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Multicomponent Reactions

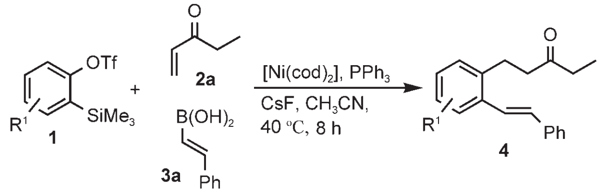
Nickel-Catalyzed Coupling of Arynes, Alkenes, and Boronic Acids: Dual Role of the Boronic Acid[**]

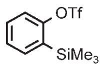
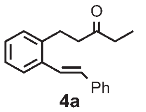
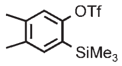
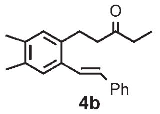
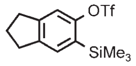
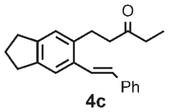
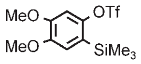
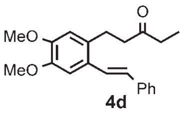
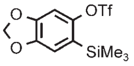
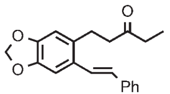
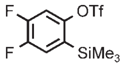
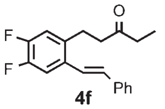
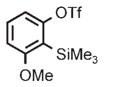
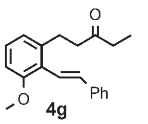
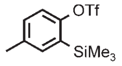
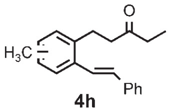
Thiruvellore Thatai Jayanth and Chien-Hong Cheng[*]

Nickel-catalyzed domino reactions that involve the coupling of two π components with main-group organometallic reagents or metal hydrides have emerged as highly useful methods for assembling complex molecular structures from simple starting materials.[1] This class of reactions has evolved significantly in scope as well as substrate choice. Most commonly employed π systems include alkynes, alkenes, dienes, allenes, aldehydes, imines, and allylic halides. The organometallic reagents employed are usually based on zinc, aluminum, zirconium, tin, boron, and silanes.[2] The utility of this concept has been demonstrated well in organic synthesis.[3] A similar reaction sequence employing arynes as a π component would be highly interesting and useful, considering that arynes are generally very reactive and generated in situ and that the reaction would lead to the formation of two different C−C bonds in *ortho* positions of a benzene ring.[4] A mild method for the preparation of arynes in situ at moderate temperatures from commercially available *o*-silyl aryl triflates **1**[5] has rekindled the interest, especially in the past few years, in employing arynes as substrates in organic synthesis.[6] As part of our ongoing efforts in employing arynes as useful substrates in organic synthesis,[7] we report an unprecedented nickel-catalyzed three-component coupling of arynes, enones, and organoboronic acids. Thus, when a solution of benzyne precursor **1a** (2-(trimethylsilyl)phenyl triflate), ethyl vinyl ketone (**2a**), and *trans*-2-phenylvinylboronic acid (**3a**) in the presence of [Ni(cod)$_2$] (cod = 1,5-cyclooctadiene; 10 mol %), PPh$_3$ (20 mol %), and CsF in CH$_3$CN was stirred for 8 h at 40 °C, coupling product **4a** was obtained in 92 % yield (Table 1, entry 1).[8] This process is the first example involving arynes and is also one of the first to utilize organoboronic acids in nickel-catalyzed multicomponent coupling reactions.[9]

A variety of arynes are compatible with this three-component coupling reaction (Table 1). The aryne precursor **1b** with two methyl groups on the phenyl ring furnished product **4b** in 93 % yield (Table 1, entry 2) and indanyl derivative **1c** afforded **4c** in 84 % yield (Table 1, entry 3). Aryne precursors that bear other electron-donating substituents such as 3,4-dimethoxy and 1,3-benzodioxole derivatives **1d** and **1e**, respectively, gave products in excellent yields (Table 1, entries 4 and 5). Furthermore, the difluoro substituted benzyne precursor **1f** gave the corresponding three-

Table 1: Three-component coupling of arynes with ethyl vinyl ketone (**2a**) and styrenyl boronic acid (**3a**).[a]



Entry	1	4	Yield [%][b]
1	 **1a**	 **4a**	92
2	 **1b**	 **4b**	93
3	 **1c**	 **4c**	84
4	 **1d**	 **4d**	95
5	 **1e**	 **4e**	88
6	 **1f**	 **4f**	67
7	 **1g**	 **4g**	85[c] (85:15)
8	 **1h**	 **4h**	87[d] (1:1)

[a] Reaction conditions: aryne precursor **1** (0.30 mmol), enone **2** (0.45 mmol), boronic acid **3** (0.30 mmol), [Ni(cod)$_2$] (0.030 mmol), PPh$_3$ (0.060 mmol), and CsF (0.90 mmol) in CH$_3$CN (1 mL) at 40 °C for 8 h. [b] Yields of isolated products. [c] The structure of the major isomer is represented. [d] Mixture of regioisomers (1:1).

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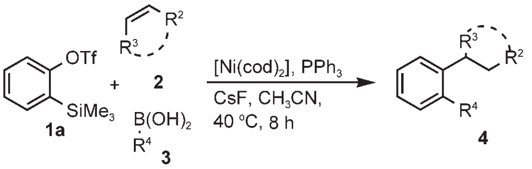
component product **4f** (Table 1, entry 6). Very interestingly, the aryne precursor **1g** with a methoxy group at the *ortho* position afforded regioisomers in 85:15 ratio in which the predominant product was that with the vinyl group from the boronic acid attached *ortho* to the methoxy group (Table 1, entry 7). In the case of benzyne precursor **1h**, the reaction gave a 1:1 mixture of regioisomers (Table 1, entry 8), as expected for the reaction of the unsymmetrical 4-methylbenzyne substrate.

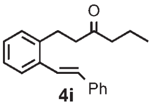
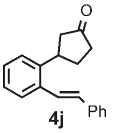
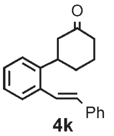
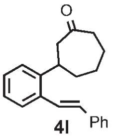
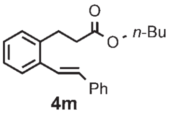
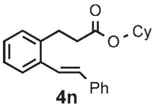
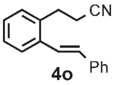
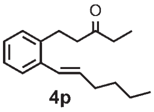
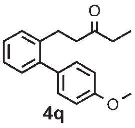
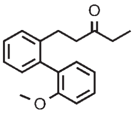
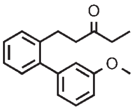
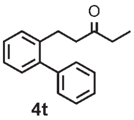
This three-component assembly works well with both acyclic and cyclic enones (Table 2). Propyl vinyl ketone (**2b**) worked smoothly under the reaction conditions (Table 2, entry 1). Cyclic enones (five-, six-, and seven-membered rings) reacted equally efficiently to yield the expected products in very good yields (Table 2, entries 2–4). Acrylates were also found to be compatible in the present reaction (Table 2, entries 5 and 6). When acrylonitrile (**2h**) was employed the three-component coupling product **4o** was obtained in 71% yield (Table 2, entry 7). When boronic acid **3a** was replaced by its pinacol ester the reaction did not proceed to give the expected product, and boroxine ((4-$MeOC_6H_5)_3B_3O_3$) gave trace amounts of product. The reaction also failed with other soft organometallic reagents based on tin ($PhC{\equiv}CSnBu_3$) and silicon ($PhSiMe_3$). The boronic acid acting as a proton source is the likely reason for this observation (see below). The boronic acid was found to be crucial for the success of this reaction. Alkenyl boronic acids worked particularly well. Thus hexenylboronic acid afforded the three-component product in excellent yield (Table 2, entry 8). Of the other organoboronic acids tested, *p*-, *o*-, and

Table 2: Three-component coupling of benzyne with alkenes **2** and organoboronic acids **3**.[a]



2a : ethyl vinyl ketone
2b : propyl vinyl ketone
2c : 2-cyclopentene-1-one
2d : 2-cyclohexene-1-one
2e : 2-cycloheptene-1-one
2f : *n*-butylacrylate
2g : cyclohexylacrylate
2h : acrylonitrile

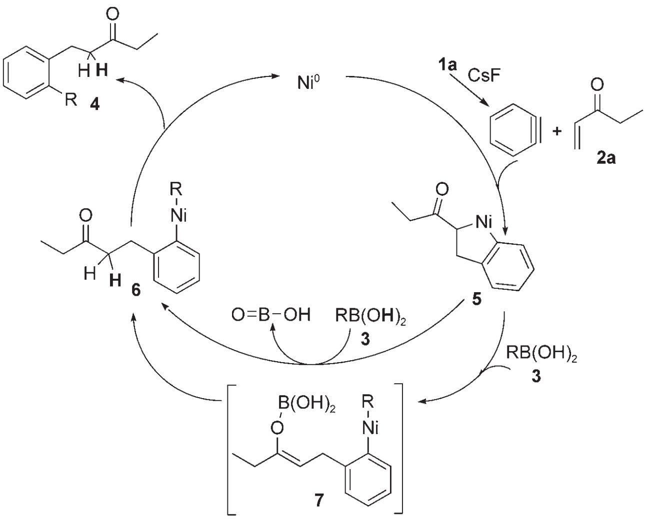
3a R^4 : $-CHCHC_6H_5$
3b R^4 : $-CHCH(CH_2)_3CH_3$
3c R^4 : -*p*-C_6H_4OMe
3d R^4 : -*o*-C_6H_4OMe
3e R^4 : -*m*-C_6H_4OMe
3f R^4 : $-C_6H_5$

Entry	1	2	3	4	Yield [%][b]
1	**1a**	**2b**	**3a**	 **4i**	94
2	**1a**	**2c**	**3a**	 **4j**	84
3	**1a**	**2d**	**3a**	 **4k**	81
4	**1a**	**2e**	**3a**	 **4l**	77
5	**1a**	**2f**	**3a**	 **4m**	75
6	**1a**	**2g**	**3a**	 **4n**	73
7	**1a**	**2h**	**3a**	 **4o**	71
8	**1a**	**2a**	**3b**	 **4p**	94
9	**1a**	**2a**	**3c**	 **4q**	84
10	**1a**	**2c**	**3d**	 **4r**	79
11	**1a**	**2a**	**3e**	 **4s**	67[c]
12	**1a**	**2a**	**3f**	 **4t**	60[c]

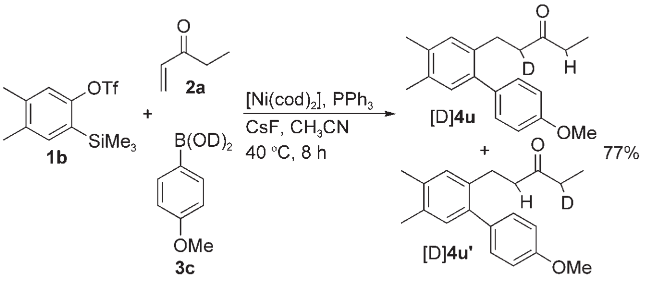
[a] Reaction conditions: aryne precursor **1** (0.30 mmol), enone **2** (0.45 mmol), boronic acid **3** (0.30 mmol), $[Ni(cod)_2]$ (0.030 mmol), PPh_3 (0.060 mmol), and CsF (0.90 mmol) in CH_3CN (1 mL) at 40°C for 8 h. [b] Yields of isolated products. [c] $P(p\text{-}C_6H_4F)_3$ was employed instead of PPh_3.

m-methoxybenzeneboronic acids (**3c**–**e**) gave the corresponding products in 67–84 % yield (Table 2, entries 9–11). Benzeneboronic acid (**3f**) provided product **4t** in 60 % yield (Table 2, entry 12). In the case of boronic acids **3e** and **3f**, phosphine ligand $P(p\text{-}C_6H_4F)_3$ was employed, as the reaction did not proceed when PPh_3 was used as the ligand.

A plausible mechanistic rationale for the present catalytic reaction is shown in Scheme 1. The catalysis is likely initiated by the reaction of Ni^0 with the enone and the aryne to form a nickelacycle **5**. Protonation of the α carbon atom of the ketone moiety by the boronic acid and transmetalation of the organic group onto the nickel center leads to **6**. Subsequent reductive elimination gives the desired coupling product and regenerates the Ni^0 catalyst. To verify this pathway, a deuterated boronic acid, $p\text{-}OMeC_6H_4B(OD)_2$, was carefully prepared and employed. As expected, deuterium was incorporated at the α carbon atoms of the ketone product (Scheme 2).[10] Protonation of **5** by the organoboronic acid likely enhances electron density at the boron center and thus the nucleophilicity of the carbon nucleophile to facilitate the transmetalation and catalysis. Thus, the organoboronic acid plays a dual role in the present catalytic process: it acts both as a proton source and as a carbon nucleophile.[11] An alternative pathway for the formation of **6** from **5** via a boron enolate **7** and subsequent protonation cannot be completely ruled out.

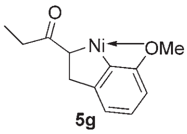


Scheme 1. Proposed mechanism for the three-component coupling reaction.



Scheme 2. Deuterium-labeling experiment.

The regioselectivity observed in the reaction of **1g** (Table 1, entry 7) can be rationalized by the formation of *ortho*-metalated complex **5g** on the basis of the coordination of the methoxy group to nickel.[12]



5g

A seven-membered ring nickel *O*-enolate generated by the oxidative cyclization of an enal and an alkyne with Ni^0 species containing a *Z* carbon–carbon double bond is documented as the intermediate for protonation during the coupling reaction.[13] However, in the present case, a seven-membered ring nickel enolate intermediate from **5** can be ruled out, considering that the seven-membered ring intermediate generated by a cyclic enone such as 2-cyclopenten-1-one and an aryne with Ni^0 would contain a strained *E* double bond in the seven-membered ring.[14]

In summary, we have demonstrated a nickel-catalyzed domino reaction of arynes, enones, and boronic acids. This reaction represents the first example of the use of arynes in nickel-catalyzed coupling reactions. The organoboronic acid acts both as a proton source and as a carbon nucleophile.

Experimental Section

General Procedure: A round-bottomed side-arm flask containing $[Ni(cod)_2]$ (0.030 mmol), PPh_3 (0.060 mmol), CsF (0.90 mmol), and boronic acid **3** (0.30 mmol) was evacuated and purged with nitrogen gas. CH_3CN (1.0 mL), alkene **2** (0.450 mmol), and aryne precursor **1** (0.30 mmol) were then added to the flask through syringes. The reaction mixture was allowed to stir at 40 °C for 8 h. At the end of the reaction, the reaction mixture was diluted with CH_2Cl_2 and filtered through celite and silica gel. The filtrate was concentrated, and the residue was purified through a silica-gel column with ethyl acetate/hexane as eluent to give pure product **4**.

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Keywords: arynes · boronic acids · enones · multicomponent reactions · nickel

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