C–H Activation

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C–H Alkenylation of Azoles with Enols and Esters by Nickel Catalysis**

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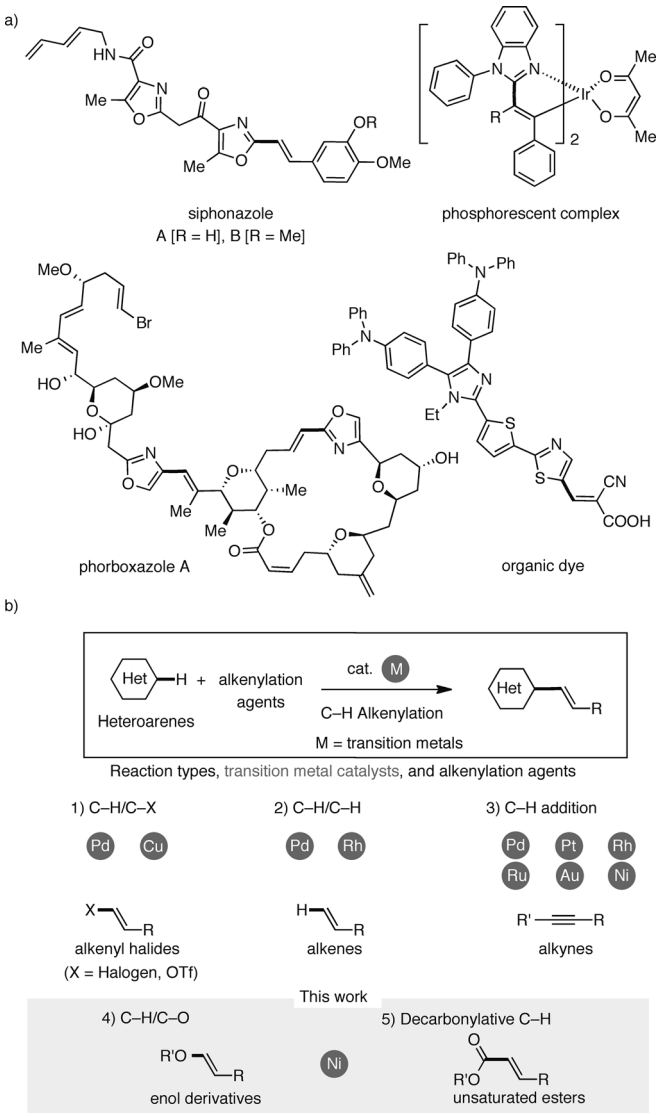
Transition metal catalyzed alkenylation is one of the most reliable methods for making alkenyl-substituted arenes as exemplified by the Mizoroki–Heck reaction.[1] Recently, direct C–H alkenylation[2] has received growing interest as an emerging tool for constructing alkenylated arenes and particularly alkenylated heteroarenes, since they are predominant motifs in biologically active natural products, pharmaceuticals and organic materials (Scheme 1 a).[3] Representative reaction types of C–H alkenylation include (Scheme 1 b): 1) C–H/C–X alkenylation (X = halogens including triflates) of heteroarenes with alkenyl halides by using palladium and copper catalysts,[4] 2) C–H/C–H alkenylation (oxidative Mizoroki–Heck reaction) of heteroarenes with simple alkenes by using palladium and rhodium catalysts,[5] and 3) C–H addition of heteroarenes to alkynes by transition-metal catalysts.[6] There also exist other C–H couplings which are outside the realm of the above-mentioned category.[7]

Meanwhile, our group has developed a number of unique C–H arylation reactions of heteroarenes catalyzed by transition-metal complexes.[8–10] For example, we recently discovered the first nickel-catalyzed C–H/C–O coupling of heteroarenes and phenol derivatives[10a] as well as a decarbonylative C–H coupling between heteroarenes and aryl esters.[10b] These catalytic processes are unique among other C–H arylation methods not only because they allow incorporation of unconventional aryl electrophiles in C–H arylation (phenol derivatives and arenecarboxylates), but also because these reactions are uniquely promoted by an enabling supporting ligand, 1,2-bis(dicyclohexylphosphino)ethane (dcype), on a nickel(0) catalyst (other closely related ligands display extremely low or no promoting effect in these catalyses).



Scheme 1. a) Useful alkenyl-substituted heteroarenes. b) A classification of the type of direct C–H alkenylation of heteroarenes.

Based on these auspicious discoveries, we questioned whether unprecedented C–H alkenylations of heteroarenes would become possible with a Ni/dcype catalyst by using enol derivatives [Scheme 1 b, 4)] and α,β-unsaturated esters [Scheme 1 b, 5)] as alkenylation agents. The C–H/C–O alkenylation of heteroarenes is rare,[11] and the decarbonylative C–H alkenylation is thus far unknown. Herein, we report the C–H

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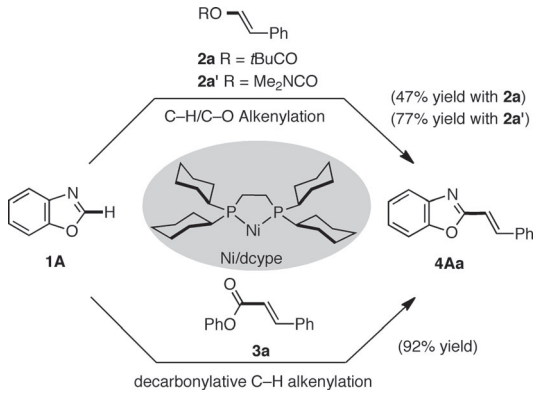
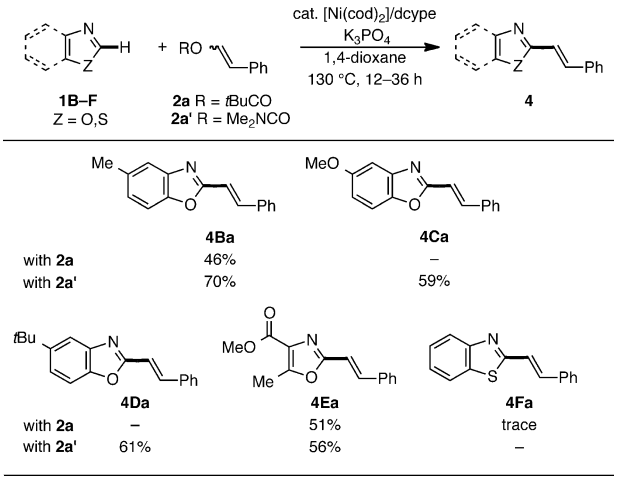
alkenylation of azoles with enol derivatives and unsaturated esters catalyzed by Ni/dcype, which is advantageous because of the low cost of the catalyst as well as the expansion of the scope of the alkenyl substrate. The application to the convergent formal synthesis of siphonazole B is also described.

We began by investigating the coupling of benzoxazole (**1A**) with styryl pivalate (**2a**), carbamate (**2a′**), and phenyl cinnamate (**3a**) as alkenylating agents (Scheme 2). Gratifyingly, by slightly modifying our original reaction conditions for C–H/C–O arylation and decarbonylative C–H arylation,[12] the Ni/dcype catalyst displayed activity for the target reactions to afford the alkenylazole **4Aa**. For example, **1A** was coupled with **2a** (1.5 equiv) in the presence of $[Ni(cod)_2]$ (10 mol%), dcype (20 mol%), and K_3PO_4 (2.0 equiv) in 1,4-dioxane at 130°C for 12 hours to produce **4Aa** in 47% yield (C–H/C–O alkenylation). When styryl carbamate (**2a′**) was used instead of pivalate **2a**, **4Aa** was obtained in 77% yield. The decarbonylative C–H alkenylation also took place very smoothly. Phenyl cinnamate (**3a**) served as an alkenylating agent in the coupling with **1A** under the influence of $[Ni(cod)_2]$/dcype/K_3PO_4 at 150°C to give **4Aa** in 92% yield. Notably, it was again found that dcype is the only enabling ligand for these nickel catalyses. Other ligands displayed essentially no activity for these C–H alkenylations.[12]



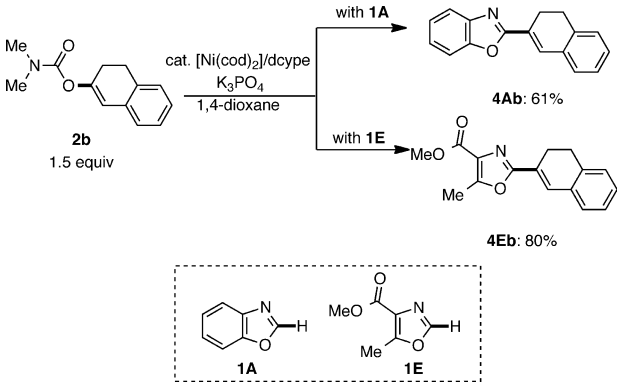
Scheme 2. Nickel-catalyzed C–H/C–O alkenylation and decarbonylative C–H alkenylation of azoles. Reaction conditions: **1A** (0.4 mmol), **2a**, **2a′**, or **3a** (0.6 mmol), $[Ni(cod)_2]$ (0.04 mmol), dcype (0.08 mmol), K_3PO_4 (0.8 mmol), 1,4-dioxane, 130°C (for **2a** and **2a′**) or 150°C (for **3a**).

With the optimized reaction conditions in hand, the substrate scope of the C–H/C–O alkenylation using various azoles with styryl pivalate (**2a**) and carbamate (**2a′**) was investigated (Scheme 3).[13] Benzoxazoles with substituents at the C5 position (methyl, methoxy, and *tert*-butyl) nicely reacted with either **2a** or **2a′** to afford the corresponding styrylated products **4Ba**, **4Ca**, and **4Da** in moderate to good yields. Oxazole derivatives were also found to react with **2a** and **2a'** to give the corresponding product **4Ea** in 51% and 56% yields, respectively. Unfortunately, however, benzothiazole did not react with **2a** and **2a′** under the present reaction conditions.



Scheme 3. Substrate scope of C–H/C–O alkenylation. cod = cyclo-1,5-octadiene.

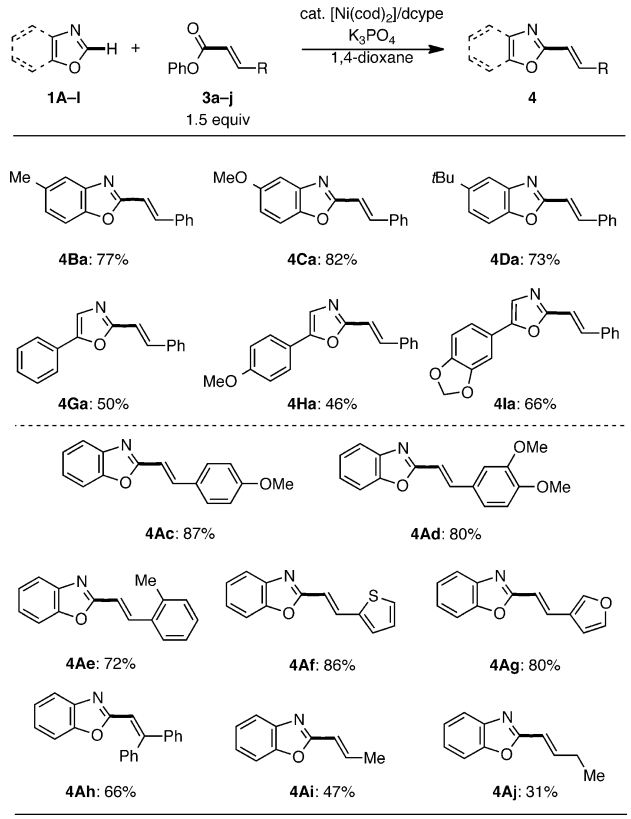
The success of this C–H/C–O alkenylation using enol derivatives offers the opportunity to assume carbonyl compounds, in particular ketones, as a source of alkenyl groups in synthesis. Indeed, the enol carbamate **2b**, which can be readily prepared from β-tetralone in one step, smoothly coupled with azoles **1A** and **1E** to furnish the alkenylated-azoles **4Ab** (61%) and **4Eb** (80%), respectively (Scheme 4).



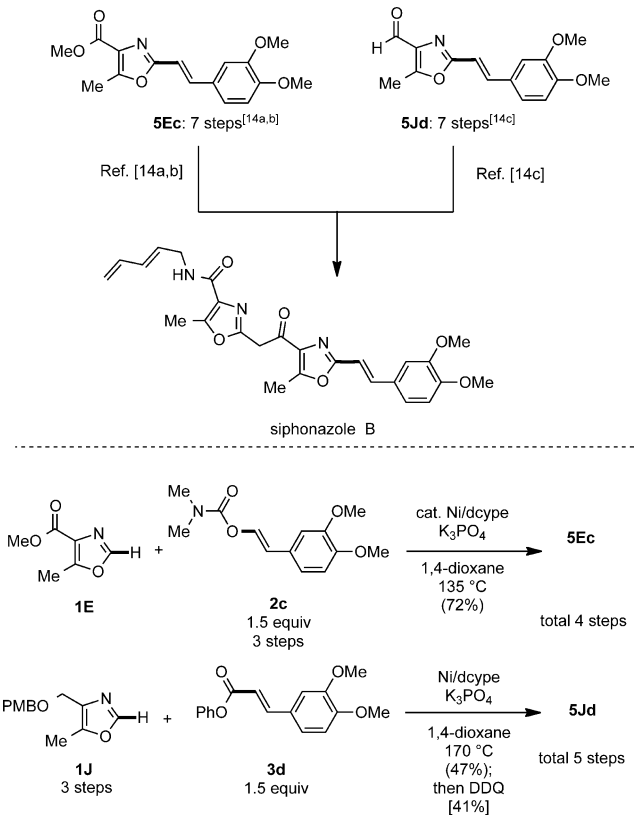
Scheme 4. C–H/C–O alkenylation using the ketone-derived enol carbamate **2b**.

It should be noted that the aromatization of **2b** and the products **4Ab** and **4Eb**, a reaction which could be a serious side reaction for these compounds, did not take place under the C–H/C–O alkenylation conditions. These results underscore the synthetic utility of the present coupling using enol derivatives.

Scheme 5 shows the scope of decarbonylative C–H alkenylation catalyzed by the $[Ni(cod)_2]$/dcype/K_3PO_4 system. The scope with regard to azole substrates was examined using phenyl cinnamate (**3a**) as the alkenylating agent. Benzoxazoles bearing 5-methyl, 5-methoxy, and 5-*tert*-butyl groups reacted with **3a** to give the products **4Ba**, **4Ca**, and **4Da**, respectively, in high yields. The 5-aryloxazoles **1G–I** underwent coupling with **3a** in moderate yields. The scope of



Scheme 5. Substrate scope of decarboxylative C–H alkenylation.



Scheme 6. Convergent synthesis of siphonazole B intermediates by nickel-catalyzed C–H alkenylation. DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, PMB = *p*-methoxybenzyl.

α,β-unsaturated esters (alkenylating agents) was examined using **1A** as the azole component, and was found to be broad. A range of aromatic and heteroaromatic substituents at the β position of the phenyl acrylates **3c–g** was tolerated and furnished the corresponding decarbonylative coupling products **4Ac–Ag** in high yields. Coupling proceeded well with substrates having a sterically demanding *ortho*-substituent (**3e**) and 3,3-diphenylacrylate (**3h**). The coupling of substrates having aliphatic substituents at the β position of the phenyl acrylate structure **3i** and **3j** also took place to give **4Ai** and **4Aj**, respectively, albeit in somewhat lower yields. Thus, this coupling reaction shows a broader scope for α,β-unsaturated esters over enol derivatives. However, unsubstituted α,β-unsaturated esters as the alkenylating agent as well as other heteroarenes such as thiazoles and imidazoles did not react under the present reaction conditions.

Finally, as a showcase of these new azole alkenylation methods, we applied them to the synthesis of siphonazole B, a natural product isolated from a metabolite from *Herpetosiphon* sp.[3a] Although siphonazole B has already been synthesized by Moody and co-workers[14a,b] and Zhang and Ciufolini,[14c] their syntheses took many steps because of a parallel repetition of linear synthetic sequences. To address this problem, we attempted the convergent synthesis of siphonazole B by using our nickel-catalyzed C–H alkenylation reactions (Scheme 6). Although **5Ec** and **5Jd** are the intermediates in the previous synthesis, each fragment needs to be synthesized in seven linear steps. Thus, we retrosynthetically break up both intermediates into oxazoles (**1E** and **1J**) and alkenyl precursors (**2c** and **3d**), and coupled them using the $[Ni(cod)_2]$/dcype/K_3PO_4 system. The C–H/C–O alkenylation of **1E** with (*E*)-**2c** furnished the coupling product **5Ec** over four linear steps. The decarbonylative C–H alkenylation of **1J** with **3d** occurred as well under similar reaction conditions at 170 °C. The follow-up deprotection and oxidation afforded the aldehyde **5Jd** over five linear steps (including the preparation of **1J**). Thus, the total synthesis of siphonazole B is be shorter than previous reports. Additionally, the nickel-catalyzed C–H alkenylations have an advantage that both alkenylating agents (enol derivative and unsaturated ester) are easily prepared by a Wittig reaction, and can be directly coupled without producing halogen waste.

In summary, we have developed two new C–H alkenylations of azoles, that is C–H/C–O alkenylation and decarbonylative C–H alkenylation, which are uniquely catalyzed by Ni/dcype. These newly developed azole alkenylation reactions were successfully applied to the convergent formal synthesis of siphonazole B. Determining the role of dcype in the catalysis and the expansion of substrate scope, particularly with respect to heteroarenes, are ongoing.

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[12] See the Supporting Information for details and further screening of reaction conditions.

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