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Nickel-Catalyzed C–H Coupling with Allyl Phosphates: A Site-Selective Synthetic Route to Linear Allylarenes

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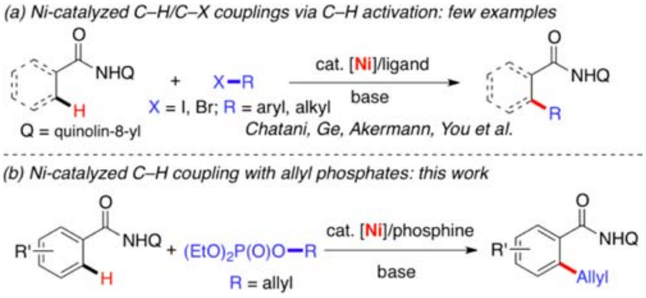
S *Supporting Information*

ABSTRACT: It is reported that a nickel/phosphine catalyst allows the C–H allylation to occur effectively with the allyl site selectivity predominantly governed by steric effects. This reaction provides a facile and predictable route for the selective preparation of linear allylarenes from readily available benzamides and allyl phosphates.

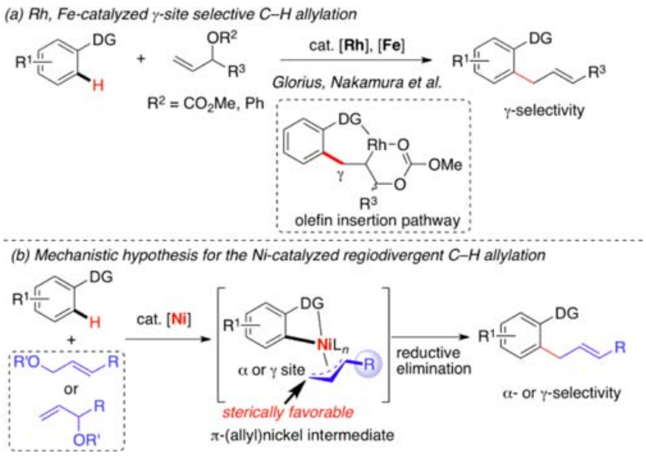
The use of first-row transition metals such as nickel in developing sustainable catalytic strategies to construct appealing structural motifs has attracted much attention in the synthetic community.[1] In particular, the functionalization of C–H bonds provides a powerful method toward diversely functionalized molecule synthesis.[2] The pioneering investigation by Chatani demonstrates that cost-attractive nickel salts enable improving the transformation of inert C–H bonds in the assistance of an 8-aminoquinoline auxiliary.[3−6] More recently, the groups of Chatani,[7] Ge,[8] Akermann,[9] and You[10] greatly broadened the reaction scope (Scheme 1a). Unfortunately, successful examples in the field are still scarce and currently studies are limited to couplings with C–X (X = I, Br) bonds. Inspired by a recent achievement on nickel-promoted C–H couplings with unactivated aryl C–O bonds,[4a,e,11] herein, we demonstrate a nickel-catalyzed allylation via chelation-assisted C–H activation, allowing for the incorporation of allyl scaffolds into the ortho position of benzamides, leading to linear allylarene derivatives in high selectivity (Scheme 1b).[12]

Scheme 1. Ni-Promoted C–H Functionalization



Owing to the advantage of easy functionalization of allyl moieties by numerous methods, the exploration of an efficient strategy to introduce these attractive structural motifs has inspired broad interests.[13] However, a long-standing challenge in the reaction is the control of allyl regioselectivity. Glorius[14] and Nakamura[15] elegantly demonstrated a chelation-assisted C–H allylation by use of allyl oxygen electrophiles, which largely expands the scope from electron-rich and -deficient arenes[16] to directing-group-containing substrates (Scheme 2a).[17] Note that these transformations are typically dominant in γ-regioselectivity. Compared with this olefin insertion pathway, we hypothesized that, after the cleavage of the *o*-C–H bond, an π-(allyl)nickel cyclometalated species can be formed regardless of whether linear or branched allyl oxygens were utilized, which may undergo a facile reductive elimination at a position of less steric hindrance to give a linear α- or γ-selective allylated product (Scheme 2b).[18] To the best of our knowledge, such a selectivity-predictable approach involving chelation-assisted C–H activation remains an elusive but efficient strategy to buildup target-oriented allylarene frameworks.

Scheme 2. Chelation-Assisted C–H Allylation



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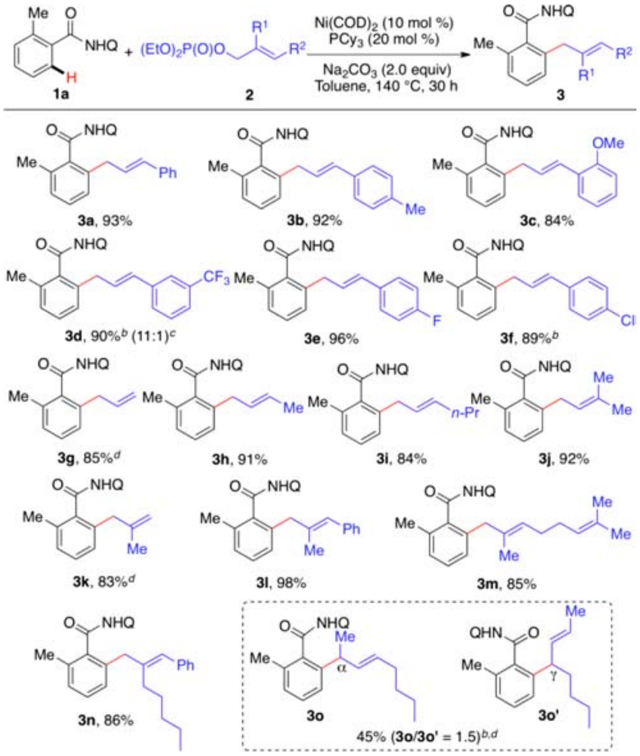
We started our investigation by treating cinnamyl alcohol and its derivatives with 8-aminoquinoline-containing benzamides. In the presence of 10 mol % of Ni(COD)$_2$, 20 mol % of PCy$_3$, and 2 equiv of Na$_2$CO$_3$, the use of cinnamyl alcohol, ether, acetate, and carbonate as allyl partners did not give the desired allylarene (see the Supporting Information for parameter optimization). In contrast, it was found that cinnamyl phosphate allows the formation of the allylated product **3a** in excellent yield (Scheme 3). Meanwhile, the Ni(II) salt of Ni(OTf)$_2$ enables the improvement of this transformation, leading to **3a** in 90% yield. In addition to PCy$_3$, other ligands such as P*t*-Bu$_3$·HCl, PPh$_3$, and carbenes also permit the reaction to occur smoothly, even though slightly lower yields were obtained. It is worth mentioning that the C−H allylation proceeds with complete *α*- and *E*-selectivity, and the related olefin-migration isomer was not detected in these cases.

Scheme 3. Scope of Allyl Phosphates[a]

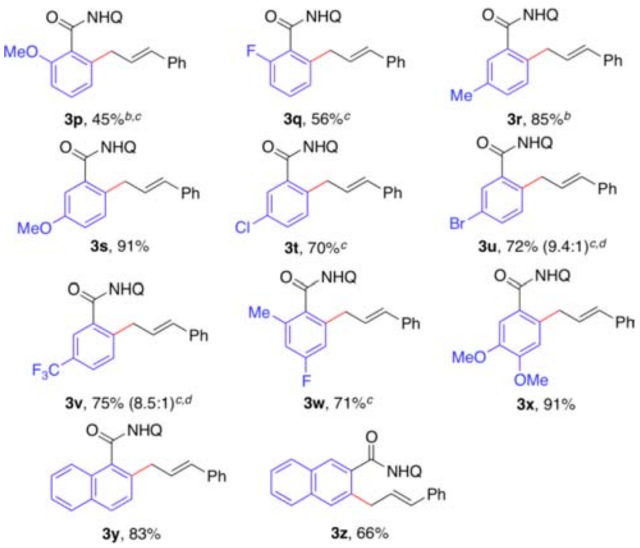


[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), Ni(COD)$_2$ (0.02 mmol), PCy$_3$ (0.04 mmol), Na$_2$CO$_3$ (0.4 mmol), Toluene (1.0 mL), 140 °C, 30 h; isolated yields. [b] Ni(OTf)$_2$ (0.02 mmol) was employed. [c] The ratio of **3d** and the related olefin-migration isomer was determined by ^{1}H NMR. [d] 160 °C.

The scope of allyl phosphates was explored by treatment with benzamide **1a** (Scheme 3). The presence of electron-donating or -withdrawing substituents on the scaffolds of cinnamyl phosphates has no obvious influence on the transformation, giving linear allylarenes **3b**−**3f** in good to excellent yields (84%−96%). In addition to cinnamyl phosphates, alkyl-substituted partners are also suitable in the allylation (**3g**−**3j**). As expected, the reactions of 2-methyl and pentyl-bearing allyl phosphates occur effectively giving allylated products **3k**−**3n** in 83%−98% yields. Notably, a sterically demanding secondary allyl phosphate furnishes a mixed regioisomer **3o** and **3o′** in the transformation, which may be generated from two distinctive S$_E$2 and S$_E$2′ reaction pathways.

Encouraged by these results, we then turned our attention toward probing various substituents on benzamides. As shown in Scheme 4, the replacement of *ortho*-methyl with methoxy or fluoride on benzamide leads to a low conversion (**3p** and **3q**). Electron-donating methyl and methoxy groups can be successfully introduced to the meta position of allylarene derivatives (**3r** and **3s**). Interestingly, the formation of a corresponding olefin-migration isomer in small amounts was observed from 3-bromo or trifluoromethyl-containing substrates (**3u** and **3v**). In contrast, the use of disubstituted benzamides produces single monoallylation products **3w** and **3x** in good yields. Additionally, the reactions of 1- and 2-naphthamides also take place smoothly under standard conditions (**3y** and **3z**).

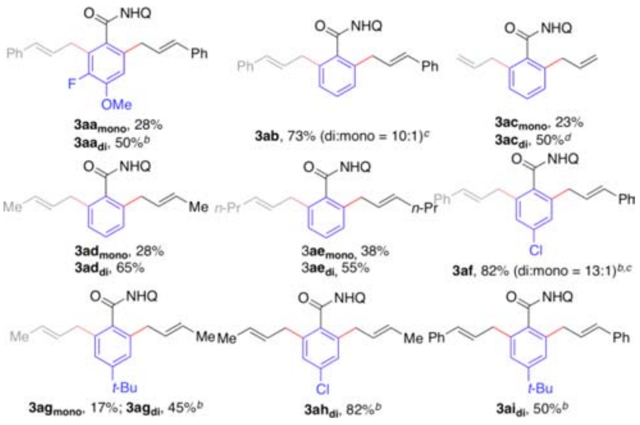
Scheme 4. Synthesis of Monoallylated Products[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol), Ni(COD)$_2$ (0.02 mmol), PCy$_3$ (0.04 mmol), Na$_2$CO$_3$ (0.4 mmol), Toluene (1.0 mL), 140 °C, 30 h; isolated yields. [b] 160 °C. [c] Ni(OTf)$_2$ (0.02 mmol) was employed. [d] The ratio of allylarene and the olefin isomer was determined by ^{1}H NMR.

Compared with forming a monoallylated product from 3,4-dimethoxy-substituted benzamide, the replacement of 3-methoxy with fluoride affords mixed mono- and diallylation products **3aa** (Scheme 5). It may be ascribed to the effect of less steric hindrance of the fluoro substituent, resulting in a high reaction rate for the diallylation. In particular, simple benzamide furnishes diallylated arenes as major products in the conversion (**3ab**−**3ae**). 4-Alkyl and chloro-bearing benzamides proved to be effective, leading to mixed or diallylated products **3af**−**3ai** in good yields. It was noteworthy that the C−H allylation of **1a** can be conducted on a large scale; the allylated product **3a** was achieved with complete *α*- and *E*-selectivity (eq 1).

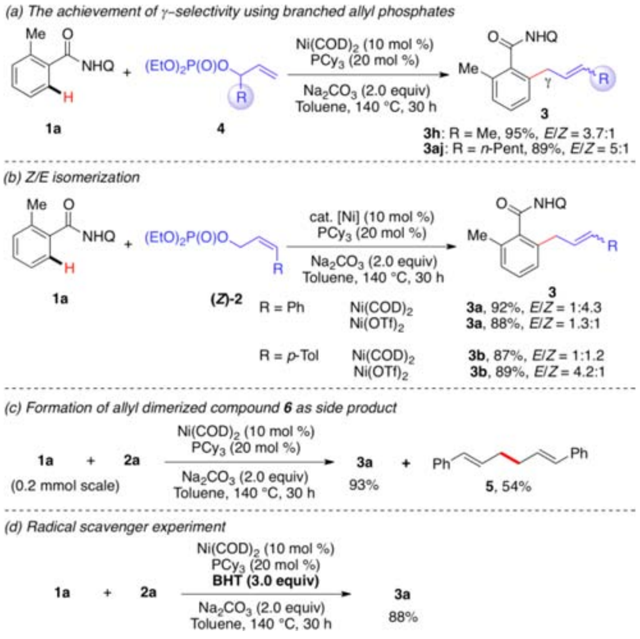
Scheme 5. Nickel-Catalyzed Diallylation[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.6−1.2 mmol), Ni(COD)$_2$ (0.02 mmol), PCy$_3$ (0.04 mmol), Na$_2$CO$_3$ (0.4−0.8 mmol), Toluene (1.0 mL), 140 °C, 30 h; isolated yields. [b] Ni(OTf)$_2$ (0.02 mmol) was employed. [c] The ratio of mono- and diallylation products was determined by ^{1}H NMR. [d] 160 °C.

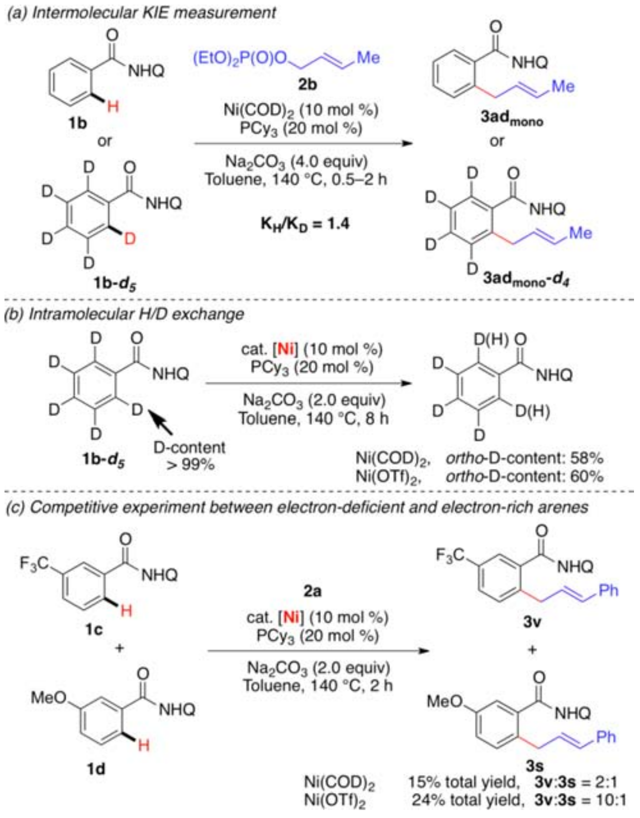
To gain mechanistic insights into the allyl regioselectivity, branched secondary allylphosphate **4** was chosen to react with benzamide **1a**. As shown in Scheme 6a, only formation of linear stereoisomeric products with complete γ-site selectivity was observed. This result suggests that the allyl site selectivity was heavily influenced by the steric environment around allyl phosphates, and reaction is favored at a position of less steric hindrance. Interestingly, the employment of *Z*-allyl phosphates affords mixed *E*/*Z* stereoisomers in the reaction (Scheme 6b). Note that the C−H allylation of **1a** provides an allylic dimer **5** as a side product (Scheme 6c). In the absence of **1a**, the same compound was also detected under standard conditions. It was thought to be derived from a disproportionation of the related π-(allyl)Ni(OR) complex.[19] Further study reveals that the addition of a radical scavenger of 2,4-di-*tert*-butyl-4-methylphenol (BHT) into the catalytic system has no obvious influence on the conversion, suggesting that the single-electron-transfer (SET) mechanism may be excluded in the reaction pathway (Scheme 6d).

Scheme 6. Mechanistic Insights



Because no related diallylation compound was detected within 2 h in the reaction of **1b** with 2-butenyl phosphate, the measurement of the intermolecular kinetic isotope effect (KIE) for the transformation was performed next (Scheme 7a). A low KIE value of 1.4 was obtained, implying that the cleavage of the *o*-C−H bond of benzamide may not be rate-limiting step in the catalysis. Meanwhile, a significant H/D exchange between the NH moiety and *ortho*-D was observed, suggesting that a reversible and rapid C−H bond cleavage may be involved in the conversion (Scheme 7b). Moreover, the competitive experiment shows that an electron-withdrawing substituent on the benzamide favors the transformation. This result indicates that a concerted-metalation−deprotonation (CMD) mechanism can be considered for the cleavage of the *ortho*-C−H bond (Scheme 7c).

Scheme 7. Mechanistic Experiments



In summary, we have developed a nickel-catalyzed C−H allylation with allyl phosphates. This reaction enables highly selective installation of allyl scaffolds into the ortho site of benzamides with the assistance of an 8-aminoquinoline auxiliary. Unlike the Rh- and Fe-catalyzed transformations,[14,15] the allyl regioselectivity in the reaction was predominantly governed by the steric hindrance of allyl partners, allowing for the predictable and scalable preparation of linear allylarene derivatives by the use of cost-attractive nickel catalysts.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed optimization data; experimental procedures; characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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