Nickel-Catalyzed Intermolecular Enantioselective Heteroaromatic C–H Alkylation

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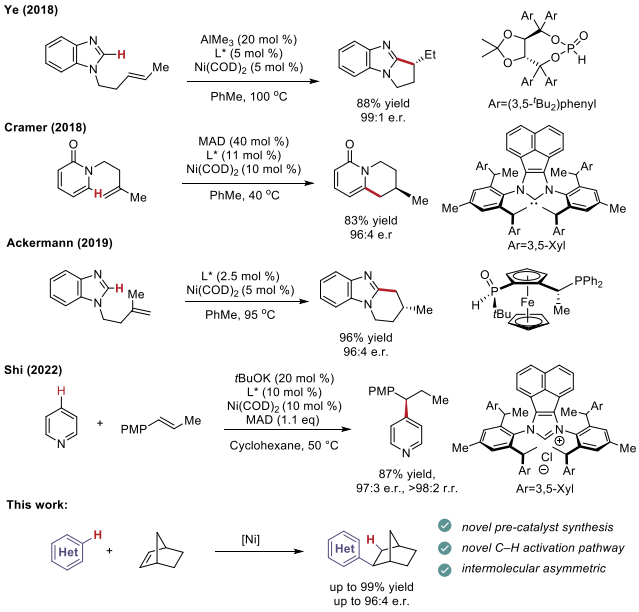
ABSTRACT: Regio- and enantioselective functionalization of heteroarene C–H bonds in the absence of directing groups is a long-standing challenge in the field of C–H activation. Herein, we present an approach involving nickel-catalyzed intermolecular enantioselective C–H alkylation of heteroarenes. The process can be carried out under mild conditions using nickel(0) catalysts with N-heterocyclic carbene (NHC) ligands in the absence of Lewis acid co-catalysts. A series of NHC nickel complexes stabilized with 1,5-hexadiene were synthesized via an operationally simple approach, resulting in improved functional group tolerance and heteroarene scope. Mechanistic investigations are consistent with a ligand-to-ligand hydrogen transfer (LLHT) pathway where the C–H bond activation precedes a rate-determining reductive elimination step.

Heteroaromatic rings are common motifs in natural products and FDA approved pharmaceuticals.[1] Direct functionalization of heteroaromatic C–H bonds has the potential to streamline the synthesis of complex molecules by avoiding the need for pre-functionalization steps.[2] Despite their prevalence, aromatic C–H bonds are relatively inert and often similar in reactivity, rendering their selective functionalization challenging, especially in intermolecular, non-directed processes.[3] Over the past several decades, enormous advances have been made in the field of selective C–H functionalization through the exploration of transition metal catalysis. These newly developed methods offer orthogonal opportunities to existing strategies for the synthesis of natural products, functional materials as well as exploration of structure-activity relationships by avoiding the pre-installation of functionalities required for traditional cross-couplings.[4] Selective transformation of heteroaromatic C–H bonds, however, typically rely on the use of directing groups and second- or third-row transition metal catalysts.[5] To this end, functionalizing heteroarenes that lack directing groups using earth abundant transition metals remains underdeveloped.[6]

Our interest in nickel-catalyzed C–H functionalization stems from nickel's relatively high earth abundance and complementary reactivity compared with second and third-row transition metals.[7] A nickel catalyzed C–H alkenylation reaction that first reported by Nakao and Hiyama[8] was extensively explored computationally by Perutz and co-workers.[9] The authors proposed that C–H activation proceeds through a novel ligand-to-ligand hydrogen transfer (LLHT) pathway rather than the formation of a discrete nickel-hydride via oxidative addition. Under this framework, a variety of aromatic C–H bonds have been functionalized using the combination of nickel(0) pre-catalysts and NHC or phosphorus-based ligands.[10] Enantioselective LLHT processes are more rare, with intramolecular asymmetric cyclization being described by Ye[11], Cramer,[12,] Ackermann[13] and Shi[14] groups, enabled by the design of novel ligand scaffolds (Scheme 1). In 2018, the Ye group reported a Ni-Al bimetallic enantioselective C–H *exo*-selective cyclization of imidazoles with alkenes promoted by secondary phosphine oxide (SPO) ligands.[11a] Shortly after, the Cramer group developed a modular synthesis of IPhEt ligand family, which was first reported by Galway and co-workers.[15] These catalytic systems were successfully applied to the C–H functionalization of pyridones[12a, 12c], pyrroles and indoles.[12d] Independently, the Ackermann group discovered that the combination of nickel and JoSPOphos allowed for the asymmetric C–H functionalization of imidazoles without the need of external Lewis acids, and they further illustrated this novel catalysis with a well-defined nickel(II)-JoSPOphos complex.[13a] Recently, Shi and co-workers reported the intermolecular enantio- and regioselective nickel-catalyzed C–H functionalization of pyridines with styrenes,[14c] demonstrating the unique selectivities of ANIPE-type ligands.[16]

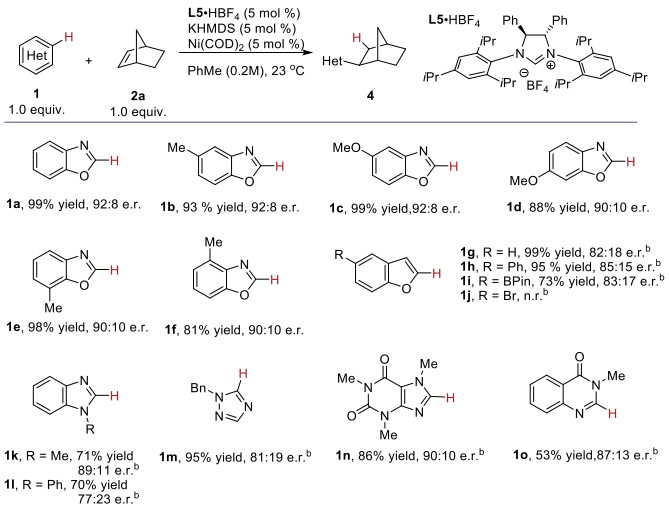
Scheme 1. Nickel catalyzed asymmetric heteroaromatic C–H alkylation via ligand-to-ligand hydrogen transfer (LLHT)



While important advances have been made in enantioselective intramolecular cyclization processes, the corresponding enantioselective intermolecular transformations are underdeveloped and represent an important gap in the field.[14c] To address this challenge, we report herein a method for the intermolecular enantioselective C–H alkylation of heteroarenes under mild conditions using a hindered NHC ligand with backbone chirality. An NHC ligand motif not previously utilized in enantioselective LLHT processes is paired with a strategy for the utilization of discrete 1,5-hexadiene-supported nickel(0) complexes to improve catalytic activity, increase functional group tolerance, and widen substrate scope of the transformation.

We began our efforts by exploring the alkylation of benzoxazole with norbornene (nbe) using nickel catalysts. After screening several common chiral ligands for enantioselective nickel catalysis, we found that NHCs derived from commercially available chiral diamines provided appreciable enantioinduction while maintaining good reactivity. Upon optimization of the reaction conditions through variation of ligand structure, solvent, temperature, and additives (see supporting information), we set out to demonstrate the utility of this method by exploring the scope of heteroarenes (Scheme 2). The optimized conditions involve *in-situ* preparation of an active chiral catalyst via the use of 5 mol % **L5**•HBF_4, KHMDS and $Ni(COD)_2$. The process is tolerant of electron-neutral and electron-rich benzoxazoles substituted at various positions (**1a-1f**) to give the alkylation products with good yields and enantioselectivities. Selective functionalization of benzofurans was also observed for C2 C–H bonds leaving functional groups such as boronic esters intact (**1g-1i**). LLHT products were not observed when using 5-bromobenzofuran as substrate (**1j**), which could be attributed to the facile activation of C(sp^2)–Br bond in the presence of low-valent nickel catalyst. Benzimidazoles previously studied by Ackermann[13a] and Ye[11a] for enantioselective cyclizations were also reactive in the intermolecular system. We showed that nbe reacted with *N*-Me and *N*-Ph benzimidazoles (**1k, 1l**) to yield the C–H functionalization products with moderate enantioselectivity at 60 °C (*vide infra*). Interestingly, a C5-alkylated 1,2,4-triazole was exclusively obtained with high regio- and enantioselectivity despite the more hindered environment (**1m**). Other nitrogen containing heteroaromatic rings including caffeine (**1n**) and 3-methylquinazolin-4(3*H*)-one (**1o**) also underwent efficient couplings to give the desired product in good yields and 90:10 and 87:13 e.r. respectively. All of the alkylation products were obtained as a single, exocyclic diastereomer originating from steric biases.

Scheme 2. Enantioselective heteroaromatic C–H functionalization scope [a]

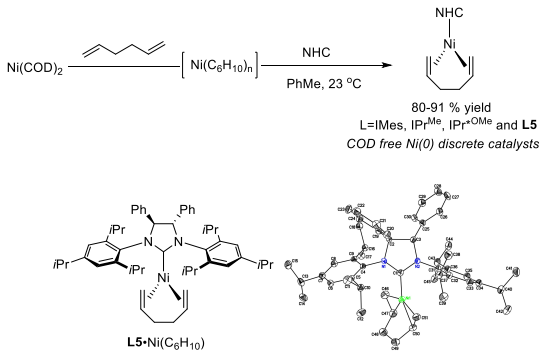


[a] Reactions were performed at 0.10 mmol scale and yields were reported for isolated products. [b] Reaction was carried out at 60 °C.

When examining benzoxazoles bearing electron-withdrawing substituents, however, the desired alkylation products were not obtained using the standard protocol described above. We postulated that the increased acidity of benzoxazole's C-2 C–H bond could lead to deleterious side reactions with 1,5-cyclooctadiene (COD) from the nickel pre-catalyst, resulting in unproductive off-cycle intermediates. The diminished reactivity of benzoxazoles bearing electron-withdrawing groups has similarly been observed by Ong and co-workers in their study of hydroarylation of cyclic dienes.[17] The inhibitory effect of COD in C–H activations was previously described by our laboratory in the development of alkyne hydroarylation reactions involving LLHT pathways.[7a, 7c] This feature originates from the participation of COD in a competing LLHT C–H activation that results in a stable off-cycle π-allyl complex that minimizes the concentration of the active catalyst for productive catalysis. This side reaction was prevented by employing 1,5-hexadiene-supported nickel pre-catalysts[18] leading to a more efficient alkyne hydroarylation at reduced temperatures. Motivated by this finding, we set out to develop the synthesis of NHC nickel complexes stabilized by 1,5-hexadiene from easily accessible nickel precursors under operationally simple conditions. Inspired by work done by Wilke and co-workers on the synthesis of 'bis(olefin)nickel-ligand complexes'[19] as well as Belderrain and Nicasio's nickel bis-styrene complex,[20] we anticipated that ligand exchange from COD to 1,5-hexadiene followed by trapping with free NHC ligands would allow facile access to a variety of sterically demanding NHC nickel complexes. Using this approach (see supporting information), we were able to synthesize 1,5-

hexadiene nickel complexes bearing IMes, IPr^{Me}, IPr*^{OMe} as well as the optimal ligand for the enantioselective transformation described above (**L5** in Scheme 2), whose structure was unambiguously confirmed using x-ray crystallography (Scheme 3).

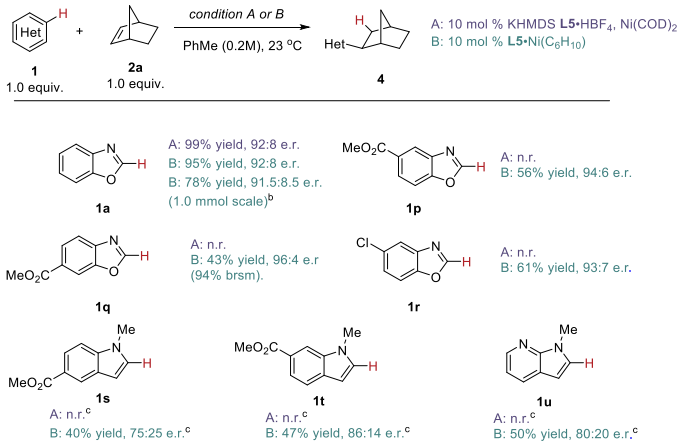
Scheme 3. Synthesis of NHC nickel complexes stabilized with 1,5-hexadiene [a]



[a] ORTEP diagrams of **L5**-Ni(C_6H_{10}) with thermal ellipsoids at 50% probability. Hydrogens have been omitted for clarity.

With these novel catalysts in hand, we first tested their reactivity using benzoxazole (**1a**), and comparable results were obtained (Scheme 4). Moreover, the synthesis of enantioenriched alkylation products could be carried out using as low as 2.5 mol % **L5**-Ni(C_6H_{10}) at 1.0 mmol scale without diminished enantioselectivity. We employed this catalyst with previously problematic substrates including those that feature electron-withdrawing substituents. While the *in-situ*-generated chiral catalyst at 10 mol % loading gave no reaction, **1p** and **1q** underwent alkylation smoothly to give desired products using the discrete nickel catalyst **L5**-Ni(C_6H_{10}), where excellent enantioselectivities and clean reaction profiles were observed. Most surprisingly, products arising from chemoselective C–H functionalization were observed as the sole product with 93:7 e.r. in the presence of competing C–Cl bonds, which are susceptible to facile activation with low-valent nickel catalysts (**1r**). The corresponding bromide substrate **1j** (Scheme 2) was unreactive under condition B with defined pre-catalyst L5•Ni(C_6H_{10}). Lastly, substituted indoles and azaindoles could also be included into the scope simply by raising the reaction temperature to 60 °C (**1s-u**), thus demonstrating the broad functional group compatibility of this Lewis acid free approach to C2 alkylated heteroarenes.

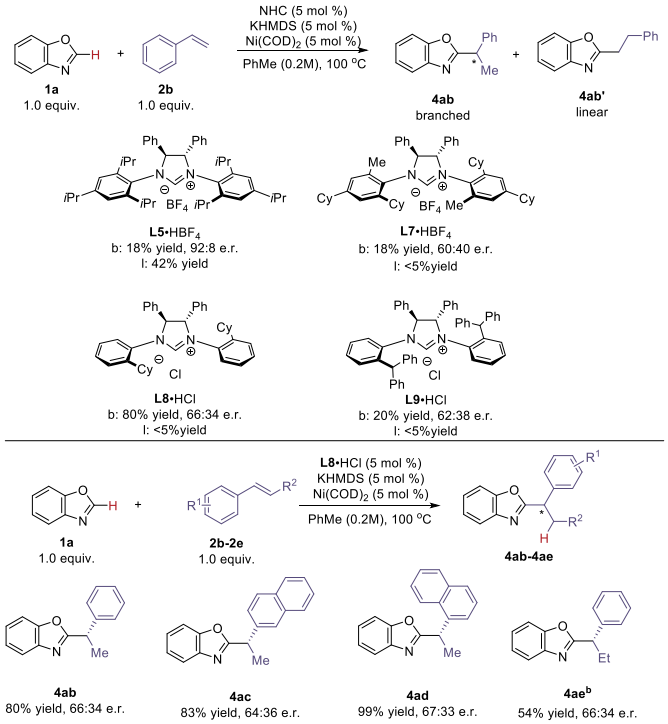
Scheme 4. Broaden the scope with a pre-synthesized 1,5-hexadiene catalyst [a]



[a] Reactions were performed at 0.10 mmol scale unless noted. Yields were reported for isolated products. [b] Reaction was carried out with 2.5 mol % catalyst at 0.4M in PhMe. [c] Reaction was carried out using 2.0 equiv. nbe at 60 °C.

Enantioenriched 1,1-diaryl ethanes, which are recognized as valuable units in active pharmaceutical ingredients, are challenging structural motifs to access.[21] We hypothesized that this newly developed enantioselective hydroarylation strategy could enable access to enantioenriched 1,1-diaryl ethanes and allow for a rapid buildup of molecular complexity. As outlined in Scheme 5, an initial screen of several chiral NHCs that showed activity in the above studies revealed that ortho-substitution on the *N,N*-diaryl imidazolium scaffold had a large effect on reactivity and enantioselectivity. Though **L5**•HBF_4 exhibited poor regioselectivity control (linear to branched), steric effects were important in the observed enantioselectivities. Changing the identity of the aryl groups on imidazolium in **L7**•HBF_4 improved regioselectivity, though enantioselectivity was diminished. Further decreasing the steric hinderance with mono-substituted *N,N*-diaryl imidazolium **L8**•HCl suppressed the formation of linear product while increased the yield of the branched product, albeit with negligible improvements in enantioselectivity. As modification of the mono-substituted arene of the imidazolium did not give improved results (**L9**•HCl), we opted to explore the preliminary scope of this reaction with **L8**•HCl, which gave the best reactivity and regioselectivity. 1,1-diaryl product **4ab** was formed in 80% yield and 66:34 e.r. when reacting benzoxazole (**1a**) with styrene (**2b**). This method could be applied to 1- and 2-vinyl naphthalenes (**2d**, **2c**), accessing exclusively the branched product with moderate control of enantioselectivity. Excellent regioselectivity for the benzylic position was observed with trans-β-methylstyrene (**2e**), albeit modest yield and enantioselectivity. While the combination of regioselectivity and enantioselectivity of hydroarylations of simple styrenes falls short of the levels needed for synthetic application in its current form, the insights provided into the role of NHC structure in modulating the reaction outcome will be useful in guiding further study.

Scheme 5. Asymmetric alkylation with styrene and its derivatives [a]

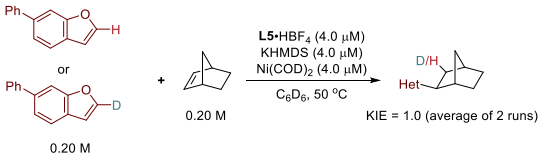


[a] Reactions were performed at 0.10 mmol scale and yields were reported for isolated products.[b] with 2 equiv. nbe.

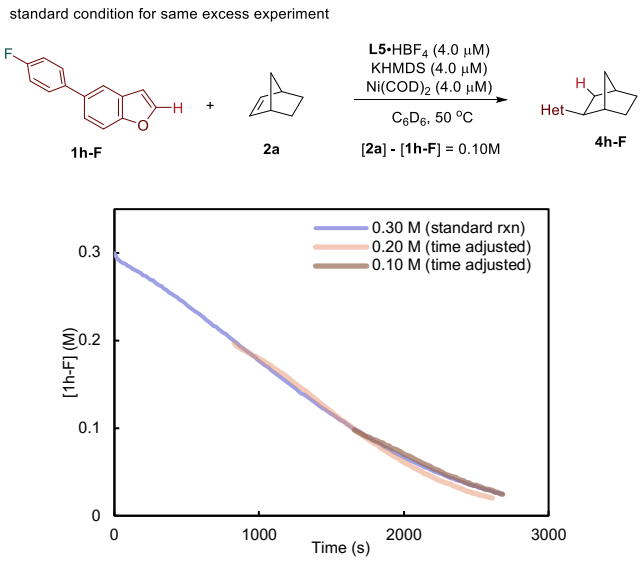
Having established this catalytic system to efficiently perform alkylation of heteroarenes with nbe and styrenes, we next turned our attention to investigating the mechanism of the transformation. Based on previous nickel-catalyzed C(sp^2)–H functionalization studies, we hypothesized that this reaction operates through a ligand-to-ligand hydrogen transfer (LLHT) mechanism where a concerted oxidative addition, migratory insertion bypasses the formation of a discrete nickel-hydride intermediate.[9] C–H functionalization that proceed through LLHT often exhibit a characteristic fast, reversible C–H activation and rate-determining reductive elimination.[7c] To probe this characteristic, we conducted parallel KIE experiments with deuterium-labelled 5-phenylbenzofuran at 50 °C. The absence of kinetic isotope effect (KIE=1.0) suggests that C–H activation is not involved in the rate-determining step, as expected in the LLHT mechanism (Scheme 6a).

"Same excess" experiments were performed by maintaining the absolute concentration difference between nbe and arene to gain initial insights about the reaction progression.[22] As shown in Scheme 6b, the overlay of three kinetic profiles indicates that neither catalyst deactivation nor product inhibition were occurring. Next, varying the concentration of each component, the rate of the reaction was determined to be first order in arene and catalyst, and inverse first order in nbe (see supporting information for details).

Scheme 6a) Parallel KIE experiments.

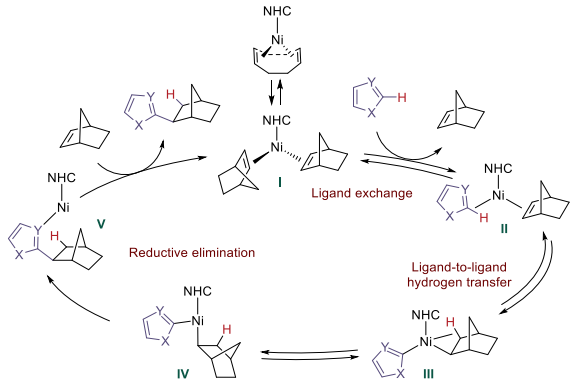


Scheme 6b) Same excess experiment



Parallel three experiments were run with initial **1h-F** concentration [**1h-F**]$_0$ = 0.30, 0.20 and 0.10 M respectively ([**2a**] – [**1h-F**] = 0.10M). Reactions were monitored with ^{19}F NMR, time adjusted.

Scheme 6c) Proposed mechanism.



Based on the above observations and by drawing analogy with previous mechanistic studies,[7a, 9, 10h, 13b] we propose the following mechanism for the enantioselective C–H alkylation of heteroarenes (Scheme 6c). The catalytic cycle is initiated by ligand exchange between nbe and heteroarene to form intermediate **II**, which then undergoes reversible ligand-to-ligand hydrogen transfer (LLHT),[23] resulting in the generation of aryl-bound nickel(II) species **III**. Previous studies by Hartwig and others have shown that the isomerization of **III** to a T-shaped intermediate **IV** precedes reductive elimination.[10h, 24] From intermediate **IV**, rate-determining reductive elimination delivers **V**, which, upon a fast ligand exchange with nbe, regenerates the catalyst, which is in good agreement with the result from "same excess" experiments that show no product inhibition.

The inverse first-order dependence in nbe is consistent with the dissociation of nbe in the **I** to **II** conversion, and the order analysis additionally indicates that nbe does not reassociate with the nickel center in the conversion of from intermediate **III** to **IV** (Scheme 6c). This absence of reassociation of alkene has also been observed by Hartwig and co-

workers in their studies of anti-Markovnikov hydroarylation reactions.[10h] In contrast, previous studies by our group described a zero-order dependence in alkyne in the hydroarylation of alkynes, which was attributed to association of the alkyne to the nickel center prior to reductive elimination through a mechanism that otherwise patterns that described for nbe hydroarylation.[7c]

In conclusion, a strategy for the intermolecular enantioselective hydroarylation of alkenes using a nickel-catalyzed ligand-to-ligand hydrogen transfer approach has been developed.[23] The strategy involves an operationally simple approach using structurally well-defined NHC nickel(0) complexes that incorporate 1,5-hexadiene as ligand to improve reactivities. The method was applied to the enantioselective C–H functionalization under mild conditions with a wide heteroarene scope. This method was further examined with simple styrene derivatives, delivering 1,1-diaryl ethanes in good yields and modest enantioselectivities. The identification of a well-defined, sterically demanding C2-symmetric chiral NHC complex allows for intermolecular alkylation of a wider range of heteroarenes to occur without the need for Lewis acid additives. Mechanistic investigations are described by mapping the fundamental steps via kinetic profiles, which further support a LLHT pathway to activate the heteroaryl C–H bond and illustrate mechanistic differences that result from the nature of π-systems employed. This study provides important insights into the features that optimize catalyst performance in the enantioselective intermolecular functionalization of C(sp^2)–H bonds and explores a range of arenes and alkenes that participate in the transformation.

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SUPPORTING INFORMATION

Experimental procedures; full spectroscopic data for all new compounds; and copies of ^1H, ^{13}C NMR, HPLC and SFC spectra. X-ray crystallographic data for **L5**-Ni(C_6H_{10})

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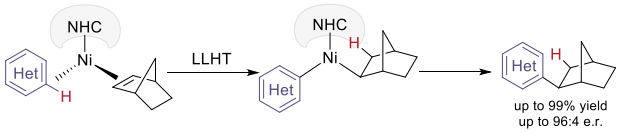
TOC graphic



• Intermolecular, enantioselective coupling • Broad heteroarene scope

• Enhanced reactivity and selectivity of an NHC/1,5-hexadiene ligand combination