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Nickel-catalyzed Heck reaction of cycloalkenes using aryl sulfonates and pivalates†

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Nickel-catalyzed Heck reaction of cycloalkenes delivers unusual conjugated arylated isomers. Nickel(0) catalysts ligated by chelating dialkylphosphines effectively activate not only aryl triflates as electrophiles, but also less reactive aryl mesylates, tosylates and pivalates. The omission of bases allows nickel hydride species to exist long enough to perform *in situ* olefin isomerization of initial Heck adducts.

Palladium catalysts have been working horses of Heck reaction, which routinely arylates alkenes and provides aryl olefins after *syn* β -hydrogen elimination.¹ One limitation, however, is the slow oxidative addition of common palladium(0) complexes towards unactivated aryl electrophiles such as mesylates, tosylates and pivalates. For example, Pd-catalyzed intermolecular Heck reaction of tosylates is limited to alkenyl and activated heteroaryl ones.²

The application of cheap, easily available nickel complexes in Heck-type reactions dates back to the late 1980s, which has enabled Heck-type reactions of various types of alkenes of different electronic properties.³ For example, nickel/dppf enabled Heck reaction of styrenes with aryl pivalates and tosylates leading to (*E*)-stilbenes.^{3f} In another case, nickel/1,4-bis(dicyclopentylphosphino)butane promoted branched-selective arylation of α -olefins using aryl triflates, mesylates, tosylates and carbamates.³ⁱ Recently, there has been a surge of interest in applying nickel catalysts to achieve asymmetric Heck-type reactions⁴ and domino bifunctionalization of alkenes.⁵ For example, our group disclosed nickel-catalyzed asymmetric Heck reaction of

2,3-dihydrofuran and N-Boc-dihydropyrrole derivatives, which involved fast isomerization of the initial Heck isomers as compared to more stable ones.^{4e} Nickel(0) catalysts can effectively activate strong C–O bonds in aryl pivalates, mesylates and tosylates.⁶ The oxidative addition of nickel(0) complexes to organic electrophiles is exogonic and has a lower barrier than analogous palladium complexes. Additionally, arylnickel(II) species can have a faster insertion of alkenes than palladium analogues, although the subsequent β -hydrogen elimination from arylnickel(II) species may be slower.⁷

In typical Heck reactions of cyclic alkenes, non-conjugated isomers are usually formed as major isomers, owing to *syn* requirement of β -hydrogen elimination,⁸ which formed the basis of asymmetric Heck reaction of cycloalkenes.⁹ Our group previously reported palladium-catalyzed Heck reactions that afforded conjugated arylcycloalkenes using aryl triflates and bromides.¹⁰ Mechanistically, palladium hydride species, under optimal conditions, promoted extensive alkene migration of the initially Heck isomers into conjugation with the added aryl rings.

Aryl electrophiles herein are expanded beyond reactive triflates, including more challenging aryl mesylates, tosylates and pivalates. Usually, during the synthesis of conjugated arylalkenes, cross-coupling reactions using alkenyl electrophiles or alkenyl metal reagents are required otherwise.¹¹ These arylated cycloalkenes are often used in the stereoselective synthesis of natural products¹² and medicines.¹³ Importantly, there is increasing recognition in medicinal research that incorporation of saturated carbocycles with distinct 3D shapes, in place of flat (hetero)aryl rings, can help to develop high-affinity binders and/or prevent promiscuous binding.¹⁴

Herein, we disclose the nickel-catalyzed Heck process of cycloalkenes, which affords conjugated isomers of arylalkenes. Initially, we used a model reaction of 4-methoxyphenyl triflate and cyclopentene and aimed to optimize nickel catalysts (Fig. 1). In the screening of common diphosphines, we found that 1,2-bis(dicyclohexylphosphino)ethane (dcype) afforded an 83% yield of 1-arylcyclopentene **2a** as the sole isomer detected in the mixture. No allylic Heck isomers were detected in the

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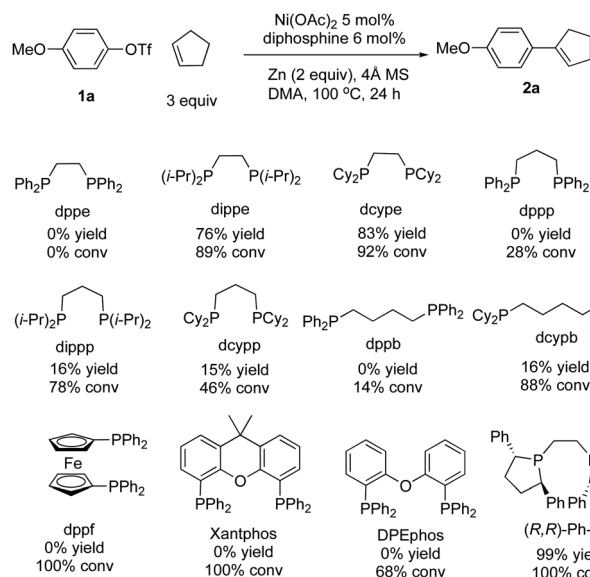
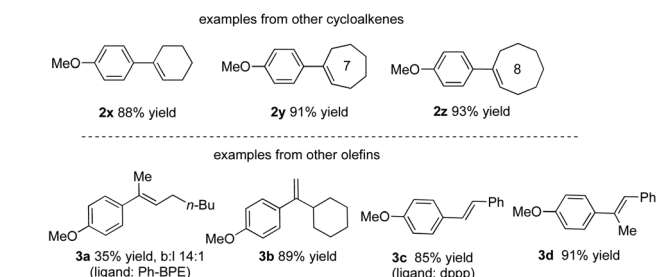
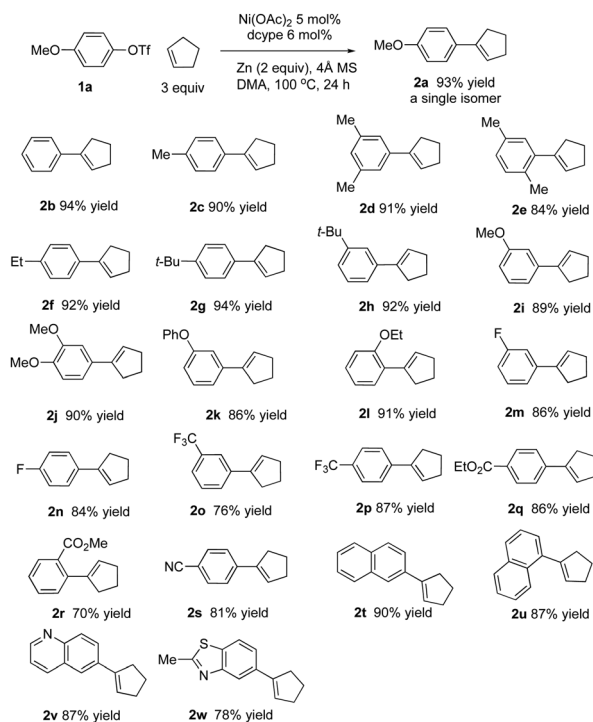


Fig. 1 Optimizations of diphosphines for the nickel-catalyzed model reaction.

early hours of the reaction (by GC and GCMS). Dippe led to a 76% yield. At 1 mmol scale, 83% conversion and 72% yield of **2a** were detected after 72 hours, along with some anisole as a side product. Dcype and dcypp on propylene and butylene backbones, however, afforded <20% yield of **2a**, along with reduction to arene as the main side reaction. Nickel complexes of chelating diphenylphosphines such as dppe, dppp and dppb had very low reactivity toward aryl triflate and no olefin insertion occurred. In the presence of nickel complexes of dppf, Xantphos and DPEphos, however, high conversion of aryl triflate was detected, but the reduction to anisole became the main process. Moreover, a diphospholane Ph-BPE formed a very active nickel catalyst, which delivered **2a** in 99% yield. Nickel salts of chloride, bromide, iodide, acetate and acetoacetate can form active nickel(0) catalysts of dcype *in situ*.

DMA was the optimal solvent for this process, while in other polar solvents such as DMF, NMP and DMSO, the model Heck reaction also proceeded well. Zinc dust from Aldrich with particle size <10 μm was chosen to reduce (dcype)NiCl₂ to the active nickel(0) species. No external bases were added, and thus zinc dust also helped to reduce nickel hydride species to nickel(0). Moreover, activated molecular sieves were added to prevent unwanted hydrolysis of aryl triflates at high temperatures caused by trace amounts of water in DMA.

Next, we used the $\text{Ni}(\text{OAc})_2$ /dcype catalyst in Heck reactions of cyclopentene as a model cycloalkene with a wide range of aryl triflates (Scheme 1). Many aryl triflates reacted efficiently, including those with electron-donating and withdrawing groups (**2j–p**), as well as those with *ortho*-substituents on the aryl rings (**2l**, **2r**). Polar groups, esters and nitriles were compatible (**2q–s**), but ketones and aldehydes underwent side reactions including aldol condensation. Triflates of nitrogen-containing heterocycles, quinoline and benzothiazole gave the desired adducts in good yields (**2v–w**), but not pyridyl ones. The optimal

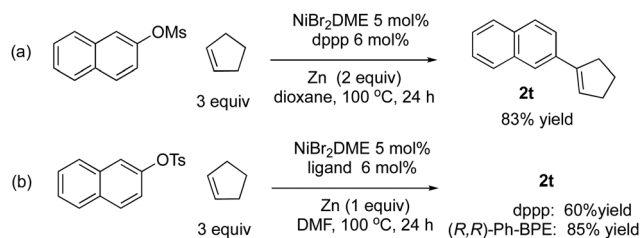


Scheme 1 Heck reaction of (hetero)aryl triflates with cycloalkenes, styrenes and aliphatic olefins.

procedure also produced arylcycloalkenes in good yields from cyclohexene, cycloheptene and cyclooctene (**2x–z**), but a low yield from cyclononene. 3-Phenylcyclohexene was also tested, but it had lower reactivity.

In anisylation of 1-octene, nickel/dcype afforded full conversion and 33% yield of three Heck isomers (branched/linear 4.4:1). The main isomer **3a** was derived from fast olefin isomerization of the initial Heck adduct. Nickel/Ph-BPE improved branched selectivity to 14 : 1, although the yield (35%) was not better and the reduction still remained significant. In the reaction of cyclohexylethene, internal arylation was the dominant process to yield adduct **3b** as the sole isomer. The internal regioselectivity observed herein is opposite to terminal arylation of allylbenzene as reported by Watson *et al.*^{3f}

The procedure was also applied to anisylation with styrene and *trans*-phenyl-1-propene, affording (*E*)-stilbene derivatives^{3f} **3c** and **3d** selectively. In the reaction of styrene, nickel/dcype furnished only 30% conversion and 30% of **3c**, which was improved to full conversion and 85% yield by nickel/dppp.



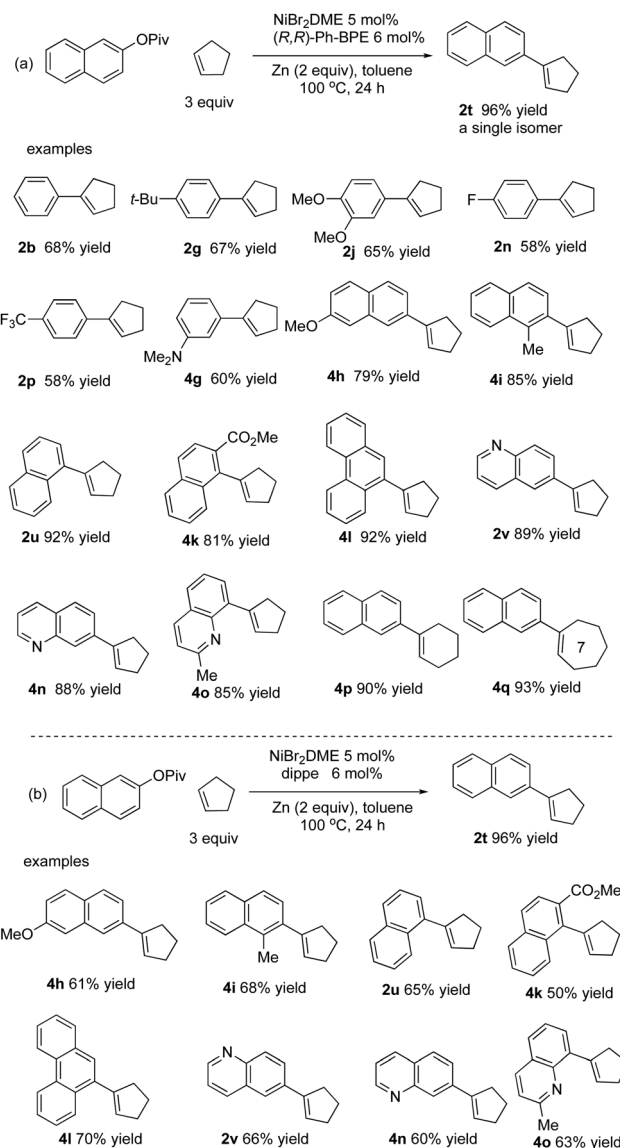
Scheme 2 Heck reaction of a model aryl mesylate and tosylate.

The nickel/diphosphine catalysts can effectively activate aryl mesylates and tosylates. In a model study of 2-naphthyl mesylate, for example, nickel/dcype furnished 40% of product **2t** along with 50% yield of naphthalene. After fine-tuning of the catalysts, nickel/dppp helped to minimize the reduction and produced adduct **2t** in 83% yield in 1,4-dioxane (see Scheme 2a). Nickel/dppp also afforded a 60% yield of **2t** from 2-naphthyl tosylate, along with some naphthalene. The yield of **2t** was improved to 85% yield, on using strongly donating Ph-BPE as ancillary ligands in DMF (Scheme 2b).

Nickel/Ph-BPE also efficiently promoted the Heck reaction of aryl pivalates with cyclopentene. Aryl pivalates with both electron-rich and electron-deficient groups on phenyl rings (**2j**, **2n**, **2p**) reacted with cyclopentene in moderate yields, while reduction accounted for most of the material balance (Scheme 3a). Notably, the nickel(0) catalysis was not impeded by extended π rings such as phenanthrene and quinoline (**4l–o**). The reactions of cyclohexene and cycloheptene also gave excellent yields (**4p–q**). But coupling with 1-octene failed to occur with less than 10% conversion of the 2-naphthyl pivalate and reduction detected. Another catalyst nickel/dippe promoted similar Heck reactions and provided conjugated isomers in 50–70% yields in most cases (Scheme 3b). At 1 mmol scale, 76% conversion and 67% yield of **2t** were received after 72 h, in the presence of nickel/(*R,R*)-Ph-BPE; with the dippe ligand, 100% conversion and 71% yield of **2t** along with some naphthalene.

Notably, in the model reaction of 2-naphthyl pivalate with cyclopentene under Watson's conditions, Ni(cod)₂/dppf afforded 81% conversion and the allylic isomer in 60% yield (allylic *vs.* conjugated isomers 14:1). Details: 10% Ni(cod)₂, 12% dppf and K₃PO₄ in toluene; heating at 125 °C for 36 h.^{3f} Obviously, isomerization of the initial Heck products was absent due to fast removal of nickel hydride species by K₃PO₄ at high temperature. Under another Watson's conditions (10% NiCl₂DME, 12% dppf and zinc dust), only 20% conversion and reduction were detected without any Heck isomer formed. For example, on reacting with 1-octene, Ni(cod)₂/dppf provided 83% conversion and Heck isomers with 47% yield (branched/linear ratio 1:4.7). Thus, its terminal selectivity with α -olefins was opposite to our internal selectivity (see **3a** in Scheme 1).

In summary, nickel complexes ligated through strongly donating diphosphines, for example, dcype and Ph-BPE, catalyzed selective Heck reaction of cycloalkenes to produce conjugated arylalkenes exclusively. In contrast, non-conjugated isomers were produced under other Ni-catalyzed Heck procedures.^{3f,3m} As a key feature, external bases were intentionally omitted so that nickel hydride



Scheme 3 Heck reaction of aryl pivalates and cycloalkenes.

species can live long enough to allow extensive olefin isomerization of the initial Heck isomers.

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Conflicts of interest

There are no conflicts to declare.

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