

Highly Selective Nickel-Catalyzed Three-Component Coupling of Alkynes with Enones and Alkenyl Boronic Acids: A Novel Route to Substituted 1,3-Dienes

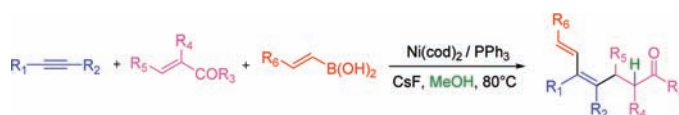
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ABSTRACT



A highly regio- and stereoselective nickel-catalyzed three-component coupling of alkynes with enones and alkenyl boronic acids to afford highly substituted 1,3-dienes is described. The reaction can also be extended to cyclization of enynes with coupling to alkenyl boronic acids. A possible reaction mechanism involving a five-membered nickelacycle as a key intermediate is proposed.

Nickel-catalyzed three-component coupling of two different π -components with an organometallic reagent is an efficient method for constructing complex organic molecules.¹ Previously, a number of three-component couplings involving alkynes with alkenes and various organometallic reagents

or metal hydrides have been demonstrated.^{2–5} Among the coupling reactions, only a few examples are known using alkynes, enones, and various organometallic reagents. Thus, Ikeda's group found a series of nickel-catalyzed coupling of alkynes, enones with organostannane, organozinc, and organoaluminum reagents.^{2a–d} In 2006, Shinokubo et al. reported a rhodium-catalyzed coupling of aryl boronic acids with internal alkynes and acrylates that led to the formation of functionalized dienes.⁶ Recently, we have reported intermolecular benzyne/alkene/organoboronic acid^{7a} and alkyne/enone/bis(pinacolate)diboron couplings.^{7b} In addition, Montgomery and co-workers reported the intramolecular

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sequential coupling of enynes with various organometallic reagents.^{1d,3} However, to the best of our knowledge, there have been no reports of using intermolecular coupling of alkynes with enones and alkenyl boronic acids.

Our continued interest in metal-catalyzed three-component coupling reactions⁸ prompted us to explore an efficient method for the intermolecular coupling of alkynes with enones and alkenylboronic acids. Thus, treatment of 1-phenyl-1-propyne (**1a**) with ethyl vinyl ketone (**2a**) and (*E*)-styrylboronic acid (**3a**) in the presence of Ni(cod)₂ (10 mol %), PPh₃ (10 mol %) and CsF in MeOH at 80 °C for 16 h provided a highly substituted 1,3-diene **4a** in 89% isolated yield (Table 1, entry 1). 1,3-Dienes are very useful synthetic

stereoselective with both double bonds in **4a** being *E* stereochemistry. This depends on the substituents R¹ and R² on the alkyne substrate. In most cases the two substituents are *cis* to each other.

To find the optimized reaction conditions, the reaction of **1a** with **2a** and **3a** in the presence of Ni(cod)₂ and PPh₃ was examined with various additives and solvents. The reaction in MeOH gave a three-component product **4a** in 45% yield in addition to the 1,4-addition product of **2a** and **3a**, *E*-PhCH=CH-(CH₂)₂COEt (**5a**)¹⁰ in 35% yield. To improve the yield of **4a**, various additives were examined (see supporting information). Among them, CsF gave **4a** in 96% NMR yield (Table 1, entry 1) along with trace of **5a**. Additives BEt₃ and ZnCl₂ are less effective giving **4a** in 51 and 15% yields with **5a** in 15 and 5% yields, respectively. The effect of solvents is also vital to the catalytic reaction. The best solvent is MeOH in which **4a** was obtained in 96% yield. CH₃CN is also effective giving **4a** in 58% yield. Other solvents such as THF, DMF, and toluene were totally ineffective for the catalytic reaction (see the Supporting Information for detailed studies). On the basis of these optimization studies, we choose Ni(cod)₂ (10 mol %), PPh₃ (10 mol %), CsF (2.0 mmol) in MeOH at 80 °C for 16 h as the standard conditions for the following catalytic reactions.

A variety of alkynes **1b–j** were successfully used for the three-component reaction with **2a** and **3a** under the standard reaction conditions (Table 1, eq 1). Symmetrical alkynes **1b–e** all gave exclusively only one stereoisomeric three-component product **4b–e**, respectively, in 78–89% yield (entries 2–5). Surprisingly, acetylene gas (1 atm) (**1f**) also reacted smoothly with **2a** and **3a** to give **4f** in 95% yield (entry 6). In addition to **1a**, other unsymmetrical internal alkyne and terminal alkynes (**1g–j**) were also examined. However, the regioselectivity of the products using these alkynes as substrates are lower. Ethyl phenylpropiolate (**1g**) afforded two regioisomeric products **4g/4g'** in a 67/33 ratio in a 63% combined yield (entry 7). Similar to **1g**, phenyl acetylene (**1h**) and 2-ethynyl thiophene (**1i**) gave regioisomeric products **4h/4h'** and **4i/4i'** in 88/12 and 85/15 ratios with 73% and 71% combined yields (entries 8 and 9). In the major products **4h** and **4i**, the unsubstituted carbon of terminal alkyne moiety is connected to the β-carbon of vinyl ketone **2a**. There is essentially no regioselectivity for 1-hexyne providing regioisomeric products **4j/4j'** in a 50/50 ratio in a 67% combined yield (entry 10).

The scope of present reaction was further extended to various enones **2b–j** (Table 2, eq 2). α-Methyl and β-methyl or phenyl substituted enones **2b–d**, underwent coupling with **1a** and **2a** to give **4k–m** in good to excellent yields (entries 11–13). Phenyl vinyl ketone (**2e**) and cyclohexyl vinyl ketone (**2f**) provided coupling products **4n** and **4o** in moderate yields (entries 14 and 15). 1-Cyclopentylethanone (**2g**) also participated in the reaction to give **4p** in 58% yield (entry 16). Cyclic enones **2h–j** also underwent three-component coupling efficiently with **1a** and **2a**. Thus, 2-cyclopentenone (**2h**), 2-cyclohexenone (**2i**), and 2-cyclo-

Table 1. Results of the Reaction of Enones, Alkenyl Boronic Acid with Various Alkynes^a

entry	alkyne 1	product 4	yield (%) ^b
1	1a : R ¹ = Ph, R ² = Me	4a	89 (96)
2	1b : R ¹ = R ² = Ph	4b	86
3	1c : R ¹ = R ² = 4-OMe-C ₆ H ₄	4c	90
4	1d : R ¹ = R ² = <i>n</i> -Bu	4d	78
5	1e : R ¹ = R ² = CH ₂ OMe	4e	89
6 ^c	1f : R ¹ = R ² = H	4f	95
7 ^d	1g : R ¹ = CO ₂ Et, R ² = Ph	4g/4g' : 67:33	63
8 ^d	1h : R ¹ = Ph, R ² = H	4h/4h' : 88:12	73
9 ^d	1i : R ¹ = 3-thienyl, R ² = H	4i/4i' : 85:15	71
10 ^d	1j : R ¹ = <i>n</i> -Bu, R ² = H	4j/4j' : 50:50	67

^a Unless otherwise mentioned, all reactions were carried out using alkyne **1** (1.5 mmol), enone **2a** (1.0 mmol) and alkenyl boronic acid (**3**) (1.5 mmol) in the presence of Ni(cod)₂ (10 mol %), PPh₃ (10 mol %), CsF (2.0 mmol) in MeOH at 80 °C for 16 h. ^b Isolated yields; the yield in parentheses was determined by ¹H NMR method using mesitylene as an internal standard. ^c Acetylene gas balloon. ^d Two regioisomeric products, **4** and **4'**, exist with **4** the major and **4'** the minor isomer.

intermediates in many organic transformations.⁹ The catalytic reaction is highly regioselective with the styryl group of **3a** adding very selectively at the phenyl substituted alkyne carbon, and the other C–C bond formation occurs at the methyl substituted alkyne carbon of **1a** and the β-carbon of vinyl ketone **2a**. The catalytic reaction is also highly

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Table 2. Results of the Reaction of Alkynes, Alkenyl Boronic Acid with Various Enones^a

entry	enone 2	product 4	yield (%) ^b
11	2b : R ³ = Et, R ⁴ = H, R ⁵ = Me	4k	92
12	2c : R ³ = Me, R ⁴ = H, R ⁵ = Ph	4l	89
13	2d : R ³ = R ⁴ = Me, R ⁵ = H	4m	76
14	2e : R ³ = Ph, R ⁴ = R ⁵ = H	4n	60
15	2f : R ³ = cyclohexyl, R ⁴ = R ⁵ = H	4o	56
16	2g : R ³ = Me, R ⁴ +R ⁵ = -(CH ₂) ₃ -	4p	58
17	2h : n = 1	4q	95
18	2i : n = 2	4r	91
19	2j : n = 3	4s	90

^a Unless otherwise mentioned, all reactions were carried out using alkyne **1a** (1.5 mmol), enone **2** (1.0 mmol), and alkenyl boronic acid **3a** (1.5 mmol) in the presence of Ni(cod)₂ (10 mol %), PPh₃ (10 mol %), and CsF (2.0 mmol) in MeOH at 80 °C for 16 h. ^b Isolated yields.

heptenone (**2j**) produced **4q–s** in excellent 95%, 91%, and 90% yield, respectively (entries 17–19).

To further explore the scope of the coupling reaction, various alkenylboronic acids **3b–g** were examined for the reaction with **1a** and **2a** (Table 3, eq 3). (*Z*)-Prop-1-

Table 3. Results of the Reaction of Alkynes, Enones with Various Alkenyl Boronic Acids^a

entry	3	product 4	yield (%) ^b
20 ^d	3b : R ⁶ = <i>Z</i> -Me	4t	73
21	3c : R ⁶ = <i>E</i> -Me	4u	70
22	3d : R ⁶ = <i>E</i> - <i>n</i> -Pr	4v	75
23	3e : R ⁶ = <i>E</i> -cyclohexyl	4w	71
24	3f : R ⁶ = <i>E</i> -CH ₂ -Ph	4x	76
25	3g : R ⁶ = <i>E</i> -4-MeO-C ₆ H ₄	4y	70

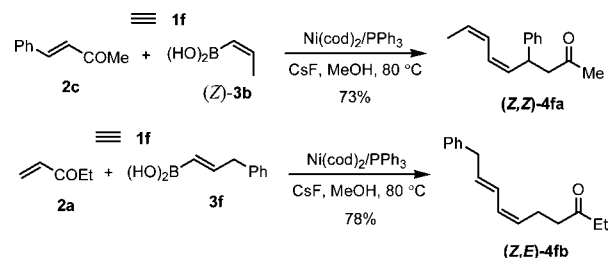
^a Similar reaction conditions as in Table 1 footnote a except various alkenyl boronic acids were used. ^b Isolated yields.

enylboronic acid (**3b**) reacted smoothly to give a highly substituted 1,4-diene **4t** in 73% yield with the disubstituted

alkene exclusively in *Z*-stereoselectivity and tetrasubstituted alkene in *E*-stereoselectivity (entry 20). On the other hand, (*E*)-prop-1-enylboronic acid (**3c**) produced coupling product **4u** in 70% yield with the two carbon–carbon double bonds exclusively in *E*-stereoselectivity (entry 21). Other (*E*)-alkenyl boronic acids including (*E*)-pent-1-enyl, (*E*)-2-cyclohexylvinyl, (*E*)-3-phenylprop-1-enyl, and (*E*)-4-methoxystyryl boronic acids **3d–g**, respectively, afforded coupling products **4v–y** in good yields with similar stereochemistry as **4u** (entries 22–25). It is interesting to note that in these three-component coupling products **4**, the two substituents from the alkyne moiety were always *cis* to each other and retention of stereochemistry of the alkenyl group of **3** in the product was observed.

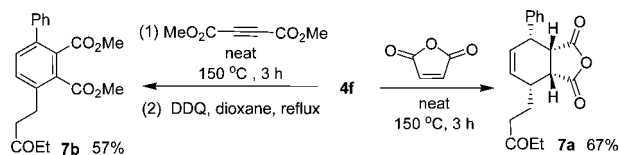
The synthetic utility of our reaction was further exemplified by the synthesis of different stereochemical dienes from acetylene gas. Thus, acetylene gas **1f** was treated with enone **2c** and (*Z*)-prop-1-enylboronic acid (**3b**) under the standard reaction condition to give (*Z,Z*)-diene **4fa** in 73% yield. Similarly, the reaction of **1f** with (*E*)-3-phenylprop-1-enylboronic acid (**3f**) and enone **2a** gave (*Z,E*)-diene **4fb** in 78% yield (Scheme 1). In these two diene syntheses, the reactions are stereospecific.

Scheme 1. Nickel-Catalyzed Stereospecific Synthesis of Dienes **4fa,b**



The application of diene **4f** in the Diels–Alder reaction was demonstrated in Scheme 2. Thus, treatment of **4f** with

Scheme 2. Applications in Diels–Alder Reactions

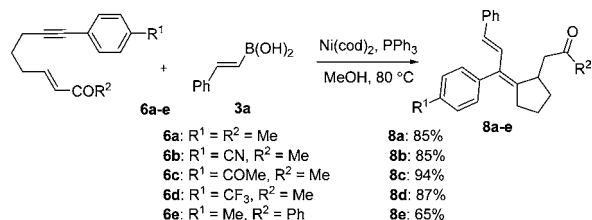


maleic anhydride gave highly stereoselective Diels–Alder adduct **7a** in 67% yield. Highly substituted benzene **7b** was readily prepared from the Diels–Alder reaction of **4f** with dimethyl acetylenedicarboxylate followed by DDQ aromatization (Scheme 2).

An intramolecular version of the coupling of enynes with alkenyl boronic acid also worked very well under the

optimized reaction conditions (Scheme 3). Thus, the reaction of enyne **6a** with **3a** gave a five-membered cyclic product

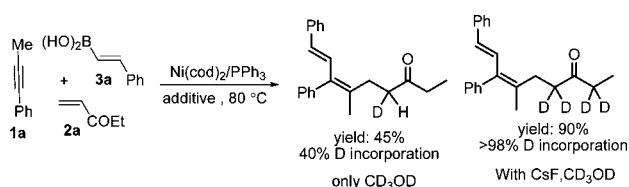
Scheme 3. Results of Nickel-Catalyzed Intramolecular Coupling Reactions



8a in 85% yield in a highly regio- and stereoselective manner. In a similar fashion, enynes **6b–e** also efficiently participated in the reaction to give cyclic coupling products **8b–e** in 85%, 94%, 87%, and 65% yields.

To understand the role of MeOH and to help elucidate the mechanism of the present catalytic reaction, isotope-labeling experiments using CD₃OD to replace normal methanol for the coupling of ethyl vinyl ketone **2a** with alkyne **1a** and (*E*)-styrylboronic acid **3a** were carried out. The reactions gave product **4a** with various degree of deuteration at the α -carbons to the ketone group as shown in Scheme 4. The reaction without CsF afforded **4a** in 45%

Scheme 4. Deuterium-Labeling Studies

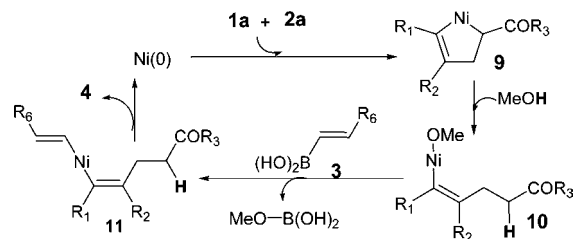


yield with 40% deuterium incorporation at the inner α -carbon to the ketone group. The experiment with CsF presence afforded **4a** with >98% deuteration at both α -carbons to the ketone group. The observed extensive deuteration of **4a** in the presence of weak base CsF is likely due to a base-assisted H/D exchange occurring in the enolate acidic positions. The observed 40% deuterium incorporation of the product in the absence of CsF indicates that methanol acts as proton source

in the catalytic reaction and also suggests that the resulted methoxy anion can be used for the base-promoted transmetalation.

A possible reaction mechanism involving a five-membered nickelacycle as a key intermediate is proposed (Scheme 5).

Scheme 5. Possible Catalytic Pathways of the Three-Component Coupling Reaction



Highly regioselective cyclometalation of alkyne and enone with Ni(0) gives a five-membered nickelacycle **9**.⁷ Selective protonation of the α -carbon of ketone moiety in **9** by MeOH provides intermediate **10**.^{1,7} Highly stereoselective transmetalation of alkenyl boronic acid **3** with intermediate **10** in the presence of MeO⁻ or CsF gives alkenyl-nickel intermediate **11**.⁷ Reductive elimination of intermediate **11** affords product **4** and regenerates the Ni(0) catalyst.

In conclusion, we have developed a highly regio- and stereoselective nickel-catalyzed three-component reductive coupling of alkynes with enones and alkenyl boronic acids to provide substituted 1,3-dienes in good to excellent yields. The scope of the catalytic reaction was successfully demonstrated with various alkynes, enones, and alkenyl boronic acids. An intramolecular version of coupling of enynes with alkenyl boronic acid was also described. Further extension of coupling of two different π -components with an organometallic reagent, and the detailed mechanistic investigation are in progress.

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Supporting Information Available: General experimental procedure and characterization details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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