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**Conference paper**

Dong Liu[a], Chao Liu[a] and Aiwen Lei*

# Nickel-catalyzed oxidative cross-coupling of arylboronic acids with olefins[1]

**Abstract:** A novel and efficient nickel-catalyzed oxidative cross-coupling of arylboronic acids with olefins to synthesize 1,2-diarylalkenes has been developed. By employing $Ni(acac)_2$ as the catalyst, TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) as the oxidant, a variety of arylboronic acids and styrene derivatives could be cross-coupled efficiently to afford the corresponding 1,2-diarylalkenes in moderate-to-good yields. Notably, high *E*-selectivity of 1,2-diarylalkenes was obtained with the aid of a high temperature of 120 °C. Moreover, boric acid esters also proved to be efficient coupling partners. Initial mechanistic studies suggest that this reaction proceeds through a radical pathway.

**Keywords:** arylboronic acids; 1,2-diarylalkenes; nickel; OMCOS-17; oxidative cross-coupling; radical pathway.

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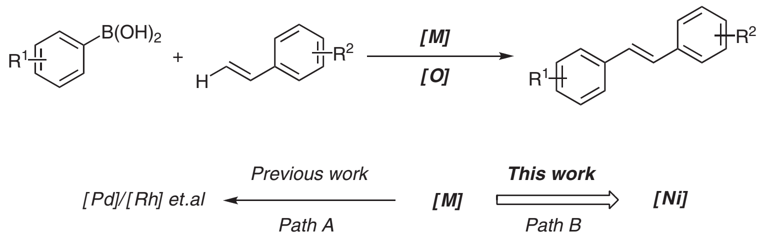
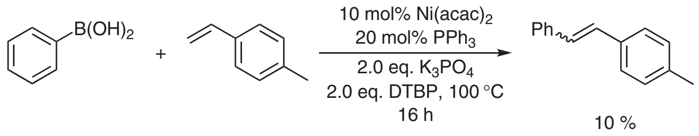
## Introduction

Transition-metal-catalyzed cross-coupling reactions have attracted considerable attention in the past few decades and have become the most powerful synthetic strategies in numerous areas of application, especially in materials science and pharmaceutical chemistry. Among them, the Heck reaction is one of the most outstanding examples [1–6]. Since its first discovery by Mizoroki and Heck [7, 8], countless investigations and applications have been reported [9–11]. In particular, urgent and growing demands of green and atom-economic chemistry have furnished an ongoing incentive for the rapid development of oxidative Heck reactions [12–21]. Initial progress generally required a high catalyst loading, high temperature, and relatively long reaction time as well as the presence of bases, ligands, and equivalent metal salts [22–28]. For example, the Oshima group reported an oxidative Heck-type reaction involving cleavage of a carbon-phosphorus bond of arylphosphonic acids in 2003. In this reaction, an excess amount of organic oxidant was used to enhance the reaction efficiency under high temperature with a prolonged reaction time. However, more recent studies have introduced improvements based upon lower catalyst loading, lower temperature, cleaner oxidants such as dioxygen or air [29–33], and frequently no need for participation of all the above-mentioned parameters [34–40], which makes this chemistry much greener, milder, and more efficient. Notably, this type of reaction could employ air or dioxygen as terminal oxidant and proceed smoothly at room temperature under base free conditions. Probably, the greatest advantage of this type of reaction was the use of polymer-supported transition-metal catalyst, which greatly improved the reaction efficiency and also could be used circulatorily. However, a persistent drawback is that almost all such reactions have to be catalyzed by noble transition-metal complexes such as palladium, rhodium, or ruthenium catalysts (eq. 1, path A). Recently, our group communicated a nickel-catalyzed Heck-type alkenylation of secondary and tertiary α-carbonyl alkyl bromides [41], which raised a question about the possibility for nickel-catalyzed Heck-type alkenylation reactions, and inspired us to conduct further research in this area. To our knowledge, only one Heck-type oxidative cross-coupling of arylboronic acids with olefins utilizing nickel catalyst has hitherto been reported, in which an excess amount of olefin reactant served as a hydrogen acceptor [21]. Herein, we demonstrate a nickel-catalyzed oxidative Heck-type alkenylation of arylboronic acids (eq. 1, path B).



(1)

Very recently, our group reported a nickel-catalyzed oxidative Csp$^3$-H arylation reaction utilizing simple cyclic ethers as the substrates [42]. A preliminary mechanistic study revealed that addition of an aryl radical to the C=O bond of a cation intermediate is probably involved in this reaction. This inspired us to investigate the scope for other radical acceptors to achieve this type of arylation reaction. Olefins have been widely applied as radical acceptors in many radical reactions [43–45]. When we subjected 1-methyl-4-vinyl-benzene to the reaction conditions of this catalytic system, with phenylboronic acid (2 equiv) in the presence of Ni(acac)$_2$ (10 mol%), PPh$_3$ (20 mol%), K$_3$PO$_4$ (2 equiv), and *t*BuOO*t*Bu (2 equiv) in DME (1,2-dimethoxyethane, 2.0 mL) at 100 °C, we were greatly encouraged to obtain the target product 1-methyl-4-styrylbenzene in 10 % yield (eq. 2). This promising result prompted us to proceed with further attempts to optimize reaction conditions.



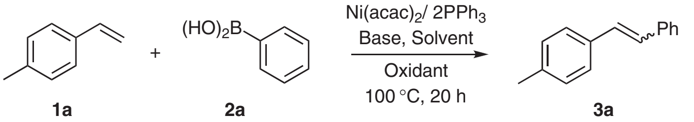
(2)

## Results and discussion

### Condition optimization

Guided by the foregoing result, we set about optimizing reaction conditions using 1-methyl-4-vinylbenzene (**1a**) and phenylboronic acid (**2a**, 2 equiv) as substrates. Firstly, we examined a series of common oxidants. Fortunately, we found TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) to be a superior choice. In this case, we obtained a 49 % yield of the target product with a fairly low *E/Z*-selectivity (Table 1, entry 1). Other common oxidants that are generally used in radical processes were ineffective (Table 1, entries 2–5). It is worth mentioning that dioxygen could also promote the reaction in the presence of catalytic amount of TEMPO, although the reaction efficiency was relatively low (Table 1, entry 6). Further base screening was unproductive, indicating the unique applicability of K$_3$PO$_4$ in this reaction (Table 1, entries 7–9). In expectation that high temperature may accelerate styrene oxidation process by peroxides, we tried to lower the reaction temperature to 80 °C. Contrary to expectations, this resulted in a decreased yield of 33 % (Table 1, entry 10). Solvent screening showed that the desired product could be obtained in higher yields both in CH$_3$CN and dioxane, whereas the former solvent displayed a higher *E*-selectivity (Table 1, entries 11 and 13). Toluene only gave 55 % yield with a moderate selectivity of *E/Z* 10.3/1 (Table 1, entry 12). To our delight, increasing the temperature to 120 °C improved the yield to 79 % accompanied with a perfect *E* selectivity which could be reasoned as the thermodynamic stability of *E* configuration at high temperature (Table 1, entry 14). Changing the ratio of

**Table 1** Conditions optimization for nickel-catalyzed oxidative Heck reaction of **1a** and **2a**[a].



| Entry | Base | Solvent | Oxidant | Yield (%)[b] | E/Z |
|---|---|---|---|---|---|
| 1 | $K_3PO_4$ | DME | TEMPO | 49 | 9.7/1 |
| 2 | $K_3PO_4$ | DME | *t*BuOO*t*Bu | 4 | 3.3/1 |
| 3 | $K_3PO_4$ | DME | $NaNO_2$ | 9 | 9.4/1 |
| 4 | $K_3PO_4$ | DME | BQ | n.d. | / |
| 5 | $K_3PO_4$ | DME | Oxone | 17 | 9.3/1 |
| 6[c] | $K_3PO_4$ | DME | $O_2$ | 22 | 8.5/1 |
| 7 | $K_2CO_3$ | DME | TEMPO | 9 | 8.6/1 |
| 8 | $Na_2CO_3$ | DME | TEMPO | 31 | 7.0/1 |
| 9 | KO*t*Bu | DME | TEMPO | n.d. | / |
| 10[d] | $K_3PO_4$ | DME | TEMPO | 33 | 5.0/1 |
| 11 | $K_3PO_4$ | $CH_3CN$ | TEMPO | 64 | 18.8/1 |
| 12 | $K_3PO_4$ | Toluene | TEMPO | 55 | 10.3/1 |
| 13 | $K_3PO_4$ | Dioxane | TEMPO | 65 | 6.0/1 |
| 14[e] | $K_3PO_4$ | $CH_3CN$ | TEMPO | 79 | E |
| 15[e], [f] | $K_3PO_4$ | $CH_3CN$ | TEMPO | 84 | E |
| 16[e], [f], [g] | $K_3PO_4$ | $CH_3CN$ | TEMPO | **87 (88)** | E |

[a] Unless otherwise noted, the reaction was carried out with **1a** (0.3 mmol), **2a** (0.6 mmol), $Ni(acac)_2$ (0.03 mmol), $PPh_3$ (0.06 mmol), base (0.6 mmol), oxidant (0.6 mmol), solvent (0.5 mL), 100 °C, 20 h.

[b] The yield was determined by GC analysis with dibenzo[*b,d*]furan as the internal standard.

[c] 20 mol% TEMPO was used.

[d] 80 °C.

[e] 120 °C.

[f] 0.03 mmol $PPh_3$.

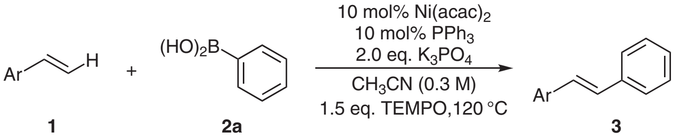
[g] 1 mL $CH_3CN$, 0.45 mmol TEMPO. n.d. = no desired product.

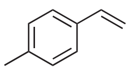
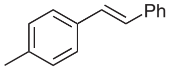
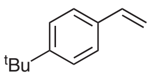
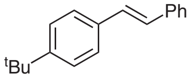
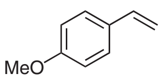
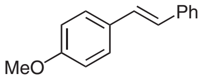
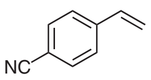
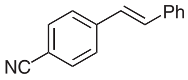
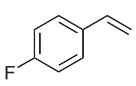
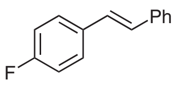
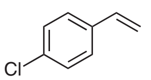
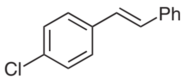
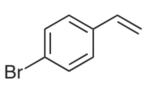
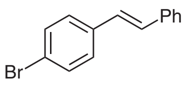
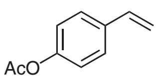
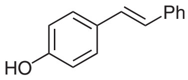
$Ni(acac)_2$:$PPh_3$ to 1:1 further increased the yield to 84 % without any loss of selectivity (Table 1, entry 15). Finally, increasing the volume of $CH_3CN$ to 1.0 mL and decreasing the amount of TEMPO to 1.5 equiv in the meantime gave the best yield of 87 %, along with an isolated yield of 88 % (Table 1, entry 16). From these attempted experiments, we determined the optimized conditions to be: $Ni(acac)_2$ (10 mol%), $PPh_3$ (10 mol%), $K_3PO_4$ (2.0 equiv), TEMPO (1.5 equiv), $CH_3CN$, 120 °C, 20 h.

## Substrate scope

With a viable oxidative Heck procedure to produce 1, 2-diarylalkenes in hand, we set out to explore the generality of this transformation. First of all, various alkenes were employed to couple with phenylboronic acid as shown in Table 2. Different kinds of styrene derivatives could be well tolerated to produce the desired products in good-to-excellent yields. As shown before, the model reaction gave (*E*)-1-methyl-4-styrylbenzene in 88 % yield (Table 2, entry 1). Styrene with *t*Bu substituent also proceeded well (Table 2, entry 2). Styrenes with both electron-withdrawing substituents such as CN and electron-rich substituents such as OMe also reacted smoothly with phenylboronic acid to yield the target product in good yields (Table 2, entries 3 and 4). Notably, halogens were not sensitive to optimized conditions. Reactions of F, Cl, and Br substituted styrenes all proceeded well with phenylboronicc acid to give the corresponding products in satisfactory yields, respectively (Table 2, entries 5–7). Interestingly, when we employed *p*-OAc styrene in this transformation, the OAc group finally hydrolyzed to OH group with the aid of strong base and high temperature to give a moderate yield of the abnormal product (Table 2, entry 8).

**Table 2** Substrate scope for the nickel-catalyzed oxidative Heck reaction of phenylboronic acid with olefins[a].



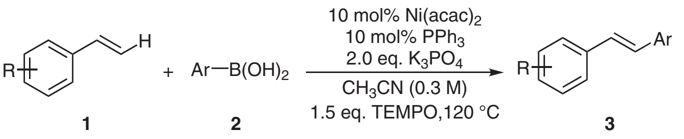
| Entry | 1 | Product | 3 | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  | **3a** | 88 |
| 2 |  |  | **3b** | 78 |
| 3 |  |  | **3c** | 67 |
| 4 |  |  | **3d** | 83 |
| 5 |  |  | **3e** | 50 |
| 6 |  |  | **3f** | 87 |
| 7 |  |  | **3g** | 68 |
| 8 |  |  | **3h** | 50 |

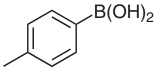
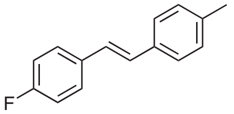
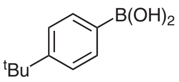
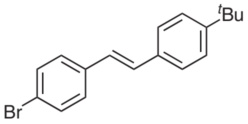
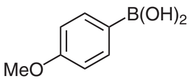
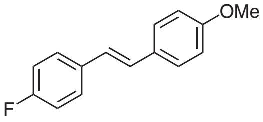
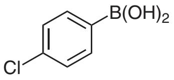
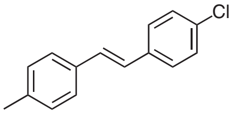
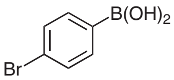
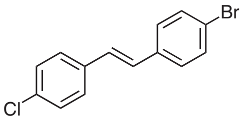
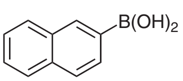
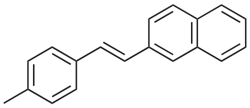
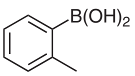
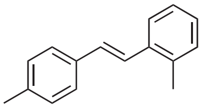
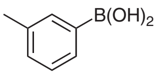
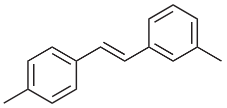
[a] Reaction conditions: **1** (0.30 mmol), **2a** (0.60 mmol), $Ni(acac)_2$ (10 mol%), $PPh_3$ (10 mol%), $K_3PO_4$ (0.60 mmol), TEMPO (0.45 mmol) in $CH_3CN$ (1.0 mL) at 120 °C for 20 h.
[b] Yield of isolated product.

We next investigated the feasibility of different arylboronic acids with substituted styrenes in the presence of nickel catalyst. To our pleasure, reactions all proceeded smoothly to afford the corresponding Heck-type alkenylation products in reasonable yields. Both *p*-methyl and *p*-tertiary butyl phenylboronic acids reacted with halogen-substituted styrenes to afford the corresponding coupling products in moderate-to-good yields (Table 3, entries 1 and 2). Similarly, electron-donating group could be well tolerated in this reaction (Table 3, entry 3). At the same time, halogenated arylboronic acids such as *p*-Cl and *p*-Br substituted phenylboronic acids converted well to give the corresponding products in moderate yields which could be further functionalized to give other more useful substructures (Table 3, entries 4 and 5). Naphthalen-2-ylboronic acid was also proved to be a good coupling partner with 1-methyl-4-vinylbenzene (Table 3, entry 6). Steric effect had a significant impact on the yield. When we employed *o*-tolylboronic acid in this catalytic system, only 37 % yield of the target product was obtained (Table 3, entry 7). While *o*-chloro phenylboronic acid only generated trace amount of the desired product. Additionally, *meta*-substituents could also be well tolerated in this reaction (Table 3, entry 8).

Notably, this reaction could also be extended to boric acid esters. Employing 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane and 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane as substrates, meanwhile increasing the catalyst loading to 20 mol%, we could obtain the corresponding Heck-type alkenylation products in 26

**Table 3** Substrate scope for the nickel-catalyzed oxidative Heck reaction of arylboronic acids with substituted styrenes[a].



| Entry | 2 | Product | 3 | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  | **3i** | 50 |
| 2 |  |  | **3j** | 71 |
| 3 |  |  | **3k** | 47[c] |
| 4 |  |  | **3l** | 52[c] |
| 5 |  |  | **3m** | 48[c] |
| 6 |  |  | **3n** | 61 |
| 7 |  |  | **3o** | 37[c] |
| 8 |  |  | **3p** | 64 |

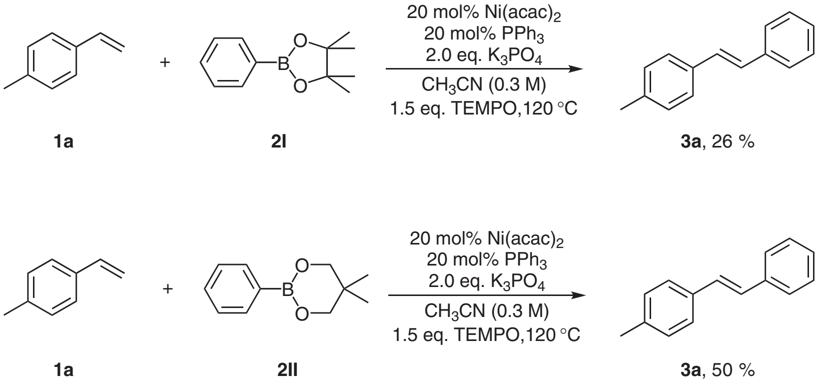
[a] Reaction conditions: **1** (0.30 mmol), **2** (0.60 mmol), Ni(acac)$_2$ (10 mol%), PPh$_3$ (10 mol%), K$_3$PO$_4$ (0.60 mmol), TEMPO (0.45 mmol) in CH$_3$CN (1.0 mL) at 120°C for 20 h.

[b] Yield of isolated product.

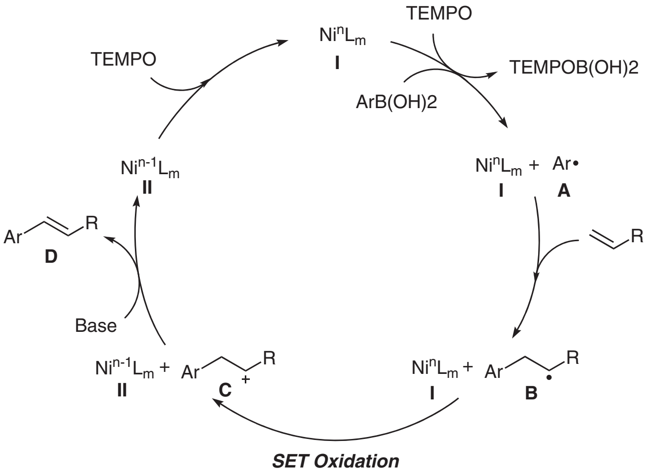
[c] 20 mol% Ni(acac)$_2$, 20 mol% PPh$_3$ was used.

and 50 % yields, respectively (Scheme 1). While phenyl potassium trifluoroborate proved not to be a suitable boron source, which did not afford any desired product at all.

To our knowledge, arylboronic acids can generate aryl radicals in the presence of transition-metal salts and oxidants [46–48]. For instance, the Hayashi group reported an iron-catalyzed oxidative coupling of arylboronic acids with benzene derivatives in 2011, which was believed to proceed through a radical-type homolytic aromatic substitution of aryl radical generated from iron salt and peroxide. Also, addition of aryl radical to alkenes has been illustrated by many research groups and believed to be easy to occur [49]. Moreover, high-valent metal salts such as nickel(II) species is able to oxidize benzyl radical to benzyl cation with the aid of



**Scheme 1** Nickel-catalyzed Heck-type alkenylation reaction of boric acid esters.



**Scheme 2** Proposed mechanism of nickel-catalyzed Heck-type alkenylation of arylboronic acids.

ligand which is also widely accepted [41, 50]. Based on these evidences, we proposed a plausible mechanism of this reaction (Scheme 2). Firstly, aryl radical **A** was generated with the aid of nickel catalyst **I** and TEMPO. Subsequent addition of **A** to olefins generated benzyl radical **B**. Further SET (single electron transfer) oxidation of benzyl radical **B** by nickel species afforded benzyl cation **C**, along with the formation of a lower-valent nickel species **II**. Final deprotonation of **C** in the presence of base generated the corresponding product **D**, meanwhile **II** was oxidized by TEMPO to species **I** to complete the catalytic cycle.

## Conclusion

We have demonstrated a nickel-catalyzed oxidative Heck-type alkenylation of arylboronic acids to synthesize 1,2-diarylalkenes. Different substituted arylboronic acids and styrene derivatives were found to be suitable substrates for this novel transformation. Notably, this reaction achieved a very good selectivity of *E*-isomer only. Moreover, this reaction opens up an effective protocol for the synthesis of 1,2-diarylalkenes getting rid of noble transition-metal catalysts. It is believed that this reaction may proceed through a radical pathway so that a plausible mechanism is given accordingly. Further studies on the detailed reaction mechanism are currently underway in our laboratory and will be reported in due course.

# Experimental section

## General procedure for the Ni-catalyzed oxidative Heck-type alkenylation reaction of arylboronic acids

$Ni(acac)_2$ (7.7 mg, 0.03 mmol), $PPh_3$ (7.9 mg, 0.03 mmol), and $K_3PO_4$ (127.2 mg, 0.6 mmol) were added in a sealed tube. The sealed tube was then filled with dry $N_2$. Under the protection of $N_2$, acetonitrile (1.0 mL) was injected in the tube via a syringe. After stirring for a several minutes, TEMPO (70.2 mg, 0.45 mmol), arylboronic acid (0.6 mmol), and alkene (0.3 mmol) were consequently injected in the reaction tube. The reaction was then heated up to 120 °C and kept stirring for 20 h. After completion of the reaction, the mixture was quenched with diluted hydrochloric acid. The solution was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and dried over sodium sulfate. The pure product was obtained by flash column chromatography on silica gel (petroleum).

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