Nickel-Catalyzed Direct Synthesis of Aryl Olefins from Ketones and Organoboron Reagents under Neutral Conditions

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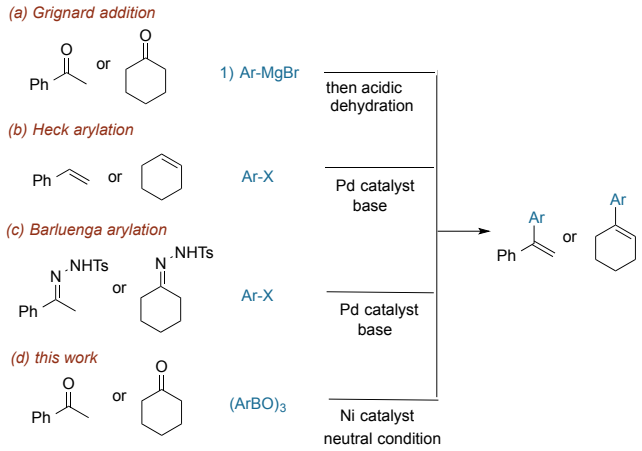
Supporting Information Placeholder

ABSTRACT: A nickel-catalyzed addition of arylboron reagents to ketones results in aryl olefins directly. The neutral condition allows acidic protons of alcohols, phenols, and malonates to be present and fragile structures are also tolerated.

Aryl olefins are very useful in the synthesis of bioactive compounds and drugs.[1] Furthermore, aryl olefins are present as structural motifs in several drugs, including isocombretastatin A, tamoxifen, bexarotene and ratanhine. Diarylethenes are also present in photo-responsive molecular switches, motors and photomedicines.[2] Among many synthetic methods to access these olefins,[3] classical syntheses include Wittig methylenation of ketones and addition of aryl Grignard reagents (Scheme 1a). The organometallic addition is followed by dehydration under acidic conditions or basic elimination after alcohol activation.[4] Unfortunately, the strongly basic reagents and acidic conditions are incompatible with sensitive groups and acidic protons, if they are present in target compounds.



Scheme 1. Representative methods for preparation of arylolefins.

Previously, we and other groups reported Heck–type arylation of cyclic olefins to produce 1-arylolefins (Scheme 1b).[5] We also disclosed α–selective Heck arylation of terminal olefins carrying either alkyl or aryl groups.[6] However, these methods are limited to simple terminal olefins and unsubstituted cyclic olefins. Another common approach, crosscoupling reactions[7] using alkenyl electrophiles or alkenylmetal reagents are not atom–economic; the reagents also need to be prepared beforehand (Scheme 1c). Notably, cross-couplings of elaborate alkenyl trilfates, derived from ketones, are often used in the preparation of complex bioactive compounds.[8] Pd-catalyzed Barluenga arylation of *N*-tosylhydrazones, also prepared from ketones, allows quick access to aryl cycloolefins and 1,1-diarylalkenes from cyclic ketones and methyl ketones, respectively (Scheme 1d).[9] Its drawbacks, however, include the need to use strong bases, which are incompatible with sensitive groups, and poor E/Z ratio of olefinic isomers in products.[10]

Herein, we report a general arylation reaction that allows formation of 1-arylolefins from various ketones directly under neutral conditions (Scheme 1e). Recently, we found, as a serendipitous finding, that a nickel-catalyzed reaction between acetophenone and phenylboroxine afforded 1,1-diphenylethylene in good yield (Figure 1), when the nickel(0) catalyst was supported by a strongly donating bisphosphine, 1,2-bis(dicyclohexylphosphino)ethane, dcype. Other common diphosphines, e.g., binap, dppe, dppp, dppb, and dppf, and monodentate phosphines such as PPh_3, PCy_3 and $PtBu_3$, Davephos and XPhos, afforded very little product (<10%). No base is needed in the reaction and we found that the addition of water (10 mol %) to dry diglyme improved the reproducibility of the reaction from run to run.

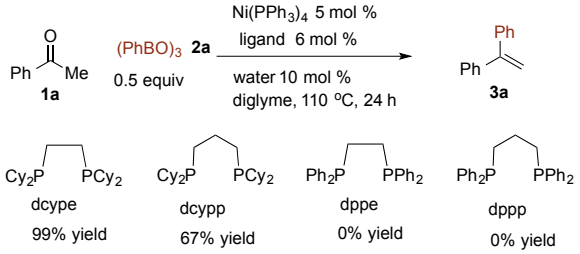


Figure 1. Ligand effect on the arylation of acetophenone.

The standard condition using dcype ligand can be applied to phenylation of a diverse array of both cyclic and acyclic ketones (Figure 2a-b). (i) Substrates carrying acidic protons gave the corresponding products in moderate to goof yields, for example, unprotected OH bonds in alcohol (**3ao**), phenol (**3b** and **3m**), NH bonds in aniline (**3c** and **3n**), amide (**3e**) and indole (**3ac**) and CH bonds in malonate (**3ar**) were well tolerated. (ii) Polar groups such as ester (**3f**), amide (**3e**), carbamate (**3ab**) and acetals (**3p** and **3ap**) were also compatible with exception of aldehydes, which gave a complex mixture including decarbonylative byproducts. (iii) Aryl C-F bonds and aryl ethers were tolerated.[11] Aliphatic and aryl C-Cl bonds led to moderate yields of expected olefins **3h** and **3j** owing to competing insertion of C-Cl bonds. Aryl bromides and iodides inhibited the desired olefin formation. (iv) The method is compatible with thiophene, furan, indole and pyridine (**3x**–**3ad**). (v) We have tested compatibility of some alcohols (as additives) in the model arylation reaction of **1a** and **2a**. Both 1° and 2° aliphatic alcohols remained intact, while 3° ones underwent complete dehydration. We noted that 2° and 3° benzylic alcohols underwent partial and complete dehydration, respectiviely. Allylic alcohols inhibited the catalytic process, probably by forming an η^3-allyl complex of nickel (see the supporting Information for details). Notably, methyl isopropyl ketone afforded terminal olefin **3af** as the major isomer with a selectivity of 8:1,

while cyclohexyl methyl ketone led to a single isomer **3ag** (Fig 2a). Phenylation of 2-methylcyclohexanone provided the less substituted isomer **3aq** as major product. Notably, 3-estrone carrying an unprotected phenol group also resulted in **3ds** in 63% yield, while 3-cholesterone afforded the conjugated diene **3at** as major isomer (Fig 2b).

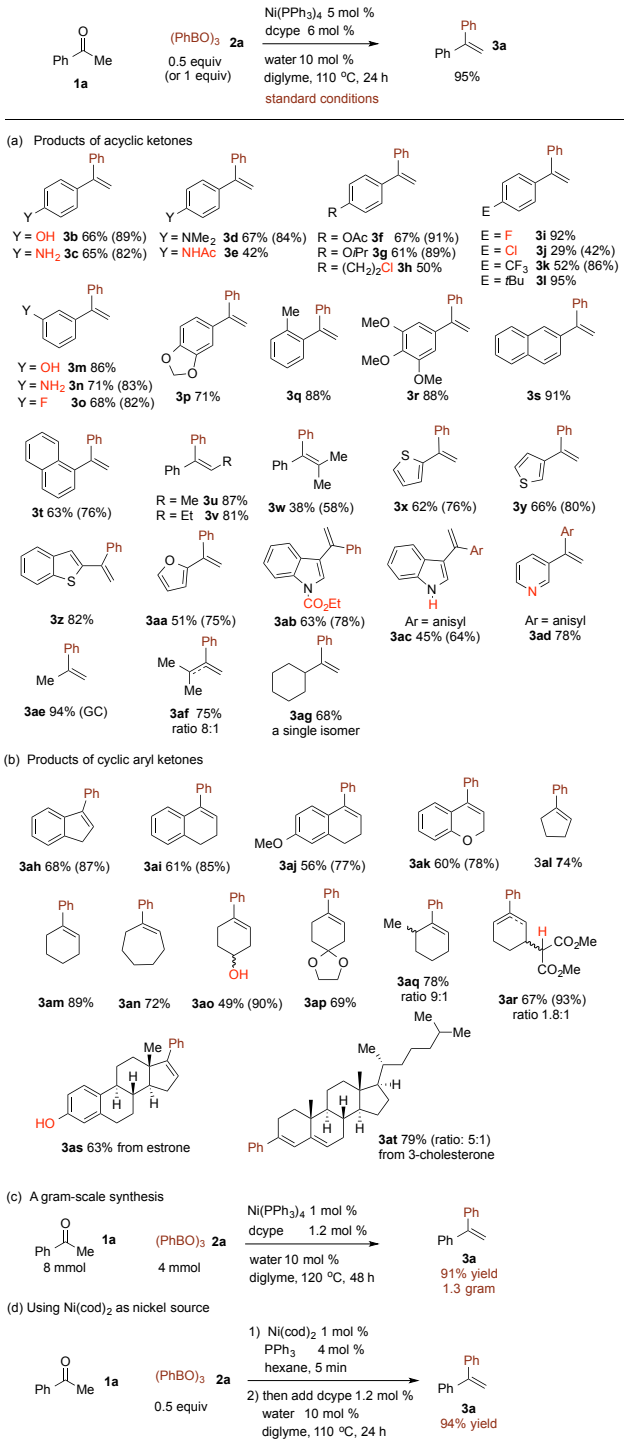


Figure 2. Arylation of ketone using phenylboroxine (yields in parentheses were obtained with 1 equiv of organoboroxine at 120 °C).

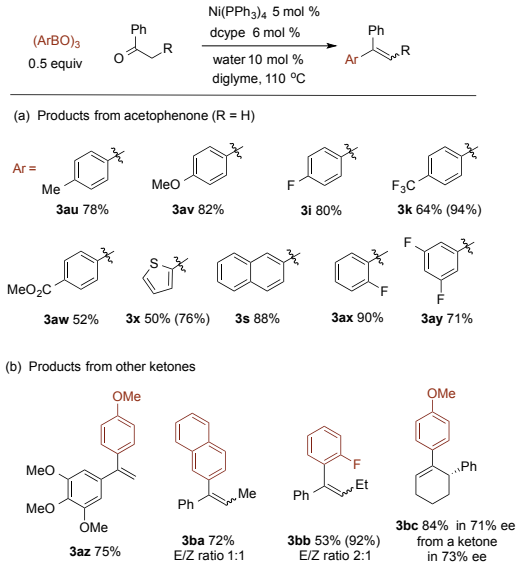


Figure 3. Arylation of ketones using other arylboroxines (yields in parentheses were obtained when 1 equiv of organoboroxine was used).

In examples wherein only moderate yields of olefins were obtained, it was caused by incomplete dehydration of carbinols in most cases. Increasing the amount of phenylboroxine to 1 equivalent helped to improve the yields in many cases (isolated yields in parentheses). The arylation condition was easily scaled up for a gram-scale synthesis using 1 mol % of nickel catalyst (Figure 2c). Furthermore, a combination of $Ni(cod)_2$ and PPh_4 can be used to replace $Ni(PPh_3)_4$ and gave essentially the same result in the model reaction(Fig 2d). However, nickel salts failed to efficiently catalyze the arylolefin formation even in the presence of zinc powder.

Arylboroxines of diverse electronic nature efficiently added to acetophenone, a model ketone (Figure 3a). In general, electron-deficient aryl rings led to lower yields of arylolefins (**3k** and **3aw**) than electron-neutral and rich ones. The addition of a *p*-anisyl ring to a substituted provided **3az**, a structural analogue of an antitumor agent, isocombretastatin A (Fig 4b).[12] Unfortunately, arylation of propiophenone and butyrophenone led to olefinic isomers **3ba** and **3bb** in poor E/Z ratios (Fig 3c-d).

In the presence of dry molecular sieve, arylboronic acids in situ condensed to form boroxines, and were directly used in arylation of ketones without further purification (Figure 4). In these cases, no water was added. Notably, a fluorescent pyrenyl ring with a low-lying LUMO, which may coordinate strongly to nickel(0) species and attenuate the nickel catalysis, also furnished the desired product **3bf** in moderate yield (Fig 4b). Alkenylation using *trans*-cinnamyl boronic acid was also attempted, but it failed to give the expected diene.

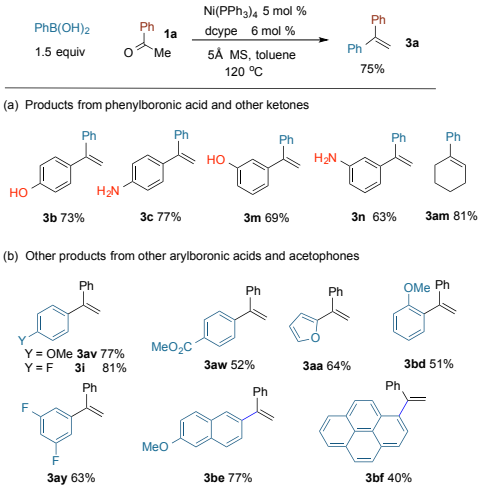


Figure 4. Arylation of ketones using arylboronic acids in the presence of molecular sieve.

In order to elucidate the mechanism of nickel-catalyzed arylation, we first monitored closely the model reaction of acetophenone and phenylboroxine (Fig 5a). We made several observations. (a) The reaction quickly formed a carbinol **D** in >90% yield within 1 h, as monitored by GC analysis of an aliquot of the reaction mixture after passing through silica gel. **D** then slowly converted to 1,1-diphenylethene in >90% yield over 24 h. (b) TEMPO inhibited the nickel catalysis, but no trapped radical species was detected. (c) A trace amount of water dramatically accelerated the formation of carbinol **D** in the initial phase of the reaction, but had little influence on the carbinol elimination to form the olefin (for details, see the Supporting Information).

Next, in order to determine the conditions necessary for dehydration of carbinol **D**, we subjected **D** to various conditions (Fig 5b). We found that *all* of $Ni(PPh_3)_4$, bisphosphine dcype and phenylboroxine were needed for the dehydration. No olefin was formed in the absence of phenylboroxine, while <10% of the product was detected if either $Ni(PPh_3)_4$ or dcype was missing. Next, we conducted competition experiments using a 1:1 mixture of **D** and **D-*d*$_3$** in one vessel. Its KIE value was determined to be 1.0 (Fig 5c). When the dehydration of **D** and **D-*d*$_3$** was conducted separately in two vessels, the value was 1.2. This indicates that the loss of the hydrogen (or proton) from the carbinol is not rate-limiting in the catalytic process.[13]

Nickel(0) complexes of phosphines easily form oxanickelacycles **A** with both aldehydes and ketones (Fig 5f).[14] Oxanickelacycles were implicated as key intermediates in some catalytic processes,[15] including 1,2-addition of organoborons to carbonyl groups that resulted in carbinols.[16] We thus propose that **A** is hydrolyzed by a trace amount of water to give **B.** The opening of **A** may be also caused by $PhB(OH)_2$ which is produced via partial hydrolysis of phenylboroxine by the added water (confirmed by proton NMR spectroscopy). **B** can undergo fast transmetalation to form phenylnickel **C**. Subsequent C-C reductive elimination of **C** formed carbinol **D** or **E** after in situ B-O exchange under catalytic conditions. Next, an S_N2-type oxidative addition[17] of (dcype)nickel(0) and **E** cleaves the benzylic C-O bond to form a cationic η^3-benzyl complex **G**.[18] We suggest that **G** is deprotonated by a boronate ion to release 1,1-diarylethene at the end. An alternative path involving β-hydrogen elimination on the nickel center will lead to a nickel hydride, which is known to quickly insert to ketones and give carbinols. Such a reductive byproduct was not detected in reaction mixtures.

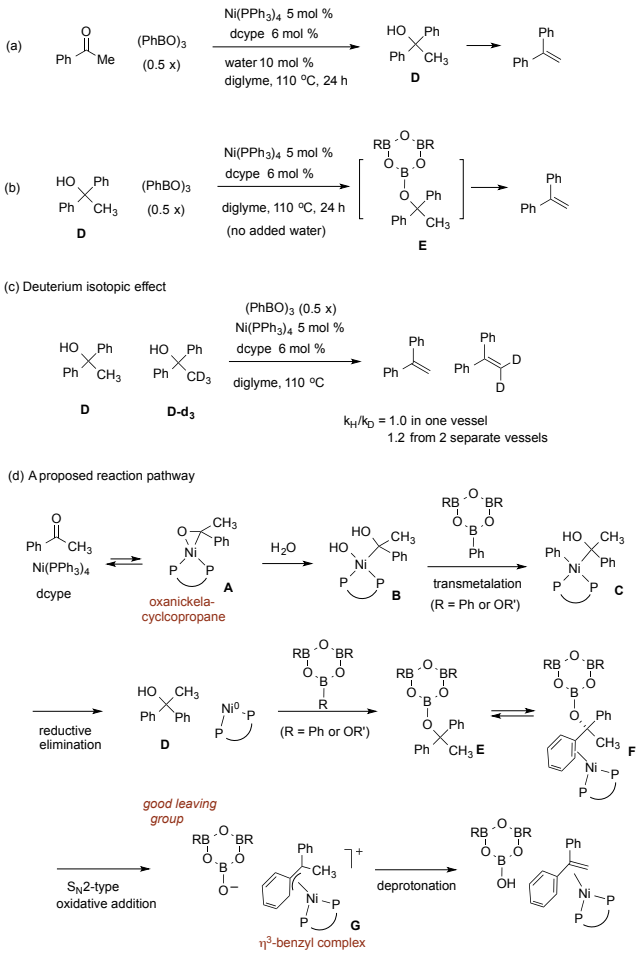


Figure 5. Mechanistic study and a proposed catalytic cycle.

Simple E1 elimination via carbocations preferentially forms more stable olefinic isomers.[19] Such a preference was *not* seen in the phenylation of phenylacetone, benzylacetone and cyclohexa-1,4-dione (Fig 6a-c). Furthermore, in phenylation of an α,β-unsaturated enone, the more stable diene **3bj'** was not formed as major product, either (Fig 6d). In all the cases, we noted that the elimination has a slight bias to occur at the more accessible methyl groups, which is indicative of an E2-like reaction.

We also made comparison of nickel-catalyzed arylation with Barluenga arylation of hydrazones by testing substrates carrying acidic protons and fragile groups (see Fig 7). Under the palladium-catalyzed conditions, **4a** carrying a malonate group gave olefinic isomers **3ar** and **3ar'** in a moderate yield, while in arylation of 3-bromoaniline **4b**, very little product was formed, along with formation of some styrene. Switching the base to potassium phosphate led to olefin **3n** in moderate yield. Importantly, in arylation of hydrazone **4c**, dienes **3bi** and **3bi'** were formed in very low yields, while the main product was a pyrazole **5b** owing to the action of the base. Furthermore, in arylation of indole-derived hydrazones **4d** and **4e**, very complex mixtures resulted in the presence of bases, which contained no desired olefins. Clearly, Barluenga arylation under basic conditions fails to deliver alkenes when fragile groups are present (For extensive conditions, see the Supporting Information).

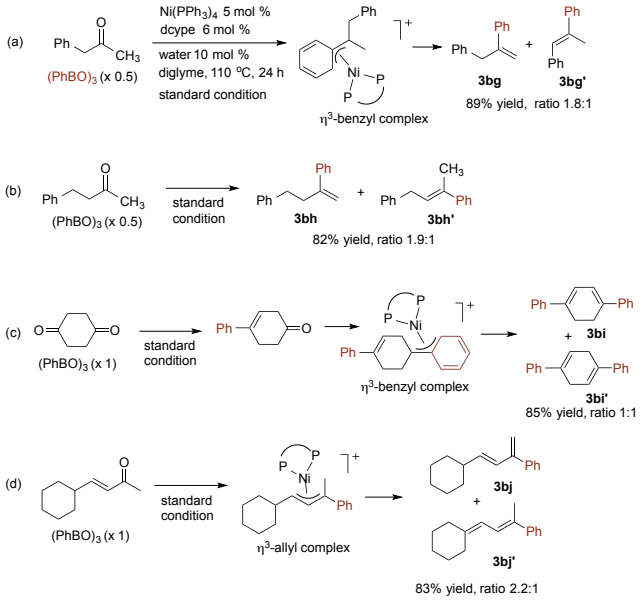


Figure 6. Catalytic arylation of unsymmetrical ketones

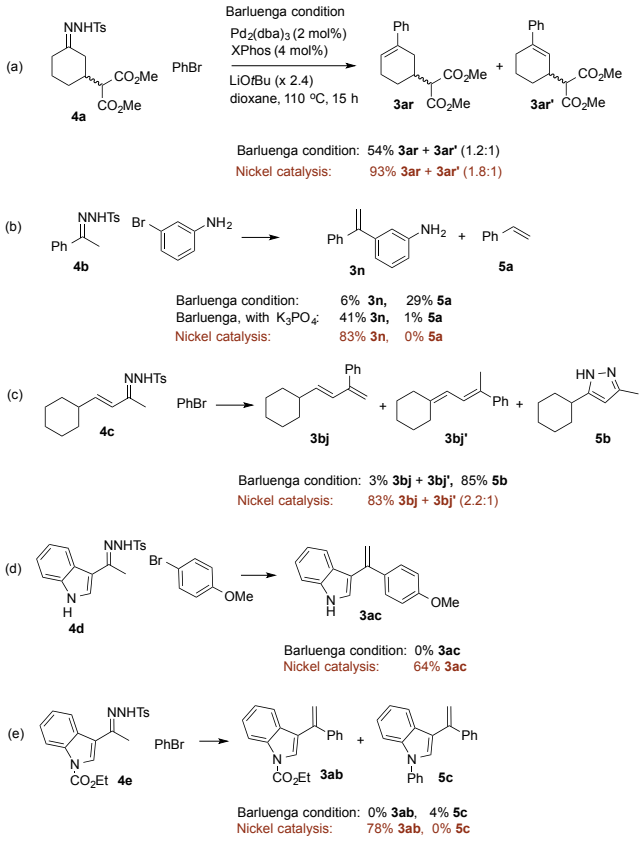


Figure 7. Pd-catalyzed Barleunga arylation of hydrazones and comparison with our nickel catalysis.

In summary, we report a general method to access aryl olefins from ketones by using arylboroxine reagents. The nearly neutral conditions allow direct preparation of arylolefins carrying acidic protons and sensitive groups.

ASSOCIATED CONTENT

Supporting Information. Procedures for conjugate addition, characterization of products, NMR spectra and MS of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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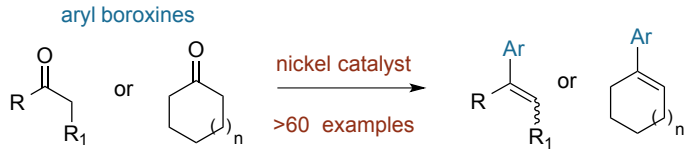

- nearly neutral condition, no added base or acid
- compatible with acidic protons & base-sensitive structures