Anti-Markovnikov Hydroheteroarylation of Unactivated Alkenes with Indoles, Pyrroles, Benzofurans, and Furans Catalyzed by a Nickel–N-Heterocyclic Carbene System

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Ⓢ Supporting Information

ABSTRACT: We report the catalytic addition of C–H bonds at the C2 position of heteroarenes, including pyrroles, indoles, benzofurans, and furans, to unactivated terminal and internal alkenes. The reaction is catalyzed by a combination of $Ni(COD)_2$ and a sterically hindered, electron-rich N-heterocyclic carbene ligand or its analogous Ni(NHC)(arene) complex. The reaction is highly selective for anti-Markovnikov addition to α-olefins, as well as for the formation of linear alkylheteroarenes from internal alkenes. The reaction occurs with substrates containing ketones, esters, amides, boronate esters, silyl ethers, sulfonamides, acetals, and free amines.

Heterocycles containing alkyl substituents at the C2 position are common structures of medicinally active compounds. In addition, natural products displaying significant biological activity often possess an indole, benzofuran, pyrrole, or furan motif containing linear alkyl groups at the C2 position.[1] During the synthesis of such molecules, the alkyl substituent at C2 is generally incorporated during the construction of the heterocycle,[2] in part because current methods for direct alkylation at the C2 position of heteroarenes with alkyl electrophiles require strong bases, such as n-BuLi or LDA, limiting the functional group tolerance. A more efficient and flexible strategy to prepare such molecules could be a catalytic C–H functionalization of heteroarenes at the C2 position. A formal, catalytic alkylation of heteroarenes to give the linear alkylheteroarene has been achieved by olefination or acylation, followed by hydrogenation. However, direct, catalytic alkylation at C2 with alkenes would form alkylarenes without the need for selective hydrogenation at the vinyl or carbonyl group in a two-step protocol.

Classical hydroarylations catalyzed by Lewis or Brønsted acids with indoles[3] or benzofurans[4] as nucleophiles are not suitable methods to prepare such derivatives because these reactions occur at the C3 position, not the C2 position, and they afford the branched alkyl product, not the linear product. Classical hydroheteroarylations of five-membered heterocyclic nucleophiles, such as pyrroles, furans, and thiophenes, occur at the C2 position, but they afford branched products.[4]

Coordinating groups, such as acyl or benzoyl,[5a] amide,[5b] or pyrimidyl,[5c,d,f] attached to the nitrogen atom[5] or the C3[6] carbon atom of an indole have been used to induce alkylations of indoles selectively at the C2 position by transition-metal catalysis. However, examples of direct alkylation of heteroarenes at the C2 position without coordinating groups are rare. Bach developed a direct Pd-catalyzed alkylation at the C2 position of NH-indoles with primary alkyl bromides involving a regioselective cascade mediated by norbornene,[7] and Yi reported a Ru-catalyzed C–H alkylation of alkenes and heteroarenes with primary alcohols.[8] However, both protocols require a terminal alkyl electrophile, which is generally prepared from the corresponding terminal alkene. To date, only one direct addition of an indole C–H bond across an unactivated terminal alkene has been reported, and this example occurred with an electronically activated indole substituted with an ester function at C3 and required a 5-fold excess of the alkene.[9]

We report a wide range of anti-Markovnikov hydroheteroarylations of unactivated olefins with heteroarenes catalyzed by a nickel–N-heterocyclic carbene (NHC) system. The scope of this reaction encompasses unactivated terminal alkenes, acyclic internal alkenes, and cyclic alkenes, and it includes indoles, pyrroles, benzofurans, and furans as the heteroarene. The reaction occurs regioselectively at the C2-position due to the selectivity of the catalyst (potential coordinating groups do not affect the regioselectivity). The process is enabled by the use of hindered NHC ligands and tolerates a series of functional groups.

During our studies of Ni-catalyzed, anti-Markovnikov hydroarylation of trifluoromethyl-substituted arenes[10] and pyridines,[11] we observed the hydroheteroarylation of N-Methylindole. The reaction formed the linear alkylheteroarene, but it occurred in low yield with the catalysts employed for the alkylation of those (hetero)arenes. To identify more active catalysts for the addition of heteroaryl C–H bonds to alkenes, we studied the reaction of N-Methylindole with 1-tridecene in the presence of a series of nickel–NHC catalysts. Table S1[12] summarizes our studies on the identification of catalysts and reaction conditions. These studies showed that reactions conducted with more sterically hindered, electron-rich NHC ligands, such as IPr^{Me} or IPr* (see Scheme 1), afforded high yields of product. Selectivity for the linear (anti-Markovnikov) product was greater than 94:6 in all cases.

Scheme 1. Ligands and Catalysts Employed for the Linear-Selective Hydroheteroarylation

**Table 1. Hydroheteroarylation of Alkenes with Substituted Indoles**[a]
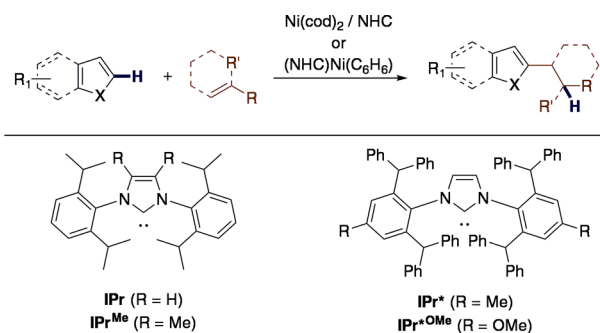
Reactions conducted without solvent occurred in excellent yield while maintaining high anti-Markovnikov selectivity. Reactions conducted with the IPr*[OMe]-ligated Ni-benzene complex as the precatalyst afforded the linear alkylheteroarene in higher yield than when starting with Ni(COD)$_2$ and free carbene, while maintaining the reactivity and selectivity obtained with the catalyst generated *in situ*.

The substituent at the nitrogen atom of the indole affected the yield of product and identity of the most active catalyst. The hydroheteroarylation of *N*-benzylindole **1b**, occurred in high yield when the reaction was conducted with the sterically less demanding IPr[Me] ligand. Indoles containing a bulky isopropyl group (**1c**) at nitrogen gave the alkylated product in lower yield than those containing *N*-methyl or *N*-benzyl groups.[12] Indoles containing a bulky, removable TBDMS group or bearing electron-withdrawing substituents at nitrogen did not afford any hydroheteroarylation product.[12] Thus, further studies were conducted with *N*-methylindoles, although *N*-benzylindoles can be used. We speculate that steric repulsion of the *N*-benzyl group with the catalyst accounts for this observation because we also observed lower yields for reactions of *N*-isopropyl- and *N*-TIPS-indole.

The scope of Ni-catalyzed additions of heteroarenes to alkenes is much broader than that of the Ni-catalyzed additions of arenes to alkenes, which was limited to reactions of trifluoromethyl-substituted arenes. For instance, *N*-methylindoles containing a variety of substituents at the 5-position (Table 1, **1d–1p**) underwent intermolecular hydroheteroarylation with terminal, linear alkenes in good to excellent yields with consistently high selectivity for the linear product. We previously reported that hydroarylations conducted with added NaO[t]Bu afforded higher yields of addition products in selected examples.[10] In a similar vein, indoles bearing functional groups that tolerate NaO[t]Bu reacted in higher yields with 0.5 equiv of added base than without base. Substrates that afforded yields below 85% in the absence of base were also tested in the presence of base. In such cases, we report the higher of the two yields.[13]

The reactions of 5-fluoro- (**1e**) and 5-methoxy-*N*-methyl-indole (**1f**) occurred with similar yield and selectivity, demonstrating that this system catalyzes the reactions of indoles containing both electron-withdrawing and electron-donating groups. No cleavage of the methoxy C–O bond in **1f** was observed, although Ni(0) species can cleave aryl alkyl ethers.[14] Thioethers underwent C–S bond cleavage, but sulfonamides were tolerated (**3ib**). Substituents suitable for cross-coupling reactions, such as boronate esters (**3gb**) and trialkoxysilanes (**3hb**), were tolerated, although the boronate ester reactant and product both underwent partial protodeboronation. The
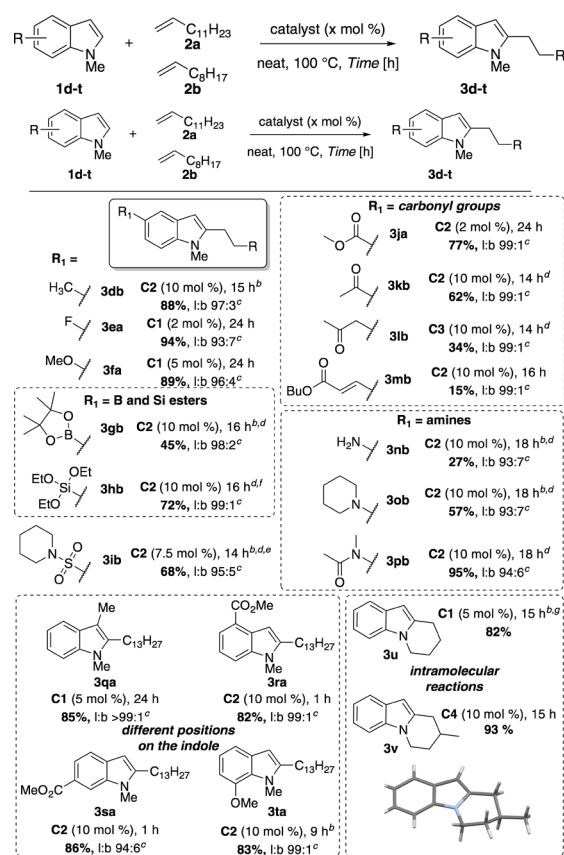
[a]Conditions: catalyst [**C1**, (IPr*[OMe])Ni(C$_6$H$_6$); **C2**, IPr[Me]/Ni(cod)$_2$; **C3**, (IPr[Me])Ni(C$_6$H$_6$); **C4**, IPr/Ni(cod)$_2$], indole (0.500 mmol), alkene (0.750 mmol); neat; 100 °C; 24 h; yields with respect to isolated compounds. [b]With NaO[t]Bu (0.5 equiv). [c]Determined by GC analysis. [d]Run in toluene (1.0 M). [e]Run on 0.150 mmol scale. [f]With NaO[t]Bu (0.1 equiv). [g]Temperature 120 °C.

reactions of indoles bearing carbonyl substituents (**1j–1m**) gave moderate to good yields of the addition products. The process also occurred with indoles bearing amine (**1n**, **1o**) and amide (**1p**) substituents, although primary aminoindole **1n** underwent hydroheteroarylation in lower yield than did tertiary amine **1o** and amide **1p**. The alkylation of indoles **1q–1t** showed that a substituent at C3–C7 on the indole is tolerated. Hydroheteroarylation in an intramolecular fashion also occurred.[15] The reactions of *N*-alkylindoles bearing a terminal olefin afforded the six-membered-ring products (**3u**, **3v**) in excellent yield.

The difference in yield observed for some reactions in the presence and absence of base results from competing isomerization of the terminal alkene to internal alkenes, as determined by gas chromatography. To probe the effect of the base on this isomerization, we monitored the Ni-catalyzed isomerization of 1-decene alone by 1H-NMR spectroscopy in the presence of alkoxide, phenoxide, and hydride bases. Among these bases, only NaO[t]Bu and KO[t]Bu fully suppressed isomerization.[12] Thus, reactions conducted in the presence of added base occur in higher yields than in the absence of base (when the heteroarene is stable to base) because suppression of alkene isomerization increases the concentration of the terminal alkene, which forms the linear alkylarene product.

Table 2. Scope of Benzofurans,[a] Furans,[b] and Pyrrole[b] in the Nickel-Catalyzed Linear-Selective Hydroheteroarylation
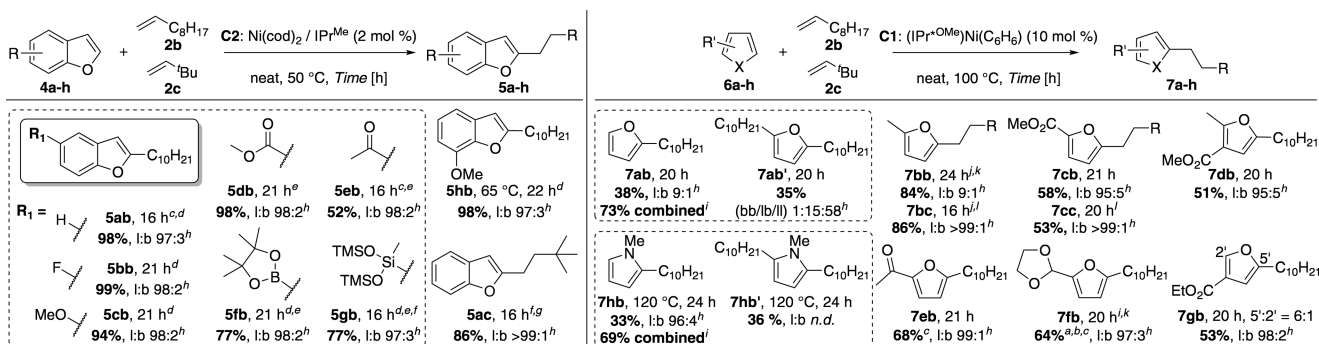

[a]Conditions: benzofuran (0.500 mmol), alkene (0.600 mmol); neat; 50 °C. [b]Conditions: heteroarene (0.500 mmol), alkene (0.333 mmol); neat; 100 °C. [c]Run on 0.250 mmol scale. [d]With NaOtBu (0.1 equiv). [e]Run in toluene (1.0 M). [f]1 mol % catalyst. [g]Using **C1**. [h]Determined by GC analysis. [i]With NaOtBu (0.5 equiv). [j]5 mol % catalyst. [k]Heteroarene (0.333 mmol), alkene (0.500 mmol). [l]Heteroarene (0.500 mmol), alkene (0.500 mmol).

Benzofurans also underwent hydroheteroarylation with terminal unactivated olefins, and this class of heteroarene was particularly reactive toward the addition process (Table 2). The reaction temperature and catalyst loading were both substantially lower for reactions of benzofurans than for reactions of indoles.[12] Like indoles, benzofurans containing functional groups that tolerate NaOtBu reacted in higher yields with 0.5 equiv of added base than without base.[13] The hydroheteroarylation of benzofurans occurred with electron-donating (**4c**), electron-withdrawing (**4b**), and carbonyl (**4d**, **4e**) substituents, as well as boronate esters (**4f**) and siloxysilanes (**4g**), on the heteroarene. Benzofurans bearing substituents at the C7 position (**4h**) also gave the linear alkylated product, but reactions of these heteroarenes required higher temperatures.

In addition to indoles and benzofurans, non-benzo-fused five-membered-ring heteroarenes[16] reacted with unactivated alkenes. Both furan and *N*-methylpyrrole afforded the C2-alkylated product in good yield and with excellent selectivity for the linear product. The right-hand side of Table 2 illustrates the scope of furans and pyrroles that undergo the hydroheteroarylation process. Heteroarenes that tolerate NaOtBu reacted in higher yields with 0.5 equiv of added base than in the absence of base.[12] Furan and *N*-methylpyrrole formed a nearly 1:1 mixture of mono- and dialkyl products in approximately 70% combined yield (**7ab**, **7hb**), but reactions of substituted furans gave products from selective alkylation α to oxygen (**7bb**–**7gb**). Potential coordinating groups, such as a ketone in **6e** or ester in **6c**, did not direct the hydroheteroarylation to the position β to oxygen. Furthermore, a potentially coordinating ester at C3 in **6g** did not direct hydroheteroarylation to the adjacent C2 position. Instead, the reaction occurred at the more sterically accessible C5 position. Similar yields were observed for the reaction of neohexene and 1-decene with the same furans (**7bb** vs **7bc**, **7cb** vs **7cc**), despite the difference in steric properties of the alkene.

Heteroarenes containing certain functional groups did not undergo hydroheteroarylation with this nickel–NHC system. For instance, substrates containing a secondary amide or methyl sulfonamide, nitrile, Weinreb amide, aldehyde, benzaldimine, β-ketoester, free or acyl-protected benzylic alcohol, or nitro group did not afford any alkylated product. Heteroarenes bearing halide substituents (Cl, Br) did not form products of hydroheteroarylation, presumably because oxidative addition of the C–X bond deactivates the catalyst. Pyrroles containing carbonyl substituents at C2 or C3 did not undergo hydroheteroarylation. In these cases, both the starting heteroarene and partially isomerized

Table 3. Scope of Alkenes in Hydroheteroarylation with Indoles[a]
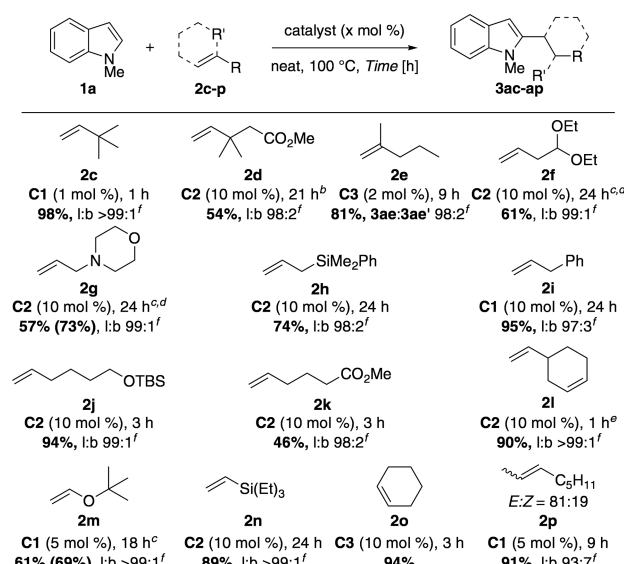
[a]Conditions: catalyst [**C1**, (IPr*[OMe])Ni(C6H6); **C2**, IPrMe/Ni(cod)2; **C3**, (IPrMe)Ni(C6H6)], indole (0.500 mmol), alkene (0.750 mmol); neat; 100 °C. [b]0.330 mmol scale. [c]Indole (0.500 mmol), alkene (0.500 mmol). [d]With NaOtBu (0.5 equiv). [e]Indole (0.500 mmol), alkene (1.50 mmol). [f]Determined by GC. NMR yields in parentheses.

alkene were recovered. We also tested the alkylation of a small collection of thiophenes, but these heteroarenes did not react with turnover numbers higher than 3.[12]

The scope of the alkenes that underwent the hydroheteroarylation process was evaluated with *N*-methylindole as the heteroarene. These data are summarized in Table 3. Terminal, monosubstituted alkenes that cannot undergo isomerization and possess sterically demanding groups (**2c**, **2d**) afforded the linear alkylheteroarenes with excellent selectivity. A 1,1-disubstituted olefin (**2e**) also underwent hydroheteroarylation in high yield with excellent selectivity. Olefins containing an acetal (**2f**), amine (**2g**), silane (**2h**), or phenyl ring (**2i**) in the allylic position underwent hydroheteroarylation in acceptable yield, whereas allylic ethers and allylic acetates did not. Olefins containing a pivalate group more distal to the C=C bond also did not undergo hydroarylation, perhaps due to isomerization to form an allylic ester that would add to the Ni(0) and deactivate the catalyst.

Alkenes containing functional groups more distal along the alkyl chain, such as protected alcohols (**2j**) or methyl esters (**2k**), underwent the hydroheteroarylation process in good yield. Nonconjugated diene **2l** underwent hydroheteroarylation at the less substituted olefin unit, although higher catalyst was required to shorten the reaction time and prevent isomerization of the remaining double bonds after the product was formed. The reaction also occurred with a vinyl ether (**2m**) and a vinyl silane (**2n**) in good yield and with excellent selectivity for the linear product. Vinyl siloxanes, styrenes, and stilbenes did not react with this nickel–NHC system.

The reactions of internal alkenes are particularly noteworthy. Cyclohexene (**2o**) underwent the hydroheteroarylation process to give the branched alkylation product, whereas hydroheteroarylation of internal alkenes, such as **2p**, did not yield the corresponding branched product by direct addition. Instead, the linear alkylarene was obtained. The linear product results from Ni-catalyzed isomerization of the internal alkene to a mixture of alkene isomers in the reaction mixture (*vide supra*). The terminal alkene then reacts to form the alkylheteroarene, and the equilibrium ratio of alkenes is re-established as the terminal alkene reacts. To achieve hydroheteroarylation across an internal acyclic alkene, such as **2p**, we evaluated the reactions of a series of octene isomers in the presence of base. With the exception of 4-*cis*-octene, which did not afford any alkylated product, hydroheteroarylation of internal octene isomers exclusively afforded the linear alkylation product.[12,17]

To gain preliminary mechanistic data on this addition process, a kinetic isotope effect (KIE) for the addition of *N*-methylindole to alkenes was measured with 2-D-*N*-Me-indole and *N*-Me-indole in separate vessels. The KIE from reactions of the labeled and unlabeled indole with 1-tridecene was only 1.3, and with norbornene was 1.4. These KIE values suggest that cleavage of the C−H bond is not turnover-limiting.[18] Rather, this KIE is consistent with reversible cleavage of the C−H bond before an irreversible step.[19] The postulated pathway (Scheme S9)[12] comprises reversible direct transfer of the C−H bond of a bound arene to the bound alkene without formation of a metal-hydride intermediate, as described previously for the hydroarylations of CF$_3$-containing arenes catalyzed by Ni(IPr)$_2$.[10] This step has been termed ligand-to-ligand hydrogen transfer and would be followed by reductive elimination to form the C−C bond.

In summary, we have developed a new protocol for hydroheteroarylation of heteroarenes with a nickel−NHC system that is selective for the linear alkylarene and that tolerates a large number of functional groups. Further mechanistic studies to reveal the effect of base and precise elementary steps of the catalytic cycle are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08039.

> Tables of reaction condition development, additional mechanistic experiments, full experimental protocols, and characterization data for all new materials (PDF)
> X-ray crystallographic data for **3v** (CIF)
> X-ray crystallographic data for **C1** (CIF)

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Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(1) Figure S1 gives a summary of several such structures containing linear alkyl chains at C2.

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(13) Scheme S6 gives a detailed description of yields obtained in the presence or absence of base for selected examples.

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(19) The KIE in the reaction of 2-D-benzofuran with 1-decene could not be obtained because fast exchange of the deuterium label between the C-2 position of benzofuran and the vinylic position of the terminal olefin occurred as a competitive reaction (Scheme S11).