod)_2$ and carbene ligands significantly improved the yield (entries 6 and 7). It is notable that a side product was formed in the cascade

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Scheme 1. Strategy for the Transition-Metal-Catalyzed Cascade Reactions of *o*-Dihaloarenes

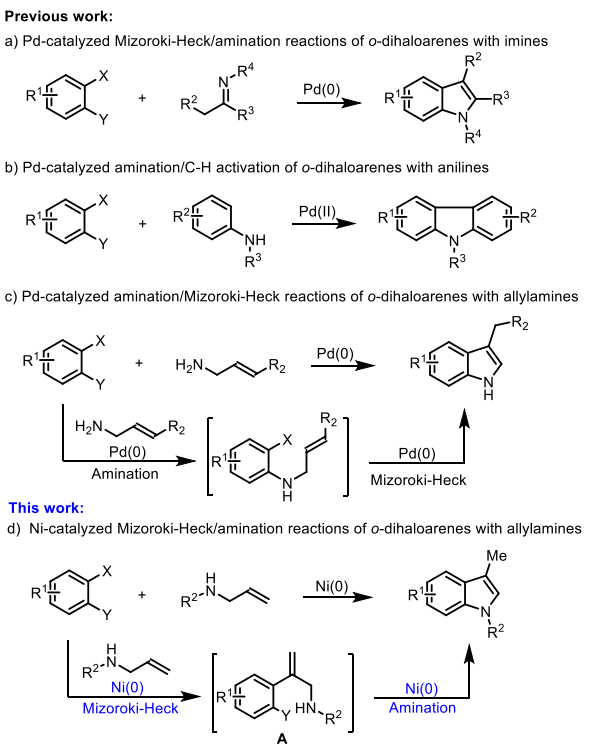
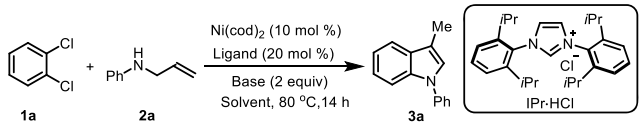


Table 1. Optimization of the Nickel-Catalyzed Mizoroki–Heck/Amination Cascade Reactions[a]



entry	ligand	base	solvent	yield[b] (%)
1	bipyridine	NaO*t*Bu	toluene	<5
2	dbbpy	NaO*t*Bu	toluene	<5
3	PPh_3	NaO*t*Bu	toluene	<5
4	dppe	NaO*t*Bu	toluene	<5
5	dppf	NaO*t*Bu	toluene	10
6	IPr·HCl	NaO*t*Bu	toluene	56
7	IMes·HCl	NaO*t*Bu	toluene	30
8	IPr·HCl	LiO*t*Bu	toluene	<5
9	IPr·HCl	KO*t*Bu	toluene	24
10	IPr·HCl	NaO*t*Bu	dioxane	56
11	IPr·HCl	NaO*t*Bu	benzene	32
12	IPr·HCl	NaO*t*Bu	*m*-xylene	45
13	IPr·HCl	NaO*t*Bu	mesitylene	69
14[c]	IPr·HCl	NaO*t*Bu	mesitylene	<5
15[d]	IPr·HCl	NaO*t*Bu	mesitylene	36
16[e]	IPr·HCl	NaO*t*Bu	mesitylene	82

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), $Ni(cod)_2$ (0.02 mmol), ligand (0.04 mmol), base (0.4 mmol), in 1 mL of solvent at 80 °C for 16 h. [b]Isolated yield. [c]Reaction performed at 60 °C. [d]Reaction performed at 100 °C. [e]24 h reaction time. dbbpy = 4,4′-Di*tert*-butyl-2,2′-bipyridine.

reaction, which was proved to be the Mizoroki–Heck reaction product by further analytical characterization (see below for further discussion). Subsequently, other bases were also investigated without any improvement of reaction efficiency (entries 8 and 9). Solvent screening showed that mesitylene was optimal (entries 10–13). A lower conversion was observed when reactions were performed at either 60 or 100 °C (entries 14 and 15). Finally, the optimal reaction conditions were finalized with a combination of $Ni(cod)_2$ and IPr carbene ligand as catalyst in mesitylene at 80 °C for 24 h (entry 16).

With the optimized reaction conditions in hand, we examined the scope of *o*-dihaloarenes **1** with *N*-allylaniline **2a** (Table 2). Versatile substituents are compatible with the reactions. With inexpensive 1,2-dichlorobenzene, the reaction gave rise to the desired indole efficiently. Notably, this method is easily scalable, and product **3a** was obtained with a comparable yield when the reaction was run on a 1 mmol scale (entry 1). The approach was found to be applicable not only to less reactive chlorides but also to bromides (entries 2 and 3). Both electron-donating and electron-withdrawing substituents on the phenyl ring of *o*-dihaloarenes **1** were well tolerated, leading to the corresponding products in moderate to good yields (entries 4–13). Notably, the oxidative addition reaction occurred first at the position of the more reactive halogen and gave the products with excellent regioselectivity (**3c**, **3d**, and **3h**). Remarkably, 7-substituted 3-methyl benzoindoles (**3b**, **3e**, **3g**, and **3i**) could be synthesized with total regioselectivity, and 5- and 6-substituted regioisomeric 3-methyl benzoindoles (**3c**, **3c′**, **3h**, **3h′**) could also be formed in this cascade reaction with moderate regioselectivity, probably due to the stereoelectronic effects. Interestingly, the reaction of 4-fluoro-1,2-dichlorobenzene **1k** with benzenamine **2a** led to the major regioisomeric 5-substituted 3-methyl benzoindole (entry 11).

Next, we explored the scope of the cascade reaction with respect to variation of allylamines **2** (Table 3). Diverse aryl substituents (R^2) of allylamines **2** were well tolerated, leading to the corresponding products in moderate to high yields (**3j–t**). Substitution with 1-naphthyl on the nitrogen position also proceeded well in this reaction (**3u**). In addition, employing a substrate bearing a heteroaromatic ring such as thiophene produced the thiophenyl-substituted 3-methylindole (**3v**). Allylamines with aliphatic substitutions were applicable in the reaction (**3w**, **3x**). Remarkably, an allylamine with a *tert*-butyl group smoothly afforded the desired product, which is difficult to be achieved by other methods.[14] However, attempts to generate 3-ethyl and benzyl benzoindoles were not successful (**3y**, **3z**). Tetrahydroquinoline product (**4**) could also be formed with the homoallylic amine **2s** as the substrate in a good yield.

To further probe the scope and utility of the strategy, a concise synthesis of the prophylactic drug **6** was performed. As depicted in Scheme 2, the desired cascade reaction product **5** could be obtained with excellent regioselectivity, which could be transformed to a prophylactic drug for diseases mediated by sodium channels[15] with high yield.

A series of control experiments were performed to study the mechanism of this cascade reaction. First, when chlorobenzene **7** was engaged in the reaction with **2a**, only Mizoroki–Heck product **8** was obtained (Scheme 3a). In addition, when the reaction between **1a** and **2a** was conducted with a ratio of 1:1, trace amounts of the side product **9** were obtained (Scheme 3b), indicating the Mizoroki–Heck reaction occurred first in the cascade reaction.

In summary, we have developed a nickel-catalyzed Mizoroki–Heck/amination cascade reaction of *o*-dihaloarenes with allylamines to synthesize indoles from readily available

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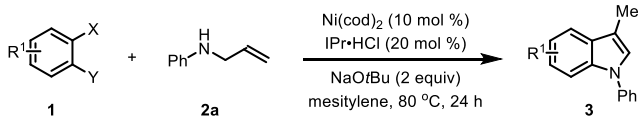
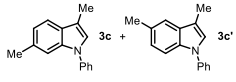
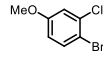
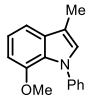
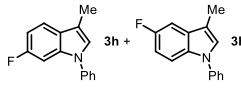
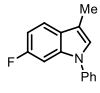
Table 2. Scope of the *o*-Dihaloarenes[a]



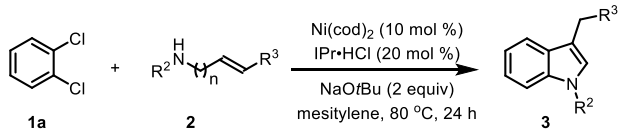
1 2a 3

Entry	Dihaloarene **1**	Product **3**	Yield (%)[b]
1	 **1a**	 **3a**	82(73)[c]
2	 **1b**	 **3a**	71
3	 **1c**	 **3a**	60
4	 **1d**	 **3b**	52
5	 **1e**	 **3c** + **3c'**	63[d]
6	 **1f**	 **3c**	61
7	 **1g**	 **3d**	53
8	 **1h**	 **3e**	61
9	 **1i**	 **3f**	72
10	 **1j**	 **3g**	60
11	 **1k**	 **3h** + **3h'**	60[e]
12	 **1l**	 **3h**	62
13	 **1m**	 **3i**	41

[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.2 mmol), Ni(cod)$_2$ (0.02 mmol), IPr·HCl (0.04 mmol), NaO*t*Bu (0.4 mmol), in 1 mL of mesitylene at 80 °C for 24 h. [b]Isolated yield. [c]The values in parentheses refer to the isolated yield of 1 mmol scale. [d]Compounds **3c** and **3c′** were isolated as an inseparable mixture of regioisomers (**3c**/**3c′** = 2:1). [e]Compounds **3h** and **3h′** were isolated as an inseparable mixture of regioisomers (**3h**/**3h′** = 1:6).

starting material. Mechanistic studies demonstrate that the Mizoroki−Heck reaction occurred first. We believe that these findings will aid the deeper mechanistic understanding and development of this straightforward method to access indoles.

Table 3. Scope of the Allylamines[a]

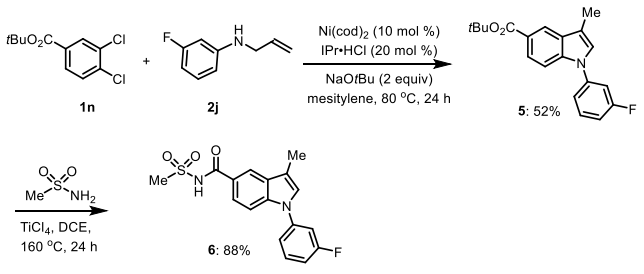


1a **2** **3**

Entry	Allylamine **2**	n	R^3	Product **3**	Yield (%)[b]
1	**2b** R^2 = 3-MeC$_6$H$_4$,	0	H	**3j**	72
2	**2c** R^2 = 4-MeC$_6$H$_4$,	0	H	**3k**	81
3	**2d** R^2 = 2, 4, 6-(Me)$_3$-C$_6$H$_2$,	0	H	**3l**	62
4	**2e** R^2 = 2-*i*PrC$_6$H$_4$,	0	H	**3m**	90
5	**2f** R^2 = 2,6-(*i*Pr)$_2$-C$_6$H$_3$,	0	H	**3n**	81
6	**2g** R^2 = 2-*t*BuC$_6$H$_4$,	0	H	**3o**	74
7	**2h** R^2 = 3-OMeC$_6$H$_4$,	0	H	**3p**	55
8	**2i** R^2 = 4-OMeC$_6$H$_4$,	0	H	**3q**	76
9	**2j** R^2 = 3-FC$_6$H$_4$,	0	H	**3r**	69
10	**2k** R^2 = 4-FC$_6$H$_4$,	0	H	**3s**	82
11	**2l** R^2 = 3-CF$_3$C$_6$H$_4$,	0	H	**3t**	55
12	**2m** R^2 = 1-naphthyl	0	H	**3u**	66
13	**2n** R^2 = 3-thiophenyl	0	H	**3v**	40
14	**2o** R^2 = Bn	0	H	**3w**	50
15	**2p** R^2 = *t*Bu	0	H	**3x**	40
16	**2q** R^2 = Ph	0	Me	**3y**	<5
17	**2r** R^2 = Ph	0	Ph	**3z**	<5
18	**2s** R^2 = Ph	1	H	 **4**	72

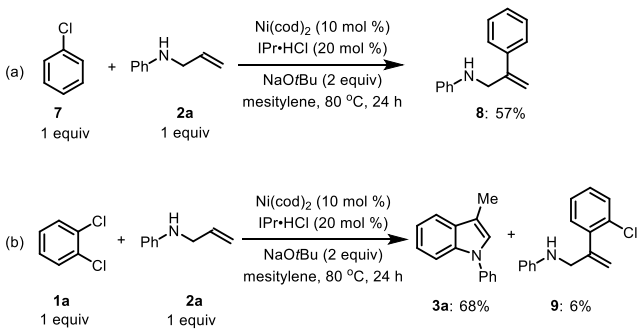
[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.2 mmol), Ni(cod)$_2$ (0.02 mmol), IPr·HCl (0.04 mmol), NaO*t*Bu (0.4 mmol), in 1 mL of mesitylene at 80 °C for 24 h. [b]Isolated yield.

Scheme 2. Derivatization of the Product 5



1n **2j**

Scheme 3. Control Experiments



7 1 equiv 2a 1 equiv

1a 1 equiv 2a 1 equiv

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Further exploration of the current method for other cascade reactions is underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02909.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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