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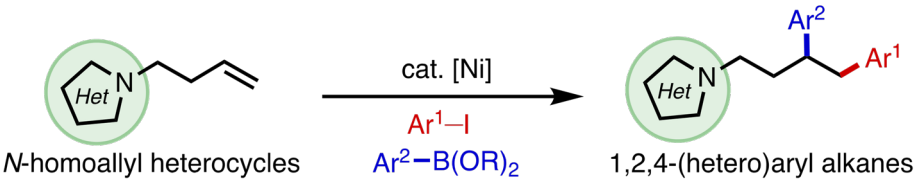

N-homoallyl heterocycles

1,2,4-(hetero)aryl alkanes

• heterocycle-directed • mild conditions • regioselective

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Ni-Catalyzed 1,2-Diarylation of Unactivated Alkenes Directed by Diverse Azaheterocycles

Yilin Cao[a], Zi-Qi Li[a], Keary M. Engle*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA, 92037, United State

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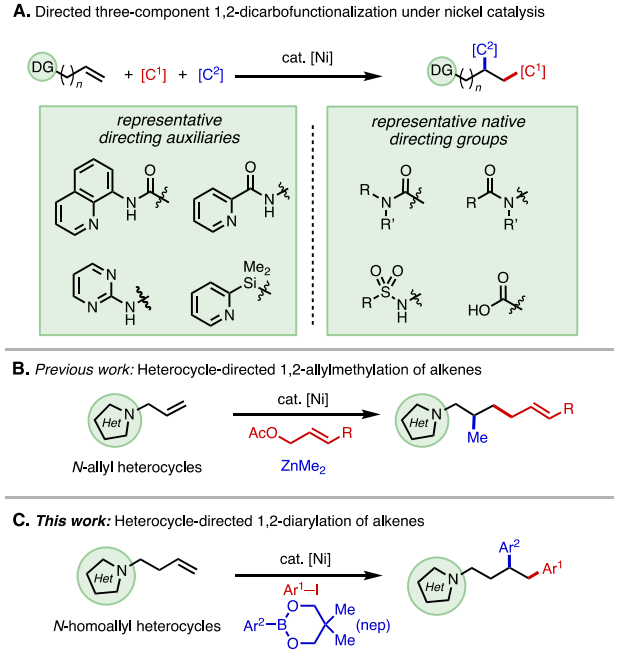
ABSTRACT

A nickel-catalyzed heterocycle-directed 1,2-diarylation of alkenes with aryl iodide electrophiles and arylboronic acid neopentyl ester nucleophiles is reported. A series of 1,2,4-tri(hetero)aryl products are prepared under mild conditions. A collection of azaheterocycle directing groups, including indazoles, pyrazoles, triazoles, and tetrazoles, enable the transformation, giving moderate to excellent yields. A large-scale reaction was performed to show the preparative utility of the method.

1. Introduction

During the past decade, nickel-catalyzed 1,2-dicarbofunctionalization of alkenes has come to the fore as a powerful tool to rapidly construct two adjacent C(sp^3)–C bonds [1]. Various directing groups are commonly employed to suppress β-H elimination, enhance reactivity, and control regio-, chemo-, and pathway selectivity of the catalytic process, including both removable auxiliaries and native functional groups (Scheme 1A). While directing auxiliaries, such as N,N-bidentate amides or N-monodentate imines, are uniquely enabling in many contexts [2-10], they generally require extra steps to install and remove [11], which compromises step- and atom-economy. Our group and others have developed three-component dicarbofunctionalization methodologies that rely only on native directing-groups, including simple amides, sulfonamides, carboxylic acids, and ketones [12-20]. Complementing these efforts, non-directed methods have also been developed through using tailored N-heterocyclic carbene ligands [21].

Scheme 1. Background and Current Work.



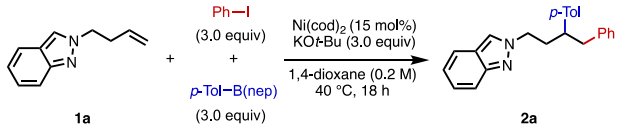
Nitrogen-containing heterocycles often appear in bioactive natural products and pharmaceuticals [22-23]. Our lab has previously reported azaheteocycle-directed regioselective 1,2-allylmethylation of alkenes with allyl electrophiles and alkyl nucleophiles [24] (Scheme 1B). Based on the importance of heterocycle-motifs in various molecules with useful functions, we envisioned that azaheterocycles, such as indazoles, pyrazoles, triazoles and tetrazoles, would be proficient monodentate directing groups for 1,2-dicarbofunctionalization of unactivated alkenes (Scheme 1C). If successful, the envisioned methodology would represent an intrinsically divergent means of accessing heteroarene-containing product libraries in drug discovery.

2. Results and Discussions

To initiate the study, we selected alkenyl indazole **1a** as our standard substrate with iodobenzene and *p*-tolylboronic acid neopentyl glycol ester (*p*-TolB(nep)) as coupling partners and $Ni(cod)_2$ as the pre-catalyst (Table 1). After extensive optimization, we were able to obtain the desired product in 78% yield by using 1,4-dioxane as solvent at 40 °C [25]. Inferior results were noted upon lowering the loading of the coupling partners or nickel catalyst (entry 3 and 4). In addition, other *tert*-butoxide salts, such as NaO*t*-Bu or LiO*t*-Bu, gave significantly diminished yields (entry 6 and 7). Use of $NiCl_2$ or $NiBr_2$ significantly reduced yield, and $Ni(acac)_2$ was found to be ineffective (entry 8 and 9). Ni(cod)(DMFU) (DMFU = dimethylfumarate) was examined as a precatalyst given its ability to promote 1,2-dicarbofunctionalization with other directing groups; however, in this case the presence of an electron-poor

olefin ligand did not increase the yield (entry 10)[26-27]. A possible explanation is that the lone pair of the Lewis basic N(sp^2) on the heterocycle coordinates sufficiently strong to prevent association of the DMFU ligand on-cycle. The 4-methylphenylboronic acid and the corresponding pinacol ester were low-yielding (entries 11 and 12). Running this conjunctive cross-coupling at room temperature (22 °C) gave a substantial drop in yield compared to the same time point at 40 °C (entry 13).

Table 1. Reaction Optimization.



Entry	Deviation From Standard Conditions	Yield (%)[a]
1	none	78 (68)
2	No $Ni(cod)_2$	n.d.
3	2.0 equiv of *p*-TolB(nep) and Ph–I instead of 3.0 equiv	38
4	10 mol% $Ni(cod)_2$	48
5	THF instead of 1,4 dioxane	58
6	NaO*t*-Bu instead of KO*t*-Bu	20
7	LiO*t*-Bu instead of KO*t*-Bu	2
8	$NiBr_2$, $NiCl_2$ instead of $Ni(cod)_2$	22
9	$Ni(acac)_2$ instead of $Ni(cod)_2$	trace
10	Ni(cod)(DMFU) instead of $Ni(cod)_2$	64
11	*p*-TolB$(OH)_2$ instead of *p*-TolB(nep)	n.d.
12	*p*-TolB(pin) instead of *p*-TolB(nep)	32
13	r.t. instead of 40 °C	10

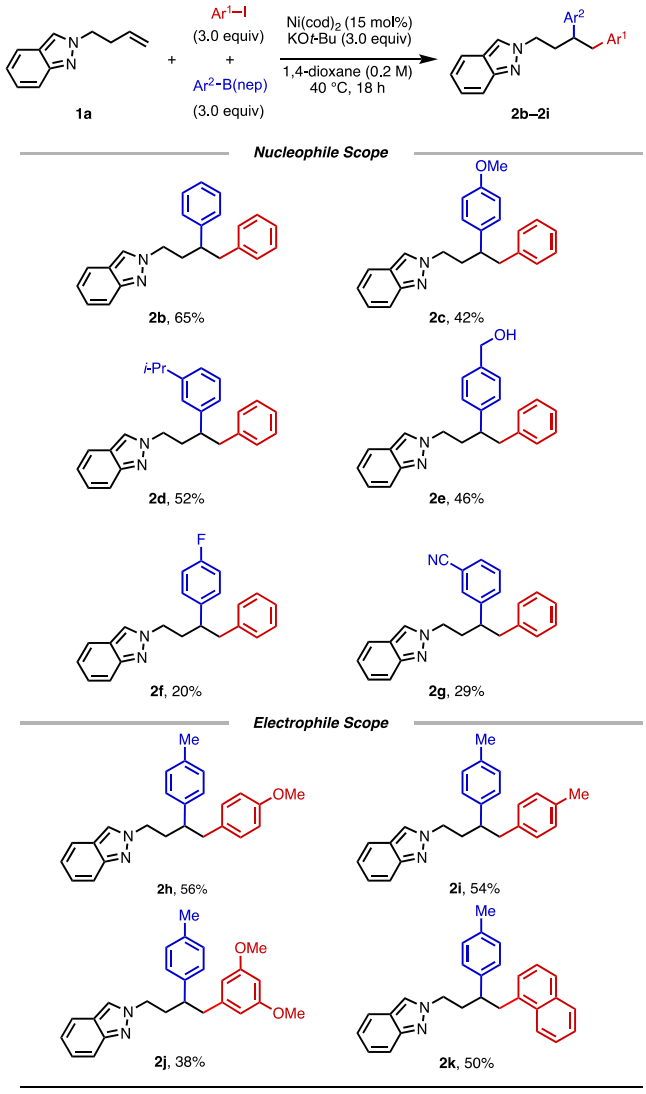
[a] Reactions performed on a 0.1 mmol scale. Percentages represent 1H NMR yields using CH_2Br_2 as internal standard; n.d. = not detected. Percentages in parentheses represent isolated yield. See Supporting Information for details regarding additional optimization tables.

With the optimal conditions identified, we next examined the substrate scope of the reaction (Table 2). Arylboronic ester nucleophiles bearing electron-donating or -withdrawing substituents in the *para*- and *meta*-position offered moderate to good yields (**2b–2g**) and excellent regioselectivity [25]. We were pleased to find that the potentially reactive hydroxyl group was well-tolerated in this reaction (**2e**). Aryl iodides with various electronic properties furnished the desired products in moderate to good yields with general trend of electron-donating groups providing higher product yields (**2f–2h**). Using the sterically demanding 1-iodonapthalene as electrophile gave the corresponding product in 50% yield (**2i**).

We next explored the scope of this method by testing alkenes with different five-membered azaheterocycles as directing groups (Table 3). *N*-Homoallyl benzo-fused diazoles and triazoles connected through either N1 or N2 provided the corresponding products in moderate yields (**3a**, **3c**). However, it is noted that varying the identity of the heterocyclic directing group did require reoptimization of base to achieve synthetically useful yields. For instance, 2-homoallyl-benzotriazole (**3b**), pyrazole (**3c**), and 1,2,3-triazole (**3e**) benefited from the use of NaO*t*-Bu as base, while 1,2,4-triazole (**3d**) and tetrazole (**3f**) offered a better yield when LiO*t*-Bu was used as base (see Supporting Information for details). We surmise that modifying the base serves to tune the transmetalation rate of the organoboron coupling partner to match the properties of the heterocycle-coordinated nickelacycle intermediate.

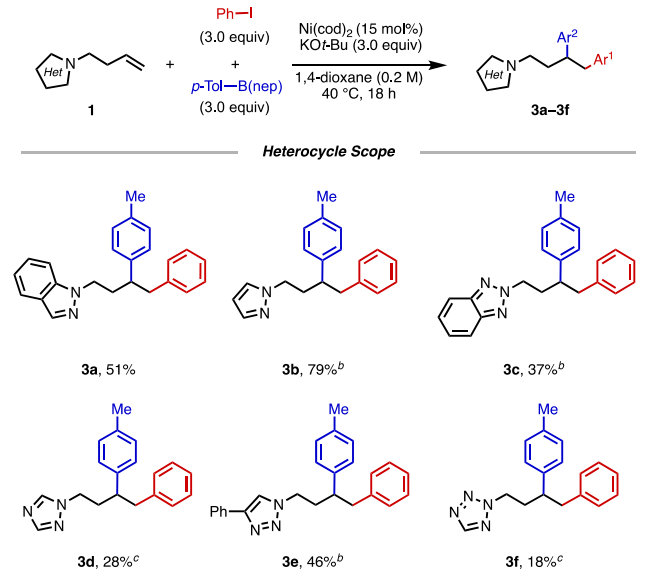
We investigated the effect of tether length between the directing group and the alkene on reaction outcomes (Table 4). Shortening the tether length from two methylene groups, as in the standard *N*-homoallyl case (**3a**), to one methylene group, as in *N*-allyl homolog gave moderate yield but substantially lower regioselectivity (**4a**). Extending the tether length by one methylene as in the *N*-bishomoallyl homolog gave low yield (**4b**). The reactivity and selective trends across this series can be rationalized by considering both the energetically favorable nature of exocyclic versus endocyclic directed organonickel migratory insertion events [2b,17b] and relative stabilities of the corresponding five- to seven-membered N(sp^2)-bound nickelacycles, where a seven-membered nickelacycle is unstable compared to the others [17].

Table 2. Nucleophile and Electrophile Scope.[a]



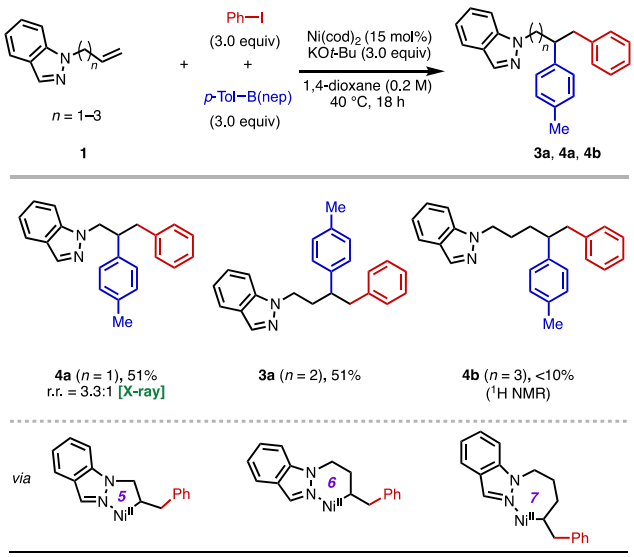
[a] Reactions performed on a 0.1 mmol scale. Percentages represent isolated yields.

Table 3. Alkene Scope.[a]



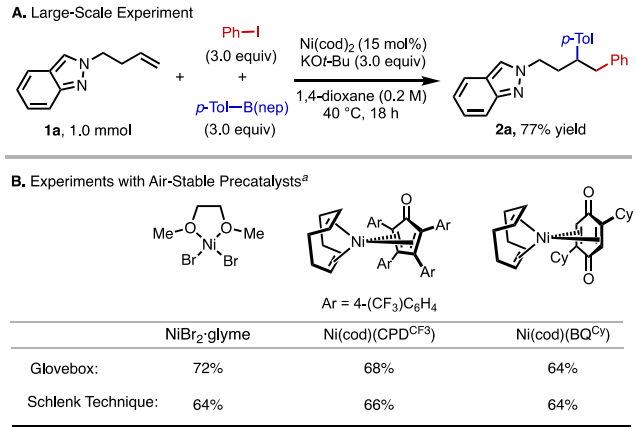
[a] Reaction performed on a 0.1 mmol scale. Percentages represent isolated yields.
[b] NaO*t*-Bu used in place of KO*t*-Bu. [c] LiO*t*-Bu used in place of KO*t*-Bu.

Table 4. Tether Length Effects.[a]



[a] Reactions performed on a 0.1 mmol scale. Percentages represent isolated yields.

When scaling up the model 1,2-diarylation using indazole **1** (1 mmol) as the substrate with iodobenzene as the electrophile and *p*-tolylboronic acid neopentyl glycol ester as the nucleophile, product **2a** was obtained in 77% yield (0.263 g), illustrating the robust nature of this reaction (Scheme 2A). Lastly, we sought to demonstrate that the reaction could be performed with other nickel precatalysts that would obviate the need for an inert-atmosphere glovebox, which is typically required for handing $Ni(cod)_2$. We were pleased to find that commercially available $NiBr_2$·glyme or two of Ni(0) catalysts developed in our lab [28-29], namely $Ni(cod)(CPD^{CF3})$ (CPD^{CF3} = 2,3,4,5-tetrakis(4-(trifluoromethyl)phenyl)cyclopenta-2,4-dien-1-one) and $Ni(cod)(BQ^{Cy})$ (BQ^{Cy} = 2,5-bis(cyclohexyl)-1,4-benzoquinone), gave comparable yields to $Ni(cod)_2$ when performed in the glovebox (Scheme 2B). The air-stable nature of these precatalysts further allowed the 1,2-diarylation reaction to be performed using standard Schlenk technique outside of the glovebox (see Supporting Information for details).



	$NiBr_2$·glyme	$Ni(cod)(CPD^{CF3})$	$Ni(cod)(BQ^{Cy})$
Glovebox:	72%	68%	64%
Schlenk Technique:	64%	66%	64%

[a] Reactions performed on a 0.1 mmol scale. Percentages represent ^{1}H NMR yields using CH_2Br_2 as internal standard.

Scheme 2. Large-Scale and Air-Stable Ni(0) Catalysts Experiments.

3. Conclusion

In conclusion, a new Ni-catalyzed heterocycle-directed 1,2-diarylation of unactivated alkenes has been developed. This reaction exhibits good regioselectivity and functional-group tolerance of various heterocycles, enriching the synthetic application and practical utility of alkene functionalization in drug discovery.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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25. The connectivity (i.e., regiochemistry) of the products is assigned in analogy to previous reports with other directing groups under similar reaction conditions (see Refs. 15–17) and in analogy to **4a** (major), which was characterized by single-crystal X-ray diffraction. In the examples shown in Tables 2 and 3, the opposite regioisomer was not observed in the crude reaction mixture, so we conservatively estimate the r.r. values to be >20:1 unless otherwise specified. In the case of fluorinated product **2f**, we independently prepared the opposite regioisomer, and analysis by ^{19}F NMR confirmed r.r. >20:1 in this case (see Supporting Information for details).
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Supplementary Material